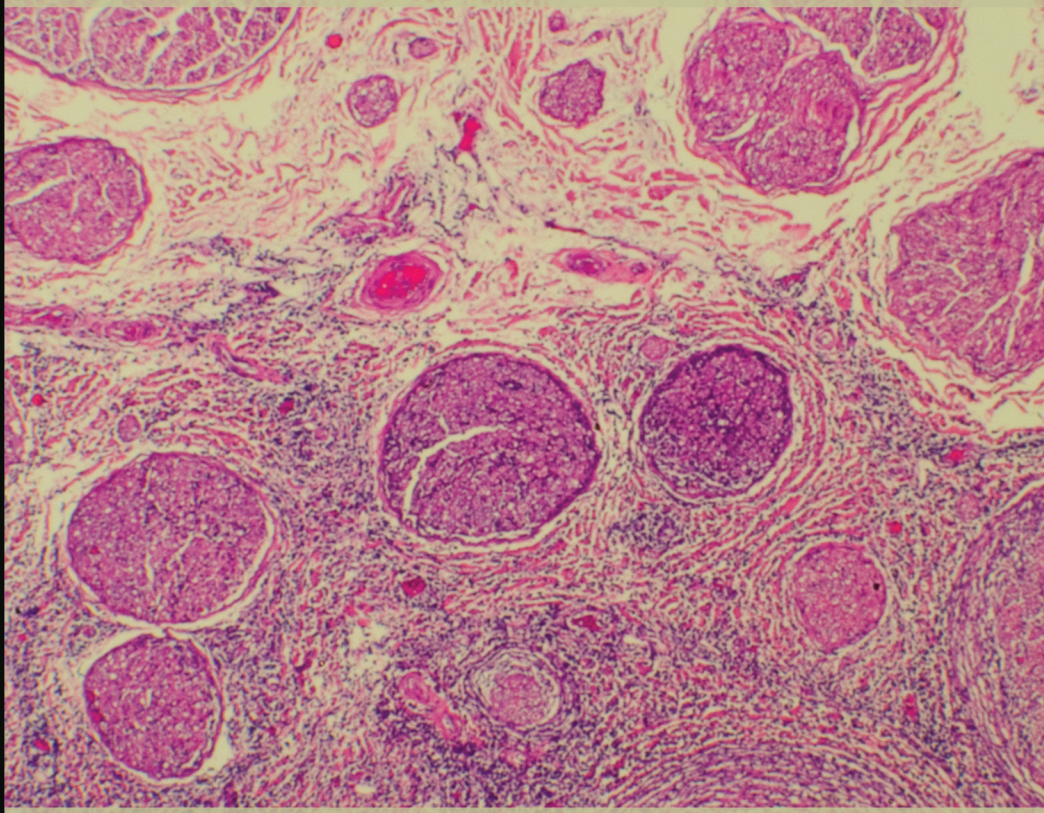
Effects of Cancer Treatment on the Nervous System, *Volume 1*



Edited by

Wolfgang Grisold, Riccardo Soffietti, Stefan Oberndorfer and Guido Cavaletti

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PART 1

CHAPTER 1.1

WHAT IS CANCER: AN INTRODUCTION

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Abstract

Cancer names a large group of diseases caused by genetically aberrant cells that step out of line from behaving as a cell in a multicellular organism, but behave like an independent organism by sustaining uncontrolled cell division, regaining mobility, growing in other tissues, and exhausting the resources of their host organism. All multicellular organisms are potentially affected by cancer.

This paper presents a short overview of the historical development of understanding the mechanisms of cancer, the hallmarks of cancer, and the development of cancer-directed therapies.

Keywords: Cancer, unlimited cell division, avoiding apoptosis, immune escape, neovascularization, metastasis

Introduction

Huge progress has been achieved across all disciplines in the prevention, diagnosis, and treatment of patients with malignant tumors. On the basis of decades of clinical and basic research, the outcome of cancer patients may be changed from a deadly threat to a chronic illness, or even to a curable disease for an increasing number of patients. However, the perception of the cancer threat in the general population has barely changed: cancer is still perceived as the ultimate threat, closely linked to suffering and death—much more than cardiovascular diseases and degenerative metabolic diseases linked to sedentary lifestyles that are still the main cause of death worldwide.

There are many reasons that explain this discrepancy, not limited to the easier "mechanical" understanding of cardiovascular disease or to our coping styles that allow us to think that we will be able to change our lifestyle habits tomorrow, to the easier acceptance of sudden cardiac death compared to what is called "a long, severe illness" in obituary notices. Cancer remains scary, a betrayal of the body, as this is a noncommunicable disease, and arises from a malignant process taking place in the host him- or herself.

The definition of cancer

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. The progression from normal cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression. Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell somewhat.[1]

Our understanding of cancer evolved with the development of diagnostic methods starting from the observation of the invasive growth of cancer, and its spread to lymph nodes and to distant organs, and of paraneoplastic phenomena, such as weight loss, sarcopenia, abnormal bleeding, and thrombosis, to the possibility of detecting cancer through liquid biopsies and by finding tumor-characteristic epigenetic changes in cell-free DNA or by refined imaging techniques that allow us to detect tumors of less than 3 mm diameter or even smaller.

Cancer appears in all multicellular organisms, including plants, fungi, and animals. Here, cancer is most certainly "the price to pay for multicellularity." We are all well aware that our individual life started from just one cell, a zygote, and that an adult human is composed of ten trillion cells in average. Each of these cells has the same genetic information, written down in our 46 chromosomes and this individual genetic information has to be reproduced at every mitosis and delivered to each daughter cell. One of the fundamental differences between unicellular and multicellular organisms is the organization of the genomes in chromosomes, which are no longer in circular DNA without a centromere. Moreover, the specialization of cells for different "duties" necessitates communication between them and their surroundings, the extracellular matrix (ECM), via specialized molecules, later called hormones, specialized structures evolving to ECM proteins with a scaffold function, or membrane-bound receptors for messenger molecules. This is an extremely shortened and simplified overview of tissue and organ formation. The

organization of differentiation of cells in multicellular organisms requires a complex interplay between the cells allowing development and growth, regeneration, and wound healing, and also senescence and the death of the organism after a variable lifespan. All these phases of life are regulated by specialized genes and the regulation of gene expression is also grounded in the genome, allowing differentiated and timely regulated gene expression for different tissues within an organism. All the fundamental pathways regulating key functions have been found highly conserved during evolution. The higher complexity of the genetic regulatory framework bears the potential for misuse, such as the evasion of cells from growth control and thus multiplication from cells that have acquired a different genetic constitution. When these genetically different cells survive and multiply within the original organism, using the resources of the host and evolve with further changes and spread in other tissues and exhaust the host organism, this is called cancer.

History of cancer

The eventful history of cancer and the development of modern cancer medicine have been summarized in *The Emperor of Diseases*, a recommendable book by Siddhartha Mukherjee.[2]

In the following, the present understanding of cancer will be described very briefly, with subjectively chosen highlights from the long evolution of the global search.

The name “cancer” dates back to ancient Greek times and was probably given due to the resemblance of multiple, enlarged, and distorted veins visible on the cut surface of a tumor or even at the surface of the body in the case of locally advanced breast cancer, which mimic the multiple limbs of a crab. Antique physicians already understood the difference between cancer and other diseases and its evolution from a localized disease to the invasion of other organs. The oldest preserved text describing cancer is found in the Egyptian Edwin Smith Papyrus, which is a copy of an older papyrus dating back to the twenty-seventh century BC. It relates the professional experience of Imhotep, who lived at the court of Pharaoh Djoser, and is structured in 48 case reports.[3] Case report 45 details physical findings of hard masses in a breast, which most probably was a case of advanced breast cancer. Contrasting with the other cases, Imhotep gives no treatment recommendation but states, “there is no therapy.” Asclepius, Galen, and other antique physicians have left pertinent descriptions of clinical pictures, as did later physicians as soon as post-mortem examinations became possible; however, no effective therapy

could be offered before the discovery of anesthesia and of aseptic surgical procedures. Nevertheless, some physicians contributed pertinent observations to the development of cancers, such as John Hill, who observed cancer in the noses of people who partook of tobacco snuff, and Percival Pott, who described scrotal skin carcinomas in chimney sweeps. Physicians of the sixteenth century understood breast cancer as coagulated milk clots, as poisoning of the organism, and even as a sort of infection. The microscopical examination of cancer tissues led to the definition of the common microscopical differences between normal cells and tumor cells: their often bigger cell nucleus, the variability of size from one tumor cell to the other, the higher mitotic rate of atypical cells as compared with normal cells, the formation of giant cells, the more frequent occurrence of apoptotic debris, the loss of typical features characterizing the differentiation of the specific tissue, the loss of orientation of the cells within the tissue, ignoring existing cell architecture, and finally the step to cell motility with the disruption of the basement membrane, the penetration into blood vessels, and, after exiting from the blood stream, ultimately the entry into other organs. All these features were observed in all tissues, indicating that cancero-genesis occurred similarly as a multi-step process in all different kinds of tissues. In fact, at least in humans, all cell types have a known malignant counterpart.

Among the 20,000 genes of the human genome, only around 100, later named “oncogenes” and “tumor suppressor genes,” have been found to be involved in the formation and evolution of malignant tumors. Those are mainly genes involved in regulating the cell cycle, responding to growth factors, and evading death signals.

Oncogenes are often present in normal cells in an inactive form as proto-oncogenes. In case of activation either by mutation or by evading negative regulation they gain their function and promote cell division. The second category of genes involved in tumorigenesis is the tumor suppressor genes, whose silencing prorogues the escape from cell-cycle control. The transformation from a normal cell to a cancer cell usually involves multiple steps.

Malignant transformation may happen at any level of differentiation for every known normal cell. Well-known examples are the different forms of leukemias and lymphomas with at least one malignant entity corresponding to each defined maturation step of hemopoietic cells. The rate of tumor formation may change, but there seems to be no exception. Even remnants of embryonic organs that are no longer maturated and built in humans bear the potential for the formation of

malignant tumors, such as yolk-sac tumors or tumors of the urachus or of the gill slits.

Among the first basic science researchers, Theodor Boveri, a German biologist working on sea urchins, stated that organisms need intact chromosomes for correct embryonic development. He postulated as early as 1902 that all causes able to disrupt the integrity of chromosomes, such as radiation, chemicals, or other physical threats, are able to cause cancer. The American geneticist Alfred G. Knudson observed in 1971 that children with familial retinoblastoma developed their tumors earlier in life than children without such a family history, who mostly developed retinoblastoma in one eye and at an older age. His theory of the "two-hit hypothesis" of the development of retinoblastoma stated that the familial predisposition was caused by an inherited genetic aberration and that the formation of a retinoblastoma in such individuals occurred earlier in life because fewer additional mutations were needed than in sporadic cases. This hypothesis led to the discovery of cancer genes. To start malignant growth, at least two different genetic changes have to be introduced in a cell of an experimental animal. For human cells, even more hits appear to be necessary. Vogelstein et al. described the multi-step evolution from the normal epithelium of the colon to mucosal hyperplasia, to the formation of mucosal polyps, and finally to their further transformation to polyps with atypical mucosa growing into an invasive colonic cancer.[4] Understanding this process and identifying colonic polyps as precursors of the lesions of cancer provided the rationale for preventive colonoscopy with polypectomy to prevent the formation of invasive cancer of the colon. Cancer of the colon is still a major cause of death, even in developed countries; nevertheless, it should be fully preventable through lifestyle changes and adherence to preventive colonoscopy. Similar stepwise evolution of malignancy was observed for other tumors as well.

Until the mid-twentieth century, cancer therapy relied mainly on two therapeutic modalities: surgery and radiation therapy. Systemic treatment mainly concentrated on supportive care, as no direct medications for cancer cell therapy were yet available. The first clinical studies with anti-cancer drugs were made shortly after World War II. Meanwhile, much progress has been made in the development of other cytotoxic drugs, and because of the increased understanding of the molecular changes caused by cancer, the development of small molecules inhibiting cancer signaling, and the development of cancer-directed immunotherapy. However, although the number of cancer survivors is increasing, so are the number of patients developing several primary cancers. There is still room for improvement in cancer diagnosis.

Understanding the mechanisms of cancer growth

In 2000, Hanahan and Weinberg compiled the accumulated knowledge in cancer research and formulated their hypothesis of the six hallmarks of cancer: the acquired genetic traits that are necessary and sufficient to transform normal cells into tumor cells.[5]

First hallmark: sustained growth of cells

To maintain tissue homeostasis, the rhythm of cell divisions of normal cells is tightly regulated; nevertheless, the control mechanisms of normal tissue homeostasis are not fully understood. Normal tissues and organs seem to sense how much cell division is needed to obtain or maintain the dimension of the specific organ. No cell undergoes cell division without getting a growth signal. These signals are usually growth factors produced by other cells and sensed by a transmembrane growth-factor receptor—mostly a tyrosine kinase. The signal is transmitted into the cell and further downstream into the cytoplasm involving a signaling cascade of other enzymes, finally reaching the cell nucleus. In the case of growth signaling, actions to prepare cell growth and mitosis are undertaken. However, to grow in a Petri dish, normal cells need to be stimulated by their growth factor. Further supply is needed from their tissue-specific integrins for them to become attached to their used-matrix proteins; and even with all requirements fulfilled, they will not grow further once a monolayer of cells is reached. Only tumor cells are able to grow in serum-free media, producing their own growth factors and producing several cell layers.

To obtain the sustained growth of tumor cells, the normal pathway of growth stimulation has been modified at each step. Tumor cells have been found to be able to produce their own growth factors in an autocrine loop, whereas in normal tissue no autocrine stimulation takes place; there, the growth factors are produced by another type of cell.[6]

Moreover, tumor cells present much higher growth factor receptors on their cell surface than normal cells do, rending them more able to react to growth-factor stimulation. Mutations in the growth factor receptors make them fire constantly, even without external stimulation, such as the truncated epithelial growth factor variant III (EGFRvIII) in glioblastomas. Moreover, during malignant transformation, mutations alter the transfer of signals into the nucleus, favoring entrance into the cell cycle.

Tumor cells are able to influence their neighboring cells in the tissue, for example, fibroblasts, endothelial cells, and bone-marrow-derived blood cells to promote their incessant growth.

Second hallmark: disruption of negative feedback mechanisms that attenuate proliferative signaling

As tissue homeostasis is so tightly monitored in normal cells, there are a number of negative feedback loops to provide growth inhibitory signals. When normal cells enter the cell cycle, their progress through this cycle is very carefully controlled by a multitude of tumor-suppressor genes whose loss or inactivation promotes escape from negative feedback mechanisms such as the retinoblastoma gene, transforming growth factor beta, PTEN phosphatase, and mTOR signaling. Compromised negative feedback loops are widespread in cancers. Moreover, some of these mechanisms "convince" cells to enter irreversibly into postmitotic differentiated states[7] as a module of negative feedback. Tumor cells avoid this terminal differentiation—and thus also the building of functional tissue.

Third hallmark: resisting cell death

Apoptosis or programmed cell death was first described in 1842 by the German zoologist Karl Vogt. In multicellular organisms, apoptosis is the most important way of destroying old or ineffectual cells and saving their constituent parts. Each day in an average adult person more than 50 billion cells undergo apoptosis. The pathway is highly regulated and takes 30 to 120 minutes.[8] Intracellular and extracellular sensors report either damage to a cell's DNA or the receiving of pro-apoptotic signals from the cell's environment by the Fas receptor and Fas ligand system. Once a point of no return is reached, the process goes on and cannot be stopped. The different phases of apoptosis run down one after the other, leading to small apoptotic bodies that are engulfed by macrophages or other immune cells.

Cancer cells however have developed many mechanisms of evading apoptosis, ensuring their survival even with substantial genetic changes. The most common change is the loss of the TP53 function, which is the most prominent DNA-damage sensor and activates pro-apoptotic circuitry. Another important mechanism is increasing the levels of anti-apoptotic signals like Bcl-2 or survival signals like insulin growth factor 1. There are multiple ways by which cancer cells have managed to survive apoptotic signals, showing how important these traits are for tumorigenesis.[9]

Autophagy is a way to survive under challenging conditions. In such highly stressful conditions, cells manage to break down even their own organelles like ribosomes and mitochondria in order to use their constituents for energy expenditure. The cells generate intracellular vesicles, fusing with the organelles and then with lysosomes that degrade the organelles. Furthermore, autophagy pathways are highly regulated and there are links between autophagy and apoptosis. However, cells that undergo autophagy may fall into states of cell dormancy and thus this mechanism may allow them to survive radiation therapy or exposure to cytotoxic drugs and to re-enter the cell cycle when environmental conditions have improved. Thus, autophagy is not only a form of cell death, but also a potential survival strategy for tumor cells.

Such a Janus-faced outcome is even more related to the third form of cell death, cell necrosis, where the involved cell swells until it bursts. The cell constituents are scattered around in the micro-environment provoking the recruitment of inflammatory immune cells. This might lead to the presentation of tumor antigens to the immune system and enhance the activity of the immune system against the tumor; however, more often the pro-inflammatory environment directly stimulates tumor cell growth and tumor angiogenesis.

Fourth hallmark: enabling replicative immortality

In normal tissues the replicative capacity of cells is tightly regulated and after a variable amount of cell divisions—related to the specific differentiation status—cells stop dividing and survive in senescence or enter a crisis phase resulting in cell death. Normal cells might be maintained in culture even under optimal conditions only until they reach the end of their replicative potential and enter senescence or crisis. This is monitored by the shortening of the telomeres at the end of the chromosomes at each cell division. Telomeres are hexanucleotid repeats situated at the end of chromosomes protecting the end of the coding sequences of the chromosome. At each DNA duplication, telomeres are truncated—shown by the fact that the telomeres of humans at birth are about 11 KB long and only 4 KB long at old age. However, in most cancer cells the enzyme telomerase is reactivated, which elongates the telomeres and thus provides unlimited replicative capacity. The reactivation of telomerase—which is silenced in nearly all cells after the end of the embryonic phase with only a few exceptions, such as cells with high replicative potential, for example, male sperm, epithelial cells, or immune effector cells, or the much rarer

activation of an alternate pathway to maintain telomere length—enables tumor cells to escape the barriers of unlimited replication.[10]

Fifth hallmark: inducing angiogenesis

During embryogenesis, normal vessels form through the multiplication of endothelial cells and elongation within tubes and sprouting from existing vessels. In adults, angiogenesis is limited mainly to wound healing and to sustaining the menstrual cycle in females. Yet a growing tumor requires a growing supply with oxygen and nutrients and evacuation of carbon dioxide and metabolic wastes for sustaining its formerly non-existing tissue. Thus, an "angiogenic switch" activating the formation of tumor vessels is needed as a tumor reaches 2–3 mm in diameter for further growth, induced by hypoxia and by oncogenic signaling. Typically, blood vessels produced by excessive tumor angiogenesis are different from normal vasculature, showing multiple, tortuous branches, variable diameters, premature capillary sprouting, erratic blood flow and leakiness, and lacking the lean and order-oriented design of normal vasculature.[11]

Neo-angiogenesis involves a multitude of cells, not only the tumor cells themselves, but of course endothelial cells, pericytes, fibroblasts, and a lot of bone-marrow-derived cells, such as neutrophils, macrophages, mast cells, and other myeloid-derived cells infiltrating the tumor mass, whose participation in the process of tumorigenesis, immune surveillance, and immune tolerance is as yet incompletely but increasingly understood.

Sixth hallmark: invasion and metastasis

The ability to overcome normal growth barriers, such as the basal lamina in endothelial cells, to invade other tissues, or even to survive cell detachment, enter into the vasculature, exit from it, and survive within a different microenvironment from the inherent one was the most obvious characteristic of cancer cells, demonstrating how much their genetic traits have evolved from their original setting. One of the characteristics enabling the tumor cells to exhibit these features are called "epithelial-mesenchymal transition" (EMT), a process reminiscent of embryonic potentials or processes activated by wound healing that also enables invasion and metastasis. As in other hallmarks too, this multi-step process is enabled by the reactivation of functions active during embryogenesis, such as the increased mobility of cells.[12] Moreover, the role of the neoplastic stroma in stimulating invasive behavior is increasingly

understood. Macrophages at the invasive borders of tumor nodules can facilitate invasion by breaking down matrix proteins. It could be shown that macrophages stimulate breast cancer cells by producing EGF and the breast cancer cells vice versa stimulate the macrophages by colony stimulating factor 1 (CSF-1).

The changes that invasive cancer cells undergo during the metastatic process might be at least partly reversible, as the microenvironment in the new organ no longer provides stimulatory conditions as before. Thus, they may undergo a "mesenchymal to epithelial transition" in return, regaining an aspect of epithelial cells, as in the primary tumor before EMT. To become macroscopic metastatic lesions, the invading cells must resolve the problem of thriving in this new environment and the angiogenic switch. The primary tumor may send out signals maintaining the micro metastases in a state of dormancy that reverts when the primary tumor is resected. Or metastases might grow rapidly, decades after the elimination of the primary tumor, as they have solved their local growth problems.

Recently, an updated version of the "Hallmarks of Cancer" was released, taking into account the new insights made in the decade between the first and the second hallmark review. The following new hallmark was added: enabling characteristic: genome instability.

The analysis of tumor genomes, as compared with the original genome, highlights evidence of a loss of control of genome integrity in cancer genomes and of recurrent genetic amplifications and losses that might be associated with tumor growth. Genetic instability seems to favor tumor growth.

Enabling condition: tumor promoting inflammation

Another emerging enabling characteristic of tumor growth might be tumors that promote inflammation. The presence of immune cells within nearly every tumor has long been known and mostly interpreted as an attempt by the immune system to reject the tumor. But increasing evidence has accumulated that tumor inflammation is enhancing tumorigenesis and progression.

Seventh hallmark: reprogramming cell metabolism

Cancer cells definitely pursue other goals beyond differentiated tissue cells; and given their focus on cell growth and division, they are in constant need of building new cell components. It has long been known

that cancer cells depend on aerobic glycolysis as observed by Otto Warburg as early as 1930. The importance of glucose to tumors is used for diagnostic purposes, with radiolabeled F18 glucose as the reporter in the FDG-PET. Despite the low efficiency of glycolysis to produce ATP, its advantage for tumor cells lies in the potential of the synthesis of nucleosides and amino acids that are needed to assemble the constituents of new cells.[13] As the altered metabolism of tumor cells is better understood, potential therapeutic targets emerge that could be exploited therapeutically, thus opening new forms of cancer therapy.

Eighth hallmark: evading immune destruction

The role of the immune system in recognizing and eliminating malignant tumors was challenged as the tumor-promoting effects were increasingly understood. However, the immune system has undeniable tumor-protecting effects, as demonstrated by epidemiologic data showing a higher tumor frequency in persons with compromised immune systems such as transplant recipients—for example, transplant-related lymphoma, where often a remission can be obtained as soon as the "immuno-rejection prophylaxis" is reduced, as well as in animal models, which show that transplanted tumors grow much more efficiently in immunodeficient mice than in immunocompetent animals.[14] Further proof of the activity of the immune system against malignant tumors is demonstrated by the better outcomes of patients with colon cancer or ovarian cancer with a high density of infiltrating killer lymphocytes in the tumor. On the other side, tumors were shown to secrete high levels of TGF-ß and other immune-suppressive factors or to recruit regulatory T-cells or myeloid-derived suppressor cells to evade the immune response.[15] This is an actively moving research field where hopefully the next few years will bring new insights and effective therapeutic applications.

Cancer stem cells

In recent decades, it became more and more evident that not all tumor cells are able to generate a complex neoplasm and that few cancer stem cells are able to initiate and maintain the evolution of a malignant tumor. The origin of these cancer stem cells has not yet been clarified for all tumors and may vary between tumor types. Normal tissue stem cells may undergo malignant transformation to tumor stem cells, or this role may be assumed by fairer differentiated progenitor cells undergoing malignant transformation and becoming tumor stem cells. However, cancer stem

cells show common properties as unlimited self-renewal potential and resistance to radiation and to most chemotherapeutic agents. Recently, it was demonstrated that cancer stem cells have undergone an EMT transformation and are thus mobile and able to recruit a proinflammatory microenvironment to sustain their survival and to build up tumor-stroma-facilitating replication and infiltrative behavior.[16]

Tumor stroma

Most, if not all, the previously presented hallmarks involve the tumor stroma in one way or the other, showing the profound transformations and interactions of tumor cells with adjacent "stromal" cells as fibroblasts, endothelial cells, or myeloid-derived cells such as macrophages, bone-marrow-derived pericytes, or immune cells with either tumor-promoting or tumor-suppressing properties. This emerging concept shows that the formation of a malignant tumor requires more than "the tumor cell" itself, but always involves the whole organism and can no longer be understood as a locally arising problem. The potential early dissemination of EMT-transformed cancer stem cells explains clinical findings as metastases become evident years or decades after the eradication of a malignant tumor. There is still much research needed to unravel all the mechanisms exploited by malignant tumors in order to find more effective cures.

A major advance in recent years was gaining insights into the role of commensal micro-organisms in the development of the immune system and into the development of diverse pathologies and among cancers as well as in the modulation of treatment responses by the microbiota.

Microbiota

Only in the last few decades have our commensal prokaryotes come to attention; they are increasingly being investigated and their essential contributions to health and disease are being unraveled. In fact, like all multicellular organisms, we live in close contact with many micro-organisms that constitute our commensal flora, as archae, fungi, bacteria, and viruses. They colonize all barrier surfaces, for example, the skin, the oral cavity, the airways and the lungs, the gut, and in women the vagina. The gut microbiome alone outnumbers our body cells by a factor of 10:1. The microbiome interacts with its host in many essential functions, like the development of the innate and adaptive immune system.[17] During evolution, the microbiota and the host evolved together to build a symbiotic relationship, avoiding immune reactions against the symbiotic

flora as well as infections with pathogenic organisms. It is also essential for the development of a functional systemic immune system.[18]

The essential prognostic role of the microbiota in modulating immune cell infiltration of tumors and more generally, an inflammatory stroma was first recognized in colorectal cancer,[19] reflecting as well potential cancer prevention and promoting the effects of the microbiota. Dysregulation of the microbiota or damage to the barrier function, like after antibiotic therapy, can cause chronic inflammation, which is one of the main causes for the development of cancer,[20–21] as it is also on distant sites, such as in breast cancer. By regulating the function of myeloid-derived cells in the tumor stroma, the gut microbiota may also influence the response to cancer treatment. In murine experiments, the efficacy of chemotherapy with platinum compounds was dramatically reduced in antibiotic pretreated mice.[22] Moreover, the side-effects of chemotherapy and radiotherapy to the composition of microbiota and the disturbance of the intestinal barrier function modulate the systemic inflammation and the activities of the immune system. Such interactions and their potential modulation have not yet been fully elucidated. More research is needed to understand and to optimize the influence of microbiota, tumor development, tumor prevention, and therapy.

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CHAPTER 1.2

EPIDEMIOLOGY OF NERVOUS SYSTEM INVOLVEMENT IN PATIENTS WITH CANCER

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Abstract

The involvement of the nervous system occurs in up to a quarter of patients with cancer, either as metastatic disease or as an adverse event of cancer treatment. Metastatic disease may manifest as a circumscribed lesion in the brain or spinal cord, or be a more widely disseminated spread of tumor cells to leptomeningeal spaces, peripheral nerves, roots, or plexuses. While solid metastases may occur as the first sign in a patient with previously unrecognized cancer or years after the primary diagnosis, leptomeningeal or neural metastasis is typically a late complication of cancer with poor prognosis and limited treatment options. While lung, breast, and colorectal cancer account for the majority of solid metastases, hematologic malignancies, lung cancer, breast cancer, and melanoma are frequently involved in leptomeningeal and neural metastasis. The incidence increases with advancing age, with variation according to the primary cancer. Of note, CNS metastases account for a large fraction of tumors in the nervous system, readily outnumbering primary brain tumors by a factor of 10. Thus, with ageing societies and the prolonged survival of cancer patients (due to improved diagnostic assessments, therapy, and long-term patient management), their incidence is expected to further increase and pose a rising challenge to health care systems. In contrast to primary brain tumors, however, epidemiological data of patients with CNS metastases are not systematically monitored through cancer registries, which grossly limits our knowledge of their societal impact and the resources needed, as well as hampering the development of strategies for primary or secondary disease prevention.

Keywords: Epidemiology, brain metastases, incidence, outcome, population ageing

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Introduction

In 2018, 18.1 million individuals were diagnosed with cancer, and this number will further increase to 29.5 million by 2040 (see https://gco.iarc.fr/tomorrow/home). In up to 35% of these patients, the nervous system is involved either through metastatic disease or due to neurotoxicity caused by cancer treatment.[1]

Metastatic disease may manifest not only as solid CNS metastasis but also as the disseminated spread of tumor cells to the leptomeningeal spaces—a process that is known as neoplastic meningitis or leptomeningeal metastasis (LM). Likewise, in the peripheral nervous system, cranial and peripheral nerves, nerve roots, and plexuses may be infiltrated by solid or hematological malignancies. Common cancer-treatment-related complications include chemotherapy induced peripheral neuropathy as well as radiation-induced leukoencephalopathy and secondary tumors, which add to considerable patient morbidity and mortality.

The purpose of this chapter is to summarize the current evidence on the incidence and outcome of the various manifestations of metastatic cancer and cancer-treatment-related involvement of the nervous system.

Metastatic disease involvement of the central nervous system

Solid metastases

The first estimates of the *incidence* of brain metastases were typically based on single center *post-mortem series*. While those varied considerably in sample size (ranging from as few as 50 to 2,300 cases), they estimated that brain metastases occur in approximately 25% of patients who had died from cancer, with significant variation according to

primary cancer type.[2–4] The highest frequencies with incidence proportions of above 50% were reported in patients with melanoma and lung cancer.[4–6] The majority of the post-mortem studies, however, were conducted in the 1980s and 90s, and thus reflected the experiences of selected tertiary care centers back then, which makes it difficult to draw conclusions for more contemporary patient populations. Thus, those early estimates do not necessarily need to be representative of unselected, more contemporary populations of patients with CNS metastases.

In contrast, evidence from *population-based studies*—which are generally considered less biased—has been scarce so far, as metastatic disease in general and CNS involvement in particular is not mandatorily reported to cancer registries. This includes brain tumor-specific cancer registries such as the Central Brain Tumor Registry of the United States or the Austrian Brain Tumor Registry.[7] As a result, accurate population-based incidence or prevalence estimates are not routinely available either in the US or in Europe. The few population-based efforts generated so far have been based on different data sources, such as death certificates, hospital admissions, or census data. Together they have reported variable incidence rates ranging from 2.8 per 100,000 in Iceland (diagnostic interval 1954–63) to 8.3 per 100,000 people per year in the US (diagnostic interval 1973–74) and 14.3 per 100,000 people per year in Scotland (diagnostic interval 1989–90). A similar incidence rate of 14.0 per 100,000 people per year was found in a more recent study (diagnostic interval 2006) in Sweden. Other studies have attempted to estimate the prevalence of CNS metastases from the prevalence of primary cancers that show a tendency to metastasize to the brain. Those studies reported prevalence estimates between 5.6%[8] and 9.6%.[9] Overall, the incidence of CNS metastases is believed to outnumber primary brain tumors by a factor of 5 to 10, and their frequency seems to increase with increasing age across most cancer types.

In contrast to adult patients, CNS metastases are exceedingly rare in children below the age of 14 years with an estimated incidence of 1.5 per 100,000 people per year. This is a significantly lower incidence compared with primary brain tumors in the same age category, which is 5.5 per 100,000 people per year. Pediatric CNS metastases differ also in terms of histological types from their adult counterparts—with germ cell tumors, sarcomas, and melanomas being the most commonly encountered types in children. On the basis of the experience of large cancer centers such as the MD Anderson Cancer Center or the St. Jude's Children's Research Hospital, the prevalence of CNS metastases in children with cancer ranges from 1.4% to 13.0%.

Anatomic location, neurologic symptoms, number and type of lesions

Cerebral metastases most frequently occur at a supratentorial location (80%) followed by the cerebellum (15%) and the brain stem (5%) (Figure 1.2.1A). As brain metastases primarily result from a hematogenous spread, their distribution in the brain grossly corresponds to the relative regional blood flow, which means they frequently occur at gray-white matter junctions within the territory of the middle cerebral artery or at watershed areas between the territories of the middle and posterior cerebral arteries (Figure 1.2.1B).

Most brain metastases are diagnosed when they become symptomatic, with a fraction of 10% being clinically silent at the time of staging. Clinically, they may present with various neurologic symptoms according to the brain region that is primarily involved. While lesions in eloquent areas of the brain are readily identified at smaller sizes, frontal-lobe lesions that are associated with more subtle behavioral changes may already be extensive in size at the time of diagnosis. Cerebellar metastases are mostly associated with signs of increased intracranial pressure such as vomiting, headache, and nausea. Seizures may be the leading symptom in 10 to 20% of patients with CNS metastases[10] with another 20% developing seizures later on during the course of the disease.[11]

Recent studies that were based on magnetic resonance (MR) imaging estimated that 72.2% of all brain metastases occur as solitary lesions[12] with breast, gastrointestinal, and renal cancer being the most commonly encountered subtypes, as opposed to oligo- and/or multi-metastatic disease, which is particularly frequent in melanoma and lung cancer. Precisely, 37% of patients have three or more brain lesions at the time of presentation.[13] The incidence of CNS metastases varies significantly according to the type of primary cancer, with lung cancer, breast cancer, melanoma, and renal cell cancer being the most commonly encountered types in adult patients. In approximately 15% of the patients, the primary cancer is unknown. For an in-depth discussion of the individual cancer types see below; the top three metastatic cancers are summarized per nervous system compartment in Table 1.2.1.

Dural metastases are much less common than parenchymal lesions and occur in only 9% of patients with cancer.[14–15] As such they constitute rare and typically late complications of systemic cancer. As dural lesions mostly result from direct extensions of skull-based metastases, they are particularly frequent in breast and prostate cancer—two primaries with a strong tendency to metastasize to the bone. A recent

study that reported one of the largest collections, so far, including 198 cases diagnosed from 1994 to 2003, found highly variable patient age ranging from 4 months to 84 years. In addition to top-ranking prostate and breast cancer, lung and stomach cancer were also among the commonly encountered types.[14] Frequent neurologic symptoms in patients with dural metastases include either compression of cranial nerves or non-traumatic subdural hematomas. In contrast, up to 20% of patients are asymptomatic.

Metastases to the spine are especially frequent and occur in approximately 40% of cancer patients[16] with breast, prostate, and lung cancer being the most common primary cancers. Of note, in up to 10% of patients with spinal metastases, the primary cancer is unknown. Spinal metastases that cause neurologic symptoms typically extend to the epidural space (95%), often from adjacent vertebra, whereas intradural (4%) or intramedullary (1%) locations are comparably rare.[17–18] Larger series of intramedullary metastases indicate a modest male predominance at a median age of 55 years. Most common primary cancers include non-small-cell lung cancer and neuroendocrine carcinoma that together account for approximately half of all cases. Among less common but regularly encountered primary cancer types are breast cancer, melanoma, renal cell carcinoma, and non-Hodgkin lymphoma.[19]

Calvarial metastases occur in 15 to 25% of patients with cancer and often in the setting of widespread bone involvement. The frontal and parietal bones are the most commonly involved sites.[20] In accordance with spinal metastases, common primary cancers that frequently spread to the calvarium include breast, lung, and prostate cancers, with prostate cancer having an intriguing propensity for the skull base. As skull base metastases frequently involve or compress one or multiple cranial nerves they are associated with a high burden of neurologic symptoms and reduced quality of life. Compared with primary osseous tumors, skull metastases occur at older ages and are associated with a shorter duration of symptoms prior to diagnosis.

Survival in patients with CNS metastases

The median overall survival of patients with CNS metastases ranges from six months to one year, which indicates a highly unfavorable prognosis for the majority of patients with brain and dural metastases.[21] Nevertheless, there has been an increase in survival of 7 to 9 months over the last decade that has been attributed to the addition of chemotherapy as compared with radiotherapy or surgery alone.[22–24] Interestingly, most patients die due to systemic disease progression rather than due to the brain metastases.

Despite an overall poor prognosis, survival differs according to primary cancer with more favorable outcomes for hematologic cancers, breast cancer, and prostate cancer, with median overall survival of 12, 9, and 4 months, respectively.[14] It is important to note that patients with brain metastases have long been systematically excluded from clinical trials due to their expectedly poor outcome, high risk for unexpected side effects, and neurologic deficits requiring medications such as steroids or anti-epileptics that may potentially interact with the drug of choice. Thus, the body of evidence concerning treatment responses to novel agents including targeted therapies has primarily come from retrospective observations and case reports. In contrast, there are only a few phase II studies investigating systemic or targeted therapies specifically in patients with brain metastases.[25–27]

Incidence and survival according to primary cancer

Lung cancer is the leading cause of cancer death in the United States and the most common tumor to metastasize to the brain. Approximately 20% of individuals with lung cancer suffer from brain metastases according to autopsy and population series.[9] Of note, approximately 8% of those patients additionally experience leptomeningeal metastasis.[28–29] Further, in patients with confirmed brain metastases but unknown primary cancer, approximately two thirds are attributable to lung cancer (see also below, unknown primary cancer). Overall, there is evidence that female patients are slightly more predisposed to develop brain metastases (21.8%) compared with male patients (18.9%). Lung cancer comprises several different histological subtypes that are categorized into non-small cell and small cell variants. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer, and its histological subtypes such as adenocarcinoma or squamous carcinoma account for the majority of CNS metastases. In total, approximately 9% of NSCLC patients develop a brain metastasis[30–31] and even though NSCLC-derived brain metastases are more frequent in male patients in absolute numbers due to a higher incidence of lung cancer in males in general, the relative frequency of brain metastases is higher in females (10% among female NSCLC as compared with 8% in male NSCLC).[31] In general, the risk for developing a brain metastasis is associated with unfavorable prognostic stages, younger age, larger tumor size, involvement of hilar lymph nodes, and/or microscopic invasion of lymphatic vessels. Recent evidence further suggests an increased risk for brain metastases in patients whose tumors harbor EGFR-activating mutations that are more prevalent in adenocarcinoma (range 8 to 60%) as

compared with squamous cell carcinoma (range 2 to 4%). However, the excess risk may be reverted into a positive predictive factor when treated with tyrosine kinase inhibitors such as erlotinib and gefitinib. Both agents have been associated with enhanced intracranial treatment response, and consequently improved progression-free and overall survival,[32] a beneficial effect that seems partly mediated by a synergistic effect with radiotherapy. Overall, small cell lung cancer is much less frequent compared with NSCLC: that is, it affects approximately 15% of all lung cancer patients. However, post-mortem series and clinical trials suggest a higher intrinsic propensity of those tumors to spread to the CNS with reported fractions of 45 to 60%.[4,33–34] This contrasts with population-based series that suggest lower metastatic rates of up to 18%.[31] Again, a slightly higher incidence has been observed in females (19%) as compared with males (17%).[31]

Melanoma is the third most common primary cancer that spreads to the brain.[9] It has a high affinity for the brain, with up to 10% of patients developing a brain metastasis, and the rate is even higher in patients with advanced stage disease.[35–36] The proportion of brain metastases derived from melanoma is considerably higher in male patients (8.7%) compared with female patients (4.8%) and in melanomas at the head and neck region (8%) compared with the extremity or trunk (5.3%). Overall, melanoma accounts for approximately 10% of all metastatic CNS lesions[37] and has a higher likelihood for multiple simultaneous brain lesions as well as hemorrhage.[38] Most CNS metastases occur after the primary diagnosis of melanoma with an estimated time to diagnosis between 22 and 37 months. Metastatic disease heavily affects the 10-year survival, which drops from 95% in patients with early stage melanoma to only 8 to 20% in patients with any metastasis. One-year survival in patients with brain metastasis ranges from 15 to 40%. Independent predictors of survival include surgical resection, solitary lesions, no additional systemic metastases, young age, good clinical performance, and a prolonged disease-free interval.[39–40] The prognosis has increased with the advent of BRAF and checkpoint inhibitors.[25,41]

Breast cancer ranks second for the total number of brain metastases. Unlike other primary cancers such as lung cancer or melanoma, patients typically develop brain metastases later during the course of the disease. One study reported a median time from first diagnosis of the breast cancer to occurrence of brain metastases of 46 months with younger patients (aged less than 35 years) and those with tumors of high histologic grade, increased tumor size (>2 cm), and positive lymph node metastases being at higher risk.[42–43] This delay to the

occurrence of brain metastases might be attributable to established screening programs with higher rates of early detection in breast cancer due to self-screening and mammograms. Median overall survival is compromised by the occurrence of a brain metastasis, dropping to 16 months after the diagnosis of a brain metastasis with variation according to HER2 status. Precisely, female patients with HER2-positive tumors have a significantly longer median overall survival, that is, 17.1 months, than HER2-negative tumors, that is, 5.2 months.[44] Other positive prognostic factors include triple-positive breast cancer, surgical resection, receipt of whole brain radiotherapy, and good clinical performance.[45] Whether treatment with trastuzumab (Herceptin) is an independent risk factor for the development of brain metastases has been debated and the results from several studies have shown conflicting results. In addition to solitary CNS lesions, involvement of the leptomeninges is also a frequent finding in patients with breast cancer. Leptomeningeal metastasis has been associated with particularly unfavorable outcome with reported median overall survival times of only 3.5 to 4.5 months.

Colorectal cancer is the most common gastrointestinal cancer to metastasize to the brain[46] and even though the incidence of brain metastasis is rare overall, the prognosis is often worse as compared with breast, lung, or renal cancers. Previous studies indicate that 1 to 4% of patients with colorectal cancer develop brain metastases.[46–47] They are equally common in female and male patients and typically occur years after the primary cancer (with a median time delay of 26 to 42 months).[13,48] Median survival after the diagnosis of a brain metastasis is especially poor with only 2 to 6 months. Survival is longest for patients undergoing surgery (11.5 months) as compared with stereotactic radiosurgery (9.5 months), whole brain radiotherapy (4 months), or best supportive care (1.5 months).[49] Esophageal cancer is similar to colorectal cancer in several aspects. First, brain metastases occur in a similar fraction of patients (up to 3.6%), and mostly several months to one year after the primary diagnosis.[48] Second, median post-metastatic survival is poor and ranges from 3 to 12 months. Finally, among the different histological subtypes, esophageal adenocarcinoma is the most common to spread to the brain.[50] Other gastrointestinal cancers that rarely metastasize to the brain include gastric, gallbladder, and pancreatic cancers (all with reported incidence proportions of below 1%). The median time from diagnosis of the primary cancer to brain metastasis is approximately 10 months, and median post-metastatic survival is especially poor with reported durations of only 4 months.

Genitourinary cancers include renal cell carcinoma, and prostate, testicular, and bladder cancers. Among those, renal cell carcinoma has the highest incidence of brain metastases with approximately 7% of patients affected.[51] Brain metastases are more likely in patients with thoracic and bone metastases (16%) as compared with metastases in the abdomen (2%). The median time from primary diagnosis to brain metastasis has been estimated to be 10.6 months.[52] Together with brain metastases from melanoma, renal cell carcinoma shares an increased risk of hemorrhage with subsequent secondary seizures. Survival is significantly more favorable in symptomatic patients as compared with those without any neurologic symptoms at presentation (where there is a median overall survival of 69.4 months versus 17.4 months).[53] Asymptomatic brain metastases are on average smaller in size but tend to occur as multiple lesions, which grossly limits surgical approaches. Due to a high endogenous resistance of renal cell carcinoma to radiotherapy, median survival has remained poor with 6 to 9.5 months in patients following treatment.[54] Still, stereotactic radiosurgery has shown promising results with local tumor control rates of above 80% for 5 to 9 months, especially in smaller metastatic lesions (less than 1 cm in size).[55–57] Brain metastases are exceedingly rare in other genitourinary cancers such as prostate, bladder, or testicular cancer with an estimated incidence of less than 1% of the respective patient populations. With the exception of testicular cancer (which is especially frequent in adolescence), median post-metastasis survival is exceedingly poor with only one month. In contrast, in testicular cancer long-term survival is not uncommon with a better outcome among patients in whom the brain metastasis has been diagnosed prior to chemotherapy (with a five-year survival rate of 45 to 53% as compared with 12 to 40% if present after chemotherapy).[58]

Gynecological cancers that rarely metastasize to the brain include ovarian and endometrial cancers as well as certain germ-cell tumors such as choriocarcinoma. In all those cancer types, brain metastases typically occur late during the disease course and are exceedingly rare overall. However, evidence suggests that with the increasing overall survival of these cancers, the incidence of brain metastases increases.[59–62] Less than 3% of all patients with ovarian cancer will develop a brain metastasis, but it is more likely in patients with high-grade ovarian cancer and at advanced disease stages.[62] The median time from diagnosis of the primary cancer to metastasis is 46 months, and median post-metastasis survival is 7 months.[62] Younger age, good clinical performance, and single lesions were identified as positive prognostic factors.[62] The incidence of brain metastases is even lower in patients with endometrial cancer with an

estimated proportion of below 1% being affected. However, in cases that do metastasize to the brain, the time span is comparably short, with a median time to diagnosis of 8.5 months.[63–64] The prognosis is poor with reported median overall survival of only 6.5 months.[64] Even though choriocarcinoma is a very rare cancer overall, it is the most common gynecologic cancer to spread to the brain, which means up to 20% of the patient population will develop a brain metastasis. Autopsy studies report even higher prevalence rates of up to 66.7 %. Due to frequent invasion and destruction of blood vessels, choriocarcinoma-derived brain metastases are especially prone to intratumoral hemorrhage, which has been found to limit overall survival.[65]

In up to 15–20% of patients with brain metastases, there has been no previous diagnosis of cancer[66–68]—an instance that is referred to as cancer of unknown primary. In approximately 80% of those patients, a primary cancer—most commonly lung cancer—will be diagnosed within 3 months from presentation of the brain metastasis.[68] In contrast, in 20% of the patients even comprehensive diagnostic staging is unable to reveal the primary lesion. Of note, the introduction of novel screening modalities such as G-18 2'-deoxy-2fluoro-D-glycose (FDG) positron emission tomography (PET) combined with computer tomography (CT) has led to increased diagnostic rates in another 20 to 40% of those patients. Also, DNA methylation profiling proved of additional value in categorizing the lesions, as DNA methylation profiles tend to be conserved between cancers (both primary and metastatic clones) and tissues of origin.[69]

Leptomeningeal metastasis

Leptomeningeal metastasis (LM), also known as meningeal carcinomatosis, is defined as the spread of tumor cells to the cerebrospinal fluid (CSF) compartment and/or leptomeninges, that is, pia and arachnoid (Figure 1.2.2C). Mostly, this process involves seeding or spread to vessels of the arachnoid or choroid plexus, whereas in other instances access to CSF spaces may result from direct extension of a solid metastasis from adjacent bone or dura or emissary veins. Once in the CSF compartment, tumor cells can seed different CNS regions via CSF routes frequently involving the basal cisterns and cauda equine region. LM typically occurs as a late event during the disease course of solid or hematologic cancers. Its precise incidence is unknown since it is clinically under-diagnosed. It is found in at least 5 to 15% of patients with leukemia or lymphoma[70] and 4 to 15% of patients with solid tumors.[71–73] Early results from autopsy series indicate that LM may occur in 20% of cancer patients with neurologic

symptoms. Clinical presentation is varied according to the differential involvement of cerebral hemispheres, cranial nerves, spinal cord, and nerve roots. While headache and cognitive changes are frequent manifestations of hemispheric involvement, diplopia due to abducens nerve palsy is the most common cranial nerve dysfunction. Weakness and segmental sensory loss are common signs of spinal cord involvement that tends to be more pronounced in distal extremities.

In parallel to solid metastatic lesions in the CNS, the incidence of LM is likely to increase with advances in MR imaging-based diagnostic assessments and prolonged patient survival. The most common cancers ranked according to absolute numbers include breast, lung, melanoma, non-Hodgkin lymphoma, and acute lymphocytic leukemia.[71,74] Even though absolute numbers are smaller than in breast cancer, small cell lung cancer and melanoma have the highest relative rates of LM, reflecting their high intrinsic propensity for LM. In more than 70% of patients, LM is associated with advanced and uncontrolled systemic disease and harbors an especially poor prognosis. In contrast, it also affects a considerable proportion, that is, 20%, of long-term disease-free patients. Without treatment, the median overall survival of patients with LM is only 1.5 months. Even with intense treatment, overall survival is mostly less than 6 months with a median overall survival ranging from 2 to 3 months. Still, the prognosis of individual patients varies according to primary cancer type, with breast cancer being associated with a better outcome (i.e., its median overall survival ranges from 3 to 5 months). Also, the recent introduction of targeted therapies seems to improve median overall survival at least in a subset of eligible patients such as HER2+ breast cancer patients who receive intrathecal trastuzumab. In those patients, a median overall survival of 13.5 to 20 months has been achieved.[75] Similarly, targeted EGFR and ALK inhibitors in the treatment of patients with non-small cell lung cancer have led to improvements in survival of up to 6 months (i.e., increasing from 3–5.5 months to 11 months). In contrast, median overall survival rates in the range of 2.5 to 4 months indicates continued poor outcome for patients with melanoma. Beyond tumor type, clinical performance, age at LM diagnosis, receipt of systemic therapy, and early response to treatment contribute to favorable survival.[76]

Several hematologic cancers including non-Hodgkin lymphoma and leukemia variants have a high propensity to metastasize to the CNS. In contrast to solid cancers, however, hematologic cancers frequently involve the leptomeninges, while parenchymal lesions are comparably rare. One of the most frequent types is acute lymphatic leukemia (ALL). Its prognosis strongly depends on age, with high cure rates of up to 80% in children but

only 30 to 40% in adults.[77] CNS involvement is especially frequent in B-cell ALL. Of interest, preclinical data in an ALL mouse model suggested that tumor cells migrate along perforating blood vessels (emissary vessels) from bone marrow to adjacent leptomeninges, a process that is mediated by local expression of integrins. Following ALL, a high propensity for LM is also observed in chronic myeloid leukemia (CML) where it mainly occurs during times of lymphoid blast crisis. Of note, imatinib, which is a potent agent for systemic disease control in CML, is for pharmacological reasons less effective in LM. In contrast, CNS involvement is rare in chronic lymphocytic leukemia (CLL),[78] but CLL-derived LM responds well to treatment and does not necessarily negatively affect patient survival. This is in line with high rates of occult disease in asymptomatic patients upon autopsy (there is disease involvement in up to 71%).[78]

Non-Hodgkin lymphoma frequently spreads to the leptomeninges with or without additional parenchymal lesions. The risk increases with higher grades of malignancy, being low in indolent lymphoma (incidence of 3 to 7%) but significantly higher (up to 30%) in aggressive lymphoma variants such as Burkitt or lymphoblastic lymphomas. However, with more intensive systemic treatments and CNS prophylaxis, the incidence seems to decrease in more contemporary series to approximately 5%.[79] Similar rates of CNS relapse have been observed for diffuse large B-cell lymphoma. Of note, the presence of additional extra-nodal metastatic sites as well as increased LDL levels were identified as independent risk factors.[80–81] In successfully treated non-Hodgkin lymphoma, most CNS recurrences occur within the first two years. Response rates of up to 83% were reported for indolent lymphoma with a median overall survival of 24 months.[82] In contrast, the outcome is significantly less favorable for aggressive lymphoma variants with one series reporting median overall survival of only 4 months.

Metastatic involvement of the peripheral nervous system

The peripheral nervous system is frequently involved in cancer patients albeit mostly through cancer treatment-associated adverse events such as chemotherapy induced peripheral neuropathy. Nevertheless, cranial nerves, nerve roots, plexuses, and peripheral nerves may well be infiltrated by solid or hematologic cancers. Of note, malignant cells may invade all nerve compartments such as the epineurium, perineurium, and endoneurium as well as its vasculature.[83]

Cranial nerves are frequently involved through compression by leptomeningeal, dural, or skull-base metastases (or very rarely through

primary cancers of the skull base), whereas they are rarely directly infiltrated by leukemia or melanoma. In hematologic cancers, cranial nerve involvement typically occurs late during the disease course, even though single cases are on record, where the neural involvement was the presenting symptom.[84–89] Lymphoma frequently involves the optic nerve, either in isolation or in combination with the CNS, orbital, and/or ocular compartment, or peripheral disease. The optic nerve is also a predilection site for leukemic infiltration of ALL in children,[90] which is commonly accompanied by involvement of the adjacent meninges. Clinically, patients present with progressive visual loss, which necessitates aggressive treatment including radiotherapy to preserve vision. In general, given the close spatial proximity of groups of cranial nerves, multiple nerves are frequently involved at the same time (e.g., through compression by a larger solid mass lesion), which leads to characteristic neurologic constellations. The orbital and parasellar syndromes, for instance, are characterized by frontal headache, diplopia, sensory loss in the trigeminal nerve, as well as proptosis and loss of vision. The middle fossa syndrome is characterized by facial pain and numbness, whereas the jugular foramen syndrome is associated with dysfunction of the glossopharyngeal, vagal, and spinal accessory nerves. Finally, the occipital condyle syndrome results in unilateral occipital pain and ipsilateral tongue paralysis.

Nerve roots are frequently involved in leptomeningeal metastasis or through local tumors. Metastases to vertebral bodies may result in mechanical compression of nerve roots.[91] In contrast, solid metastases directly to the nerve roots are exceedingly rare but have been reported in renal cancer,[92] cervical cancer,[93] and uterine cancer.[94] Clinical presentation often involves radiating pain and weakness of an extremity. Similarly, dorsal root ganglia are rarely involved in metastatic disease with less than ten cases reported, so far. Implicated primary cancers include renal cell carcinoma, breast cancer, colon cancer, lung cancer, and uterine cancer. Likewise, metastasis to the cauda equine, other than through leptomeningeal metastasis, is exceedingly rare and includes isolated cases of renal cell carcinoma[95] and lung cancer.[96–97] Clinically, patients may present with lower-back pain, saddle anesthesia, bowel or bladder impairment, weakness, and/or loss of sensation in the lower extremities.

Neoplastic plexopathies are rare overall but more commonly involved than cranial nerves or nerve roots. Metastatic involvement of the cervical, brachial, and lumbosacral plexuses is mostly associated with the late stages of systemic cancer and associated with a poor prognosis. Clinically, it results in progressive and severe pain, weakness, and the sensory loss of one or multiple extremities.[98] The most commonly

involved sites are the sacral plexus in approximately 50% of cases, the lumbar plexus in 30% of cases, and all divisions combined (cervical, brachial, lumbar, and sacral, i.e., pan-plexopathies) in 17% of cases.[99] In the majority of instances, plexuses are invaded by direct extension of tumors from regional organs or from lymph node metastases. In the case of cervical and brachial plexuses, lung and breast cancer are among the most common primary cancers (both through direct extension and via lymph node metastases), whereas the lumbosacral plexus is mostly invaded by direct extension from colon, cervix, ovary, urinary bladder, and prostate cancers. However, in a quarter of cases the lumbosacral plexus is also directly affected through hematogenic spread of breast and lung cancers as well as lymphoma. Of note, diffuse large b-cell lymphoma, Burkitt lymphoma, Hodgkin lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma have a predilection for the sacral plexus. Overall, in 25% of lumbosacral plexopathies the primary cancer is unknown.

Infiltration of peripheral nerves has been reported for breast cancer, pelvic cancer, leukemia, and melanoma.[1,100] Nerves that pass through or over bones might also be compressed by bone metastases. Predilection sites include the obturator nerve in the obturator canal, the ulnar nerve at the axilla or elbow, the intercostal nerves, the sciatic nerve in the pelvis, and the peroneal nerve near the fibular head. Solid tumors rarely spread to nerves and the few reported cases include intraneural metastases from carcinoid tumor, renal cell carcinoma, and breast cancer.

In neurolymphomatosis cranial nerves, nerve roots, plexuses, and peripheral nerves are infiltrated by malignant lymphocytes.[101] Its incidence is poorly defined with prevalence rates ranging from 1 to 40%. Interestingly, in 80% of patients neurolymphomatosis is the presenting symptom without previous history of systemic lymphoma (defined as primary neurolymphomatosis). In 10% of patients, systemic disease is diagnosed concomitantly and another 7% will suffer from additional systemic disease involvement later during the disease course. The most common type of lymphoma is diffuse large B-cell lymphoma followed by follicular lymphoma. On the basis of a larger case series of the International Primary Central Nervous System Lymphoma Collaborative Group, the average age of patients is 55.5 years with 60% being male.[101] Beyond non-Hodgkin lymphoma, 10% of patients were diagnosed with ALL in their series.[101] The most common sites are the cauda equine and lumbosacral roots, followed by cervical and thoracic nerve roots.[102] Interestingly, patients with neurolymphomatosis have a higher incidence of autoimmune diseases with anti-neural immune response,[102–4] which has

prompted the hypothesis that the lymphoma results from autoreactive B-cell clones that target neural structures.[102,105–6]

Relevance and societal impact

The International Agency for Research of Cancer (IARC) reported that 18.1 million individuals were diagnosed with cancer in 2018, and estimated that this number would further increase to 29.5 million by 2040 (Figure 1.2.2A; https://gco.iarc.fr/tomorrow, accessed July 2019). This significant rise in cancer incidence is true for the majority of cancer types with lung cancer showing the greatest relative increase (+ 5.8%). This increase seems mainly driven by prolonged survival times resulting from advances in patient management as well as the introduction of new cancer therapies such as immune checkpoint inhibitors, T-cell therapies, vaccination strategies, anti-angiogenic therapy, and various other targeted treatments. As cancer patients are living longer, they are at an increased risk of experiencing CNS involvement. Indeed, the incidence of CNS metastases is expected to rise proportionally, especially in elderly patients. According to data from Surveillance, Epidemiology, and End Results (SEER),[107] which collects data on synchronous brain metastases present at the time of primary cancer diagnosis, there is a steep increase in the incidence of brain metastases in adults until the age of 60 years, followed by a secondary decline (Figure 1.2.2B)—an age distribution that is very similar to that of primary brain tumors. Of note, the secondary drop in the incidence rate in the elderly might—at least in part—be due to underreporting of a substantial fraction of patients rather than a reduced susceptibility among the elderly. Hence, overall, the majority of brain metastasis burden is borne by older adults (55 to 65 years plus); this age cohort is expected to further expand as populations age (Figure 1.2.2C). The latest data of the World Health Organization estimate that the proportion of individuals above 65 years will increase from 9% in 2018 (based on a world population of 7.6 billion) to 16% in 2040 (based on a world population of 9.9 billion, see also https://www.prb.org/). This trend will be most pronounced in developed countries, which will uniformly depend on the elderly by 2040, in contrast to large parts of Africa, South America, and Asia, which will be less affected by demographic aging (Figure 1.2.2C).

The increasing number of cancer patients overall and brain tumor patients in particular has significant implications not only for affected patients, families, and caregivers, but also for societies at national and

international levels. To address this challenge in a proactive way, multiple strategies need to be combined.

First, systematic registration of brain metastases in cancer registries is needed to provide exact information on the disease burden and patient outcomes as well as to enable their monitoring over time. Such data are critical to inform affected patients and families, and to fully appreciate the societal impact of brain metastases in terms of health economical resources that will need to be allocated. Detailed epidemiologic knowledge seems especially crucial since previous analysis in primary brain tumors underscores their disproportionate high societal impact.

As compared with other cancers, malignant brain tumors contribute the highest mean years of life lost per patient, that is, 20 years as compared with 19 years for breast cancer, 15 years for lung cancer, and 10 years for prostate cancer, which is due to an early disease onset and short survival (median age at death 64 years).[108] In addition to the fact that patients are lost too early, malignant brain tumors also account for an incredible 7.7 million years of lived-with disability worldwide.[109] Of note, disability not only refers to focal neurologic deficits and physiologic impairment, but also extends to common cognitive deficits in medium- to long-term survivors, reduced quality of life, and above average inability to return to work with subsequent loss of income, which places entire families in precarious financial situations.[110–12]

Second, in addition to epidemiologic monitoring, opportunities for primary and/or secondary prevention of brain metastases need to be rigorously exploited.[113] In addition to continued basic research into the biologic mechanisms underlying metastatic spread, such as colonization and microenvironmental stimuli,[114–15] promising approaches for the prevention of brain metastases include molecularly selected treatments upfront,[116–17] as well as combination strategies that simultaneously target tumor and microenvironmental cells in pre-metastatic niches.[118]

Conclusion

The nervous system is commonly involved in patients with cancer either directly through metastatic spread or indirectly via treatment-related adverse events. Solid or leptomeningeal metastases constitute a source of significant patient morbidity and mortality, and their incidence is increasing with a concomitant increase in cancer burden and aging societies. Primary cancers with a particularly high propensity to metastasize to the nervous system include lung cancer, breast cancer, and

melanoma, as well as hematological cancers. In contrast to primary brain tumors, however, detailed epidemiological data on secondary brain tumors are not systematically reported. However, these data are urgently needed to fully appreciate the disease burden and assess patterns of care and outcome over time. In parallel to more standardized disease reporting, strategies for primary and secondary prevention of metastatic disease need to be pursued and exploited, including molecularly selected treatments that target tumor and/or microenvironmental cells in the pre-metastatic niche.

Figures and tables

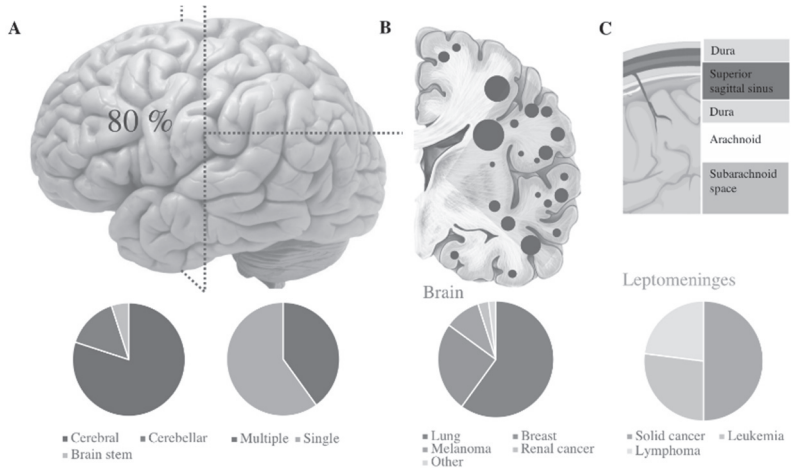

Figure 1.2.1. Brain metastasis in a nutshell. Demographic change and societal impact. **A** 80% of brain metastases occur in a supratentorial location and 37% are multiple at time of presentation. **B** Common locations (in blue) comprise the territory of the middle cerebral artery including watershed regions with a predilection for the border of gray and white matter (schematic representation). The most common primary cancers include lung, breast, and melanoma. **C** Leptomeningeal metastasis involves the spread of cancer cells (in orange) to cerebrospinal fluid spaces, and is frequently caused by hematologic and solid cancers.

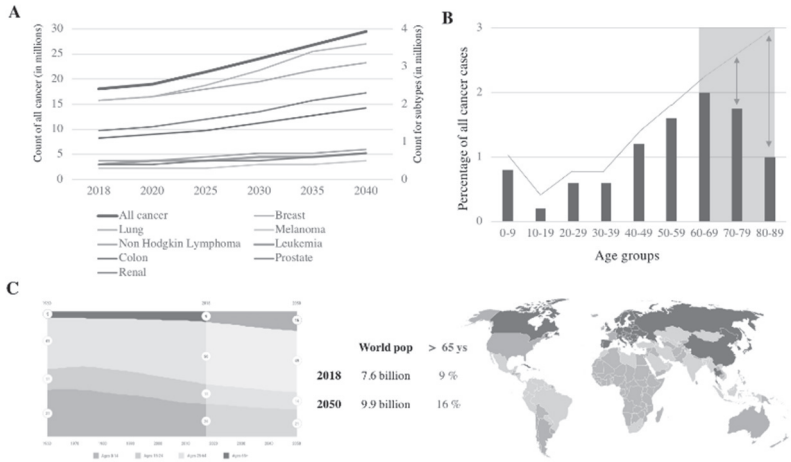

Figure 1.2.2. Demographic change and societal impact. **A** Projected increase in the incidence of cancer until 2040 is driven by increases in each of the top cancer types that commonly metastasize to the brain, adapted from IARC global cancer observatory data 2019. **B** Age distribution of synchronous brain metastases reveals an increase with age followed by a secondary decline that seems partly due to underreporting in elderly patient cohorts (purple area), modified from SEER 2010–13.[107] **C** Worldwide demographic development reveals the aging of the world population with most developed countries being dependent on older ages (in purple), WHO 2019 data.

Table 1.2.1. Top three primary cancers according to nervous system compartment.

Compartment	Top three primary cancers		
Brain	Lung cancer	Breast cancer	Melanoma
Spinal cord	Lung cancer	Neuroendocrine carcinoma	Breast cancer
Leptomeninges	Breast cancer	Lung cancer	Melanoma
Dura	Breast cancer	Prostate cancer	Lung cancer
Spine	Breast cancer	Prostate cancer	Lung cancer
Calvarium	Breast cancer	Lung cancer	Prostate cancer
Cranial nerve	Non-Hodgkin lymphoma	Acute lymphoblastic leukemia	Melanoma
Peripheral nerve	Breast cancer	Leukemia	Melanoma
Nerve roots*	Renal cancer	Cervical cancer	Uterine cancer
Plexus	Colon cancer	Lung cancer	Breast cancer

*other than involvement via leptomeningeal metastasis

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CHAPTER 1.3

FROM BENCH TO BEDSIDE

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Abstract

Preclinical requirements

The translation of fundamental discoveries into practical applications ("Bench to Bedside") includes all steps of preclinical and clinical development. Before a new drug can be given to a human being for the first time (first-in-human trial; FIH) the regulatory framework requires studies of primary and secondary pharmacology, pharmacokinetics, single-dose toxicity, repeated-dose toxicity, and genotoxicity. For supporting the subsequent stages of clinical development (late Phase I, Phase II, Phase III) further non-clinical information is required, whereby preclinical and clinical testing is not completely separated but partially overlapping.

Predictability of human risk

Analyses of the predictability of human risk on the basis of preclinical data reveal substantial complexity. The results obtained depend on a number of factors such as the type of analysis, the databases used, the nomenclature and ontologies used, the type of drugs analyzed (e.g., small molecules or biological drugs), the phases of development considered (the predictability of risk in phase 1 or later phases, or the post-marketing phase). Two studies in which the human-animal analysis of adverse events was limited to the determination of sensitivity found overall concordance rates of 70% and 48%, respectively. The first study (150 compounds) included events that occurred during clinical development, while the second looked at the adverse drug reactions of 142 registered drugs described in the package leaflets.

A big data analysis on a set of 3,290 approved drugs and formulations from regulatory submissions comprised 1,637,449 adverse events and five animal species (rat, dog, mouse, rabbit, nonhuman primate [NHP]). The diagnostic power of nonclinical observations was computed using likelihood ratios (LR), which represent the change in clinical risk when the adverse event is observed in an animal study. Many events with a high LR (>10) were identified, among them electrocardiogram changes (QT prolonged), application-site reactions, adrenal cortical hypofunctions, and inner ear and VIIIth cranial nerve disorders. However, observations with low negative likelihood, indicating that the *lack* of observation is predictive for safety in humans, were rare. A study on 182 molecules from an industry-wide nonclinical-to clinical translational database focused on predictability for first-in-human-trials and showed an overall sensitivity of 48%; the NHP displayed the strongest performance, especially for gastrointestinal (LR 18) and nervous system categories (LR 31). Of note, high specificity values (mostly >80%) were seen consistently over all species and target organs. The authors conclude that a lack of toxicity in animal studies strongly predicts safety in phase I.

Monoclonal antibodies and soluble receptors (fusion proteins) present particular difficulties in the preclinical assessment of their potential risks to humans. They need to be tested in NHPs or, alternatively, a surrogate protein can be used in rodents. In two studies on monoclonal antibodies and fusion proteins to a total of 29 cell surface or soluble targets, the concordance of preclinical and clinical findings was reviewed. Both test systems—surrogate monoclonal antibodies in rodents and human biopharmaceuticals in monkeys—showed very high concordance with human pharmacodynamics. In contrast, there was poor concordance for human adverse effects.

Keywords: Non-clinical testing, concordance animal-human concordance, adverse events, toxicity, prediction of animal studies, translation, risk assessment, safety

Introduction

Looking up the term “bench to bedside” in a medical dictionary such as, for example, the one published by the National Cancer Institute at the National Institutes of Health, USA, one finds definitions such as:

> A term used to describe the process by which the results of research done in the laboratory are directly used to develop new ways to treat patients.

This phrase may trigger the idea that the "bench to beside" process is a short one, one that gives quick results, since the results in the laboratory are "directly" used. However, the results are not "directly" used to *treat* patients; instead, they are directly used to *develop* a possible treatment. The present chapter deals with some aspects of this development.

What happens between the laboratory and the patient? What requirements have to be fulfilled before a new drug can actually be given to a patient? Since the initial administration of a new investigational drug usually has non-therapeutic (i.e., safety/tolerance) aspects, how can safety be guaranteed for the first participants in such a clinical trial? That is, how well can we predict possible safety issues?

Preclinical development

The preclinical development of a new drug is addressed by a number of international guidelines, the umbrella in Europe being the "ICH Guideline M3(R2) on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," issued in its final form in 2009.[1]

At the very beginning of clinical testing—that is, the first application of a drug in a human being ("first in man," FIM; "first in human," FIH)—there are only nonclinical data available. As the development enters subsequent stages, the nonclinical data start losing importance, but they never become entirely irrelevant. That situation remains even after marketing authorization (for example: in special situations like pregnancy and lactation, non-clinical data often remain the sole source of information to assess the human risk). Figure 1.3.1 shows the time course for the relevance of nonclinical and clinical information during the development of a pharmaceutical product.

The goals of the nonclinical safety evaluation generally include a characterization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and, when appropriate, potential reversibility.

Regarding FIH, the pertinent Guideline of the European Medicine Agency states that the purpose of FIH trials is to evaluate an investigational medicinal product (IMP) in humans for the first time, to study the human pharmacology, tolerability, and safety of the IMP, and to compare how effects seen in non-clinical studies translate into humans.[2]

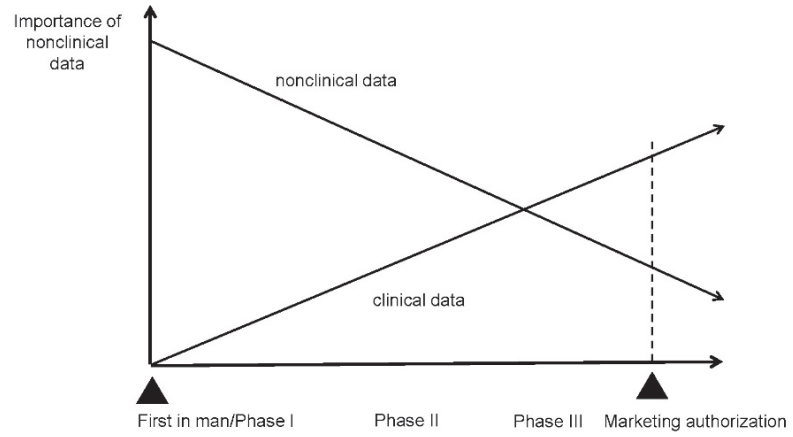

Figure 1.3.1. Relevance of nonclinical data during drug development.

The minimum preclinical documentation to enter phase 1, that is, to perform a FIM-study is shortly outlined below.

- Primary pharmacology
  These studies (*in vivo* and/or *in vitro*) are intended to investigate the mode of action and/or effects of a substance in relation to its desired therapeutic target.
- Secondary (safety) pharmacology:
  The objectives of safety pharmacology studies are primarily to identify undesirable pharmacodynamic properties that may have relevance to human safety. Vital organs or systems, the functions of which are acutely critical for life, are considered to be the most important. The recommended core battery comprises investigations on the central nervous system, the cardiovascular system (including the conductive system of the heart), and the respiratory system.
- Pharmacokinetics
  In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data in the species used for repeated-dose toxicity studies should be available before initiating human clinical trials (= data on ADME = absorption, distribution, metabolism, and excretion).

- Single dose toxicity
  Historically, single-dose toxicity studies (in which lethality was an endpoint) were required in two mammalian species using both clinical and parenteral routes of administration. After its revision in 2009 the ICH guideline M3(R2) states that information from other studies, such as appropriately conducted dose escalation studies or short-duration dose-ranging studies that define a maximum tolerated dose, could be used prior to FIM rather than acute toxicity data, and that investigations may be limited to the clinical route only. Lethality should not be an intended endpoint in studies assessing acute toxicity.
- Short repeat dose toxicity
  In principle, the duration of repeated-dose studies should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies (which is 6 months for rodent and 9 months for non-rodent studies). Thus, studies for a duration of 2 weeks would generally support any FIM, which start with the application of a single dose. All repeat-dose studies must be performed in two species (one non-rodent).
- Genotoxicity
  An assay for gene mutation (Ames-Test) is generally considered sufficient to support a FIM. For further development, a complete battery of tests for genotoxicity should be completed before initiation of Phase 2 trials.
- Further studies
  Some information is requested on reprotoxicity, but usually no extra studies are performed. The necessary information on the possible effect on sperm is obtained from the repeat-dose experiments. Information on possible antigenicity or local irritability are only performed if of concern.

The preclinical data are then used collectively to estimate an initial safe starting dose and a dose range for human trials and to identify parameters for clinical monitoring for potential adverse effects.

If the clinical development is carried on, and the later stages of phase I and the subsequent phases are entered, further non-clinical information is required to support the clinical trials. It must also be understood in this context that the preclinical and clinical testing during the various phases of development are not completely separated but are partially overlapping (Figure 1.3.2).

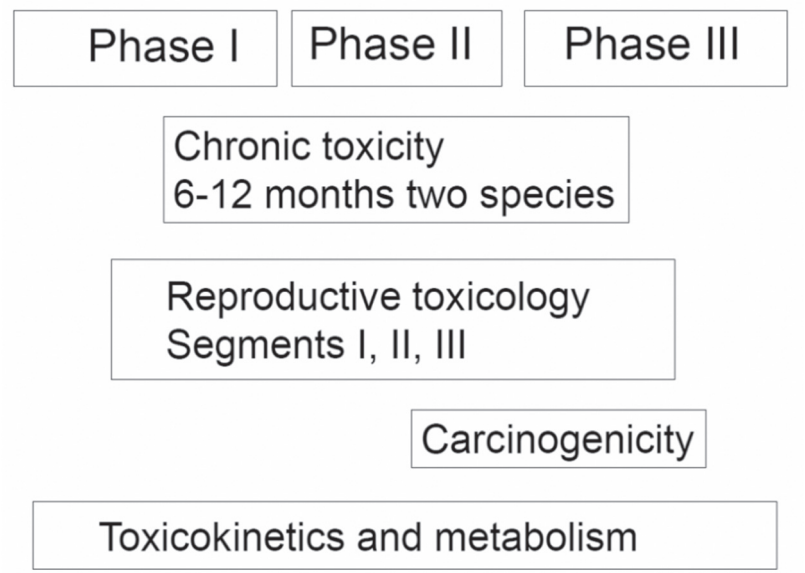

Figure 1.3.2.

Legend to Figure 2:
The development of a pharmaceutical product is a stepwise process involving an evaluation of both animal and human efficacy and safety information. Human clinical trials are conducted starting with a relatively low systemic exposure in a small number of subjects. This is followed by clinical trials in which exposure to the pharmaceutical increases by duration and/or the size of the exposed patient population. Clinical trials are extended on the basis of the demonstration of adequate safety in the previous clinical trial(s), as well as on additional nonclinical safety information that becomes available as clinical development proceeds.

Preclinical phase	pharmacology and toxicology, laboratory and animal testing, establish safety profile and dose for first-in-man
Phase 1	Human pharmacology: first-in-man, pharmacokinetics, healthy volunteers
Phase 2	Therapeutic exploratory: search for indication and dose, patients
Phase 3	Therapeutic confirmatory: confirm indication and dose

At the time of the marketing application, the dossier must include the results of a full (in rare cases near-full) preclinical safety program. It consists of long-term toxicity studies in two species of animals, a full reprotoxicity program (i.e., embryotoxicity, teratogenicity, toxicity on birth and lactation), more studies on genotoxicity and—if of concern—a carcinogenicity program. Furthermore, studies on immunogenicity and studies on local tolerance may be required. As shown in figure 1.3.2, the entire program is accompanied by the continuous collection of data on pharmacokinetics and toxicokinetics.

The extent and duration of the studies depends largely on the type of compound and the intended clinical use. A special challenge in preclinical testing exists, if the investigational medical product is not a small molecule but a protein, such as a monoclonal antibody, a fusion protein or a lymphokine. In these cases large differences may exist in animals compared to humans, for example, differences in affinity of the new candidate for its molecular target, or the human target may not even be present in animals thus necessitating the use of relevant transgenic animals expressing the human receptor. In general, a case-by-case approach is necessary to develop a meaningful safety program for a biopharmaceutical. Regulatory bodies such as the European Medicines Agency or the US Food and Drug Administration have both issued guidelines addressing the problems.

Predictivity of nonclinical data

The attempt to reduce the risk of a new drug to human beings by observing its effects in animals has a long tradition and was repeatedly driven by public tragedies. Two—now historical—examples are the Elixir Sulfanilamid disaster of 1937[3] and the Thalidomide tragedy in 1962.[4] A more recent example is the TGN1412 incident in 2006 where the administration of a novel CD28 antibody in a FIH trial resulted in severe cytokine release syndrome.[5] Each of these occurrences had a profound impact on the mode and the extent of preclinical testing required in the development of pharmaceuticals.

The rules for nonclinical testing outlined in the section above are the result of this development and represent the current standard of preclinical safety testing. The crucial question, however, is whether the models used are truly predictive for adverse effects in humans exposed to the various investigational compounds, because the results have far-reaching consequences such as the decision to continue or to stop the

development of a specific compound or to apply restrictions on the use, or method of use, of a given chemical.

The translatability of preclinical findings into human adverse events has therefore repeatedly been an object of research. Several analyses addressing the problem will be presented in this chapter.

Positive concordance

In the landmark paper of Olsen et al. (2000), a database was used that included input from 12 pharmaceutical companies on 150 compounds.[6] These were compounds where human toxicities (HT) were identified during clinical development and for which animal toxicity data were available, thus allowing it to be determined whether the animal studies identified concordant target organs in humans. Compounds that were never tested in humans because they were considered too toxic in animals or were withdrawn for other reasons were not included in the dataset. Data collected included the therapeutic category, the HT organ system affected, and the species and duration of studies in which the corresponding HT was either first identified or not observed.

The authors made clear that their analysis was limited to the determination of sensitivity, that is, the detection of true positives and false negatives, because the magnitude of data collection necessary to determine specificity (false positives and true negatives) was not practicable at the time of the study.

Overall, 221 HT were identified with the 150 compounds. The true positive concordance rate (sensitivity) was 70% for one or more preclinical animal model species. The rate was 63% for non-rodent species (= dog + primate), and 43% for rodent species (primarily rat). The best concordance was for hematological, gastrointestinal, and cardiovascular toxicities and the least was for cutaneous toxicity.

Regarding the time to the first appearance of concordant animal toxicity, it was found that 94% of first appearances were observed in studies of less than or equal to one month in duration, and in significant proportion after administration of just one dose.

Among the 150 drugs tested, 14 anticancer drugs were responsible for 25 HTs, 5 of which were neurological. The overall preclinical concordance rate in this group of drugs was among the highest rates observed (85%). As far as the neurological toxicities were concerned, the correlations were much better for non-rodents than for rodents (the cases in rodents were all peripheral neuropathies).

Tamaki[7] analyzed a dataset of 1256 adverse drug reactions (ADR, described in the package leaflets) collected from 142 drugs approved and marketed in Japan from 2001 to 2010 (excluding anticancer agents and vaccines).[7] Similar to the work of Olsen,[6] only the sensitivity (correlation rate) but not the specificity of nonclinical safety assessment was provided. The authors found that overall 48% of ADRs were predictable based on a comprehensive nonclinical safety assessment. Hematological and ocular ADRs, infection, and application-site reactions showed a correlation of more than 70%, while musculoskeletal, respiratory, and neurological ADRs showed a correlation of less than 30%.

A big-data approach

Clark and Steger-Hartmann (2018) performed a big-data analysis on a set of 3,290 approved drugs and formulations (from EMA and FDA submission documents) for which 1,637,449 adverse events were reported for both humans and animal species in regulatory submissions over a period of more than 70 years.[8] Their work is probably the most extensive analysis on animal-human predictivity currently available. The events reported in five species—rat, dog, mouse, rabbit, and cynomolgus monkey—were treated as diagnostic tests for human events.

The diagnostic power of nonclinical observations was computed for each event/species pair using likelihood ratios (LR). The LR is seen as a strong indicator and represents the change in clinical risk when the adverse event is observed in an animal study. A positive LR (LR+) of 10 or greater is considered a cut-off for strong concordance. The negative likelihood ratio, (LR-), which represents the decrease in risk if the animal observation is *not* made, was also computed.

The authors discuss extensively various problems and difficulties arising in this type of analyses, in particular how problems connected to nomenclature and ontologies may influence the obtained likelihood ratios. Table 1.3.1 presents some adverse effects with a high LR+ (shown by species or for all species combined; results taken from table 6 and 7 in Steger-Hartmann)[8].

The counts in Table 1.3.1 show that concordant events were not evenly distributed among either the species or organ classes, which partly depends on the fact that certain species are used to predict certain adverse events (e.g., the rabbit was the most common species in the past for eye studies). When the results were combined for all species, a number of statistically significant and highly predictive (LR+ > 10) events were identified, among them electrocardiogram changes (QT prolonged),

application-site reactions, adrenal cortical dysfunctions (hypothyroidism), and inner ear and VIIIth cranial nerve disorders.

Table 1.3.1. Most prevalent statistically significant observations.[8]

Observation	Likelihood ratio (LR+)	Species
Arrhythmia	18,3	dog
Leukopenia	11,2	dog
Constipation	12,3	rat
Cataract	17,6	rat
Azoospermia	13,3	mouse
Gastric ulcer	10,8	mouse
Blood creatinine increased	24,9	rabbit
Injection site reaction	15,0	rabbit
Conjunctival hyperaemia	10,0	rabbit
Alanine aminotransferase increased	16,3	monkey
Dehydration	15,7	monkey
Diarrhea	11,8	monkey
White blood cell count decreased	11,7	monkey
Inner ear and VIIIth cranial nerve disorders**	23,5	combined*
Adrenal cortical hypofunctions	17,6	combined*
Application and instillation site reactions	11,8	combined*
Electrocardiogram QT-prolongation	10,7	combined*
* combined results for rat, dog, mouse, rabbit, and cynomolgus monkey		
** Underlying contributing terms include vertigo, vestibular disorder, and VIIIth nerve (vestibulocochlear) lesions		

Observations with a low negative likelihood, indicating that the lack of observation is predictive for safety in humans, were rare. The authors list only four observations: B-lymphocyte count decreased, testicular hypertrophy, prostatic atrophy, and male genital disorder. The scarcity of negative predictive events is known (e.g., Clark 2015) and has also given rise to criticism of the use of animal experimentation.[9]

Drugs in first-in-human trials

Monticello[10] used an industry-wide nonclinical-to-clinical translational database to determine how safety assessments in animal models translate to first-in-human (FIH) clinical risk. The potential safety risks based on animal data and reported in the regulatory dossier, were followed through the completion of phase 1 trials. The blind database was composed of 182 molecules (compounds that were dropped from development before FIH were not included).

Overall sensitivity was 48% with the NHP displaying the strongest performance in predicting adverse effects, especially for gastrointestinal and nervous system categories (the positive likelihood ratios were 18 and 31, respectively; see table 3 in the paper). On the other hand, the more subjective clinical adverse events (e.g., nausea, headache, fatigue, insomnia, anxiety) were not well predicted by the animal models (LR+ only 3.6). This is to be expected and was also observed by others.[7]

In contrast to the above-mentioned studies by Olsen[6] and Tamaki,[7] which were limited to the determination of sensitivity (positive concordance), the analyses by Monticello also provide information regarding the performance of three main nonclinical test systems (i.e., rodent, dog, and monkey) in anticipating the human outcomes in phase 1. High specificity values (mostly >80%) were seen consistently over all species and target organs. Thus, a lack of toxicity in animal studies strongly predicts safety in phase 1 and reflects the fact that compounds entering clinical development have typically cleared many safety hurdles via extensive preclinical testing.

Biotechnology-derived products

Monoclonal antibodies and soluble receptors (fusion proteins) make an important contribution to the treatment of a variety of diseases. Due to their high molecular weight and complex chemical nature, they present particular difficulties and problems in the preclinical assessment of their potential risks to humans. For example, because species cross-reactivity is usually highly restricted to humans and NHP, monoclonal antibodies directed towards human targets are usually pharmacologically inactive in rodents. As a consequence, they need to be tested in NHPs, or, alternatively, the effects of a homologous monoclonal antibody applied to the respective protein in rodents needs to be studied (surrogate). Further alternatives are genetically deficient rodents or transgenic rodents that express the human target.

P. Bugelsky and P. Martin (2012) reviewed data on monoclonal antibodies and fusion proteins to altogether 29 cell surface or soluble targets to determine the concordance of preclinical and clinical findings (focusing only on the most commonly observed or most critical adverse effects).[11–12]

The authors looked at both the concordance of pharmacodynamic effects as well as adverse effects, since exaggerated pharmacology is often the most important factor in determining an adverse effect profile. This can be a direct extension of the pharmacological effect, as for example in the reactivation of cytomegalovirus seen with alemtuzumab due to long-term depletion of T cells or as a consequence of expression of the target in undesired sites, for example the cardiotoxicity of trastuzumab due to the expression of Her2 by normal cardiac myocytes.

Table 1.3.2 summarizes in part the results on those molecules that have an indication in the treatment of haematological or solid tumors (data taken from Bugelski and Martin, Figs. 1 and 2).[11] The concordance of pharmacodynamic effects (PD) was determined by comparing the pharmacodynamic effects in rodents and NHPs with human pharmacodynamics. The concordance of adverse effects was determined by comparing the occurrence of serious adverse effects in humans as identified from the product prescribing information with the occurrence of these effects in preclinical studies.

Both test systems, surrogate mAbs in rodents and the human biopharmaceuticals in monkeys, showed very high concordance with human pharmacodynamics. In contrast, there was poor concordance for human adverse effects. However, the authors argue that—in contrast to small molecules—mAbs and soluble receptor fusion proteins that are highly specific for their pharmacological target very rarely display off-target organ toxicities. Toxicology studies conducted in normal animals generally show either no adverse effects or an expected pharmacological effect. Therefore, for human mAbs, the most critical factor in understanding patient safety is to understand the full spectrum of the pharmacological effects.

Table 1.3.2. Concordance of human pharmacodynamics and human adverse events with mice receiving a surrogate construct and with cynomolgus monkeys receiving the human biopharmaceutical

	Concordance of human PD and rodent PD	Concordance of human PD and NHP PD	Concordance of human PD and rodent AE	Concordance of human PD and NHP AE
Alemtuzumab	+	+	-	-
Bevacizumab	+	+	-	±
Cetuximab	+	?	?	+
Ipilimumab	+	+	±	?
Rituximab	+	±	+	?
Trastzumab	+	?	+	-

Legend to Table 1.3.2. Summary data on the concordance of human pharmacodynamics (PD) and human adverse effects (AE) with mice receiving a surrogate construct or cynomolgus monkeys receiving the human biopharmaceutical. + indicates an accurate reflection of the major effects in humans. +/- indicates that some of the major effects in humans are not reflected in the preclinical data. – indicates that major effects in humans are not reflected in the preclinical data. ? = not determined.

Discussion

To take a drug from bench to bedside—that is, translating fundamental discoveries into practical applications—is an enormous task. A full-scale drug development follows a highly regulated path, is very expensive, and takes about 11–16 years. The present article focused on some aspects of this path, in particular the question whether the nonclinical data required before a drug is first given to a human are adequate to guarantee the safety of the participants taking part in this step of the development. Furthermore, can the nonclinical tests, which continue to be performed in support of the further steps of clinical testing, adequately predict the human risk?

Looking at some of the major publications on this topic published during the last two decades, it appears that these questions cannot be answered with a simple "yes" or "no" and that the answers—at least in part—seem contradictory. To obtain some orientation and a better understanding of this complexity, a few points must be considered.

Sensitivity versus specificity

The two studies of Olson[6] and Tamaki[7] did not attempt to collect nonclinical toxicity that was not associated with adverse reactions in humans (false positives) or toxicity that was not observed both in animals and humans (true negatives). Thus the studies provided the sensitivity (the rate of correlation) but not the specificity of nonclinical safety assessment. The focus on sensitivity is understandable, because if a compound is found to be positive for toxicity in an animal model, it is unlikely to go forward into human evaluation. Nevertheless, this approach has been harshly criticized: it has been argued that a useful toxicity test must also be able to give insight into when toxicity in the animal model is not observed in humans. In fact, some authors who included analyses on specificity in their work report poorer negative predictivity (lower negative likelihood ratios).[8]

There is, however, a notable exception. The work of Monticello[10] concentrated on predictivity in phase-1 studies and found—beside a good sensitivity—an excellent overall specificity of 84%, that is, an absence of toxicity in animal studies strongly predicted a similar outcome in the clinic. Thus, there seems to be a great difference depending on whether one looks at human risks during the very first steps of drug development or at the later phases of development or at the post-marketing phase. Monticello's results support the current regulatory paradigm of animal

testing in supporting safe entry to phase-1 clinical trials. That the current requirements on the duration of nonclinical studies prior to entry into human testing are sufficient (14–28 days) is also supported by the observation of Olson[6] that, if concordant animal toxicity does occur, it first appears in the large majority of cases in studies of less than or equal to one month in duration.

Database and drugs

Another crucial point emerging when comparing the various results on animal-human predictions is the selected data underlying the analyses. Preclinical data collections from drug development programs differ significantly from data compiled from sources of registered drugs. In the former, the data stem exclusively from rigorously controlled studies in animals (i.e., GLP applies), and toxicities in the animal often lead to the termination of further development. Certain toxicities will be preferentially eliminated on the basis of the criticality of the organ class. In the case of data collections on registered drugs, adverse events are reported via significantly different criteria and conditions and may underlie the over-reporting of human toxicities or confounders of co-morbidities. For example, in the analysis of Tamaki[7] anticancer drugs were explicitly excluded to avoid such confounders, since cancer patients are particularly prone to suffer from co-morbidities. All animal positive findings, whether true or false, preventing entry into clinical trials are not entered in a database of registered drugs. Therefore it is not surprising that the results on predictivity may be very different between studies.

Small molecules versus proteins

The two papers by Martin and Bugelski[11–12] underline the fact that human-animal predictions with protein-based drugs ("biologics") present special difficulties not encountered with small molecules. In particular, adverse effects not linked to the pharmacodynamics of the product, albeit rare, are usually not detected. For example, the known hypertensive effect of bevacizumab in humans was not observed in the nonclinical studies submitted to the EMA for obtaining marketing authorization.[13]

In fact, the first major incident in the history of the EMA occurred in 2006 with a monoclonal antibody,[5] 11 years after the agency started its work. Up to that point, the prerequisites on preclinical testing and the calculation of a safe first dose in human experimentation were sufficient to prevent harm to participants in phase-1 studies. The incident

triggered an adaptation of the required nonclinical testing program, in place since 2007.

The studies presented collectively demonstrate the significant value of nonclinical safety assessment in predicting human adverse reactions. However, they also show that there are areas of poor predictability, highlighting the need for advanced testing that enables better translation of animal toxicity to clinical settings. In fact, every effort is made to more accurately identify the human risk by consistently increasing the knowledge databases and introducing controlled vocabularies and ontologies.

On the other hand, we have to live with the fact that some animal toxicities are never seen in humans and some human adverse reactions are never identified in animal experimentation. Thus, the path of a drug from bench to bedside does not end as soon as the bedside is reached. Quite on the contrary, the full risk profile of a new compound can only be obtained by continued data collection in carefully designed pharmacovigilance and risk-management programs.

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CHAPTER 1.4

DRUG THERAPY AGAINST CANCER— AND SURGICAL TREATMENT OF CANCER

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Abstract

Part 1: The systemic treatment of cancer has been developed over the last seven decades, starting from the observation that some warfare chemicals were able to deplete blood cell counts. This approach was of course refined and, up to today, substances are systematically checked for their potential as anti-cancer drugs. Today, more than fifty different cytotoxic and cytostatic drugs are used as single agents or in combinations as chemotherapeutic regimens, using all known application routes—oral, systemic intravenous, intrathecal, and even local—to treat almost all malignant tumors.

Targeted therapies, for example, small molecules able to selectively inhibit the essential steps of cancer metabolism or cell division, became available in the early nineties. Increasingly, immune therapies—either cancer vaccines or antibodies optimally directed against tumor-specific epitopes—have allowed more efficacious treatments against cancer.

Part 2 discusses the historical and contemporary role of surgery, in particular concerning multimodal interdisciplinary treatment and the basic principles of surgery, as well as the development of minimally invasive surgery and enhanced recovery after surgery.

Keywords: drug therapy, cancer, antimetabolites, alkylating agents, antibiotics, tubulin binding drugs, proteasome inhibitors, hormones and anti-hormones, surgery, minimally invasive surgery

Introduction

For chemotherapy, there is truth in Heraclitus's aphorism "War is the father of all things." Seeking ways to overcome the toxicity of nitrogen mustard, a chemical warfare gas used by the Germans in World War I, two associated professors of pharmacology from Yale, Alfred Gilman and Louis Goodman, noticed that nitrogen mustard depleted leukocytes and lymphocytes in rabbits and explored the therapeutic potential of such compounds. They were able to shrink the tumor of a mouse. The first human subject treated in August 1942 was a patient with advanced, radioresistant lymphosarcoma. A short-lived response was obtained, but the patient died of recurrent disease in December 1942. The trial report on the pioneering use of nitrogen mustard derivatives started the development of drug treatment in cancer.[1] Interestingly, these first uses of nitrosourea derivatives reacting with DNA preceded the discovery of the double helix structure of DNA in 1953.

Pioneering work was also achieved by Sydney Faber in Boston in 1947: with a double qualification as a pathologist and a pediatrician, Faber tried to deplete tumor cells from folic acid with aminopterin and obtained a response in 10 out of 16 children treated, introducing the concept of anti-metabolites.[2]

Many other drugs for treating cancer can be identified to date, but still medical oncology is a "work in progress." Cytotoxic drugs interfere with rapidly dividing cells: they not only select tumor cells, but instead inhibit the turnover of (rapidly) dividing normal cells, such as the hemopoietic cells in bone marrow, the epithelia of the gastro-intestinal organs, and hair follicle cells. To be effective, a drug must be able to reach its target cells in a reasonably high concentration for a reasonable period of time. Thus optimizing the pharmacokinetics of cytotoxic drugs to achieve high enough concentrations in a given tumor and ways to eliminate the drugs and their potentially active and/or toxic metabolites are challenging steps in the development of therapeutic substances. Finding less toxic formulations that achieve higher concentrations of the drugs in tumor tissue than in normal tissue—for example, liposomal formulations of taxanes—makes treatments more tolerable without losing effectivity.

Even so, not a single tumor has lost its peculiarities and hazardousness so far. There is room for improvement and unmet medical

needs in all cancer diagnoses and this leads to an accelerated transition of new drugs from bench to bedside. In no other discipline has the dosing of drugs per body surface area survived to the present day; however, in oncology, this dosing strategy is currently still in use. In fact, body surface area does not allow the dose to be adapted to metabolic or cardiac function, though it does allow dose estimations to be translated between species. As such, the dose estimations for the first use in humans can be calculated from the drug dosage in experimental animals and the testing of new drugs in early clinical development can be started.

Next, we will briefly outline the substance groups currently used and new developments.

Alkylating agents

The first alkylating agents used against malignant tumors bind directly by covalent bonding to DNA and impede further cell division, as they induce cross links also within the DNA strands and from one DNA string to the other, thus interfering with DNA transcription. They are highly reactive and their action is independent from the cell cycle. Some of these nitroso-ureas are still in clinical use.

Example: A personal communication from a senior physician concerning his training in the early 1950s:

He told me that he had to administer chemotherapy to tumor patients by injecting saline into a gas filled glass bottle directly at the bedside, shaking the bottle gently, re-aspirating the liquid, and injecting it into the patient intravenously. The patients always vomited shortly after the procedure and he himself also felt nauseous and guilty, as he was not at all convinced he was doing something for the benefit of the patients.

To reduce toxicity, later, alkylating agents were developed as prodrugs, which require hepatic activation by cytochrome-P-450 mono oxygenation—drugs like cyclophosphamide and ifosfamide, procarbacine and dacarbacine, whose first-line use is now declining. A newer generation of highly effective alkylating agents is platinum salts that form DNA adducts by cross-linking purine bases, for example, cisplatin, carboplatin and oxaliplatin that have been widely used in cancer therapy since 1978.

Antimetabolites

An alternative way to interfere with the accelerated DNA synthesis in tumor cells was to provide them with the "wrong building materials," for example, anti-metabolites and alternative purine and pyrimidine compounds that block the enzymes essential for the synthesis of nucleic acids: 6-mercaptopurin and 6-thioguanine block the de novo synthesis of purines, 5-fluoro-uracil blocks thymidilat-synthetase, and methotrexate blocks dihydrofolate- reductase. Cytosine arabinoside blocks DNA polymerase and hydroxyurea blocks the reduction of ribo- to desoxyribonucleins. All these compounds continue to be in clinical use.

Antibiotics

A number of drugs with antibiotic properties were found to be effective against tumor cells. In fact, at the National Cancer Institute in the US and in other research laboratories, drug screening facilities testing drugs for their potential as cancer therapeutics were established. This led to the identification of antibiotic drugs with sufficient anti-tumoral activity for use in patients. Most of these drugs also bind to DNA and act as alkylating agents, like mitomycin C; others inhibit topo-isomerase, a DNA repair enzyme. Prominent antibiotic drugs include the anthracyclines, bleomycin, and mitomycin C.

Tubulin-binding drugs

Drugs interfering with the formation of the mitotic spindle—for example, modifiers of tubulin function—are highly effective as arresting cells in mitosis and are effective against malignant tumors. There are several classes of natural or semi-synthetic plant alkaloids used in cancer therapy, vinca alcaloids, taxanes, and epidophyllotoxins.

Proteasome inhibitors

These drugs block the action of proteasomes, cellular complexes that degrade unneeded, misfolded, or damaged proteins by proteolysis. They exert their action by preventing the degradation of pro-apoptotic factors and thus favor the apoptosis of tumor cells.

Trabectedin, an extract from the sea squirt *Ecteinascidia turbinata* that is used against ovarian cancer and sarcomas, is one of the latest "classical cytotoxic drugs" introduced in medical oncology and

interferes with DNA transcription. This drug can cause severe side effects, such as neutropenic fever, electrolyte imbalances, and myolysis, but also induces responses in so far resistant tumors.

Hormones and anti-hormones

Hormones are among the oldest and most innovative drugs used against cancer; as well as therapeutic drugs, they are used as co-medication, for example, dexamethasone is used against nausea and vomiting.

There is a strong rationale for the use of hormones, for example, soluble messenger molecules, to target cells bearing the respective hormone receptor. Both in men and in women, the most frequent malignant tumor entities derive from endocrine tissue, for example, prostate and breast cancer; however, endometrial cancer and others also react to hormonal signals. For those tumors, treatment with modified hormonal drugs that inhibit hormonal growth signals is the mainstay of treatment—for decades now and into the future. Most of these drugs show a comparatively low burden of side effects and maintain effectivity for long periods of time.

Targeted therapies

Decades of basic research have built up a better understanding of the changes in the genetic background happening during the journey from normal tissue towards a malignant tumor. In 1959, David Hungerford, as a research fellow, and Peter Nowell discovered the first characteristic tumor-specific chromosomal aberration, the Philadelphia chromosome. Janet Rowley identified this abnormal chromosome as the result of a translocation between the chromosomes 9 and 22, t(9;22) (q34;q11), in 1973. This translocation leads to an abnormal oncogenic fusion gene, BCR-ABL, and results in the expression of a constitutively abnormal growth factor on the cell membrane of affected cells, as specified in 1988 (3).[3] The development of a small molecule blocking this abnormal tyrosine kinase—later named imatinib—and its introduction into clinical use was achieved by Drucker et al. in 2001, roughly forty years after the initial mention of the first tumor-specific genetic aberration.[4]

Imatinib was the first small molecule, targeting the ATP-binding site at the intracellular part of the tumor-specific tyrosine kinase receptor BCR-ABL, but also targeting c-kit and the platelet-derived growth factors alpha and beta. It “switches off” the signaling cascade with P13K-Akt-mTor, promoting further tumor cell divisions, and activates tumor cell

apopotosis. The drug is usually well tolerated and can be given orally for long periods. However, the tumors of some patients become resistant during continuous use. These resistant patients can often be treated with second-generation targeted drugs.

After Imatinib, many other drugs targeting other receptor-tyrosine kinases or other "druggable targets" emerged and were tested for their efficacy as cancer therapeutics. These drugs can be given orally. Given the preferential expression of their targets in tumor cells, they are mostly well tolerated, even when given in a continuous schedule. The molecules are small: most of them cross the blood brain barrier and so constitute an active therapy against brain metastases. To name only a few, gefitinib and erlotinib target EGFR-1, lapatinib shows activity against Her-2neu, and osimertinib is a third-generation EGFR-1 inhibitor that is active against the brain metastases of NSCLC refractory to gefitinib and erlotinib. There are numerous multikinase inhibitors with anti-VEGF potential, such as sunitinib, sorafenib, pazopanib, and axitinib. Every year at least fifty drugs start testing in human phase 1–2 trials, but only a few achieve being licensed for general use. Most of these drugs have a characteristic side-effect profile, with cutaneous side effects and diarrhea, making them challenging for long-term use. Fortunately, targeted therapies have become a standard option for the treatment of many patients with a wide variety of tumors.

Immune therapies

Cancer vaccines

Immune therapy has been a long-term goal: making the patient's own immune system destroy the tumor. Vaccinations with tumor lysates have been tried for decades, with some spectacular case reports, but no systematic breakthrough. The function of dendritic cells is to present antigens to naive T cells at lymphoid organs in the context of the major histocompatibility (MHC) molecules and to provoke an immune answer to the antigen—except where it is recognized as a host molecule. Many efforts to refine the anti-tumor potential of dendritic cells have been made: so far, an autologous tumor vaccine against prostate cancer has been approved by the FDA.[5] Other vaccine strategies work by modifying tumor associated antigens (TAA), either cell membrane molecules, proteins, DNA, or RNA, in order to make them more immunogenic or to use viral vectors with low disease potential to transport TAAs.[6] Therapeutic cancer

vaccines are usually very well tolerated and constitute a major current research goal.

Antibodies

The next successful approach using immune-mediated mechanisms against cancer was adoptive immunotherapy with monoclonal antibodies recognizing TAAs at the cell surface of tumor cells.

The earliest and one of the most successfully used antibodies is rituximab, approved in 1997, which targets the surface molecule CD20, present in all precursor B cells, but not on mature plasma cells; it is used on nearly all B-cell lymphomas and leukemias, except multiple myeloma. Trastuzumab, targeting Her-2neu and used against Her-2neu overexpressing breast cancer, followed one year later.

A great number of new antibodies and of antibody-toxin or antibody-radioactive compounds followed and new therapeutics have been continuously designed. A major breakthrough was the introduction of checkpoint inhibitors into the clinic, for example, antibodies that target the inhibitory mechanisms used by tumors to silence the immune system. By "releasing the brakes" from the immune system by infusing antibodies against CTLA4 (cytotoxic T-lymphocyte-associated protein) in metastatic malignant melanoma or death receptor-1 or its ligand (PD-L1) in melanoma and also in a great number of hematologic and solid tumors, durable responses even in patients with advanced disease could be obtained.[7]

With the generation of chimeric antibody receptor T cells (CAR-T cells), the autologous T cells of a patient are modified ex vivo to express a receptor for a tumor-specific antigen, then expanded ex vivo and reinfused into the patient, where the engineered T cells exert the T-cell killing of the tumor cells. This principle has shown durable complete responses in patients with refractory acute lymphocytic leukemia—and, of course, efforts are made to make this therapeutic option available also for patients with solid tumors. Currently, it is very challenging to select antigens that are expressed in the tumor but not in other organs. Pilot trials with CAR-T cells directed for example against ErbB2 had to be stopped after toxicity in a few patients. The pilot results of 10 patients treated with a single infusion of CAR-T cells directed against EGFRvIII expressing recurrent glioblastoma were reported and showed that the CAR-T cells reached the target, decreasing the antigen expression by tumor cells and the expression of inhibitory molecules and infiltration by regulatory T cells.[8] Six of ten patients survived for at least 200 days. However, the

major challenges remaining to be solved in the future are to overcome the adaptive changes in the local tumor microenvironment and address the tumor's protean antigen expression.

Part 2: Surgical treatment of Cancer: Development and Basic considerations

Historical sight

"Treatment of cancer must become more surgical!" Theodor Billroth stated in 1890. It was the pioneering period of cancer surgery characterized by the immediate success of tumor removal, on the one hand, and a frequently deleterious outcome with respect to postoperative complications and mortality, on the other hand. Nevertheless, this period saw several milestones of surgery, such as the first gastric resection, colorectal resection, and esophagectomy, which built the basis for visceral surgery. This development became possible through important discoveries regarding microbiology and hygiene (in 1847 Ignaz Semmelweis discovered antisepsis), the introduction of anesthesia by W. T. G. Morton in 1846 (Mass. Gen. Hospital), and improvements in diagnosis through the introduction of endoscopy by Adolf Kussmaul in 1868 (Freiburg) and in 1881 by Josef Leiter (introduction of light in rigid endoscopy) and Johann Freiherr von Mikulicz-Radecki in Vienna. Additionally, further achievements in early abdominal radiology were reached at the end of the nineteenth century. In this era, William S. Halsted, an American surgeon trained by Billroth in Vienna, introduced the use of rubber gloves in surgery and regional anesthesia and established mastectomy as a treatment for breast cancer.

Establishment of oncologic surgery

In brief, the following decades witnessed the consolidation of oncologic resections, slightly reducing surgical mortality from more than 30% down to nearly 10% in the 1960s. With the introduction and further development of antibiotics and the evolution of intensive care, complications could be treated more and more successfully. The later growth in knowledge about the pathophysiology of sepsis led to the development of perioperative intensive care. More extensive procedures, including the removal of regional lymphatic tissue, became possible in order to extend resection margins. In parallel, pathohistology underwent remarkable refinements and prepared the way for the following phase of systematization.

Establishing TNM classification (T tumor, N nodal status, M metastases) in the 1950s built the basis for systematic surgical oncology. With the advent of computed tomography and later magnetic resonance imaging, preoperative staging became more accurate.

The mechanistic understanding of surgical cancer treatment predominated in therapy concepts until the late 1980s, when multivisceral resections were performed in order to increase the chance of curing advanced cases. Triggered by results and the experience of Japanese centers, in the West during the 1970s and 80s the focus was on systematic lymphadenectomy in oncologic visceral surgery. To improve the prognosis, surgical borders have been pushed back by extending lymphadenectomy in some entities. Nevertheless, extended surgery generally failed to reach the goal of tumour control without multimodal treatment concepts, which has only gained place over the last thirty years.

Phase of standardization and specialization

The trend toward standardization and specialization started in the 1980s. Large prospective surgical studies were conducted to increase evidence and surgical quality. Evidence-based medicine—diagnosis and treatment based on the full extent of scientific knowledge gathered by randomized trials—followed former decision processes that generally relied on personal experience and impression. International guidelines respecting the results of clinical trials were developed including classification of scientific value and a grading of recommendations. Furthermore, interdisciplinary tumor boards were created to consensually generate case-specific treatment strategies. Medical decisions thus gained transparency and traceability. Finally, in recent years discoveries in the field of immunology, molecular biology, and oncogenetics inaugurated the era of precision medicine. Beside these developments, perioperative medicine allowed preoperative optimization and preparation of patients for major visceral surgery.

Multimodal interdisciplinary treatment and basic principles of surgery

Nowadays, in almost all visceral tumor entities, interdisciplinary treatment strategies are state of the art in advanced stages, of which the vast majority of cases consist. Keeping radical resection as the mainstay of potentially curative treatment, perioperative additional treatments for intestinal cancers

such as chemotherapy and radiotherapy before and/or after surgery are able to improve the outcome regarding disease control and survival.

The principles of potentially curative oncologic visceral surgery comprise histologically tumor-free resection margins and the en-bloc removal of the regional lymphatic tissue. The extent of resection and en-bloc lymphadenectomy are not yet well defined. The benchmarking parameters of surgical quality, namely the R-Status, number, and location of removed lymph-nodes, as well as immediate outcome measures such as postoperative morbidity and mortality, are periodically evaluated. In order to define diagnostic and treatment pathways to improve the outcome, a growing number of institutions expose themselves to certification processes that are repeated periodically.

Technically, in visceral surgery we distinguish between resecting procedures (i.e., hepatic resections, left pancreatectomy, nephrectomy) and operations including resection and reconstruction (i.e., esophagectomy, gastrectomy, colorectal resections, pancreaticoduodenectomy). The latter are the more complex interventions and bear a remarkably increased potential for surgical complications compared with bare resections. Especially in the surgery of the digestive system, the type and extent of the resection and reconstruction influences quality of life.

Minimally invasive surgery and enhanced recovery after surgery

Within the last three decades minimally invasive procedures have been established to enhance postoperative recovery and reduce the burden of surgical access. Struggling with the radical principles of oncologic surgery in the early phase of minimally invasive surgery, this type of approach developed quickly and reached an equal level of oncological quality compared with open procedures for nearly all abdominal tumor entities. By adopting minimally invasive techniques and new hemostatic dissection instruments, advantages such as less blood loss, less pain, earlier bowel function, enhanced recovery, and lower complication rates can be realized. Whether recent advances in robotic surgery really contribute to patient benefits still remains unclear. With this technique, very complex laparoscopic procedures may be feasible. However, up-to-date robotic surgery is a very expensive technical feature.

With the establishment of minimally invasive surgery, rapid recovery strategies were successfully adopted. These protocols include a broad multidisciplinary package of treatment improvements regarding rehabilitation, preoperative optimization, minimally invasive surgery, the avoidance of tubes and drains, progressive perioperative and complication

management, potent analgesia, perioperative physiotherapy and immediate mobilization, and dedicated nursing and nutritional care, as well as psychological companionship.

Failure to rescue

Nevertheless, major postoperative morbidity still exists and endangers patients' lives. Thus, in major procedures such as esophagectomy, gastrectomy, pancreatectomy, biliary tract resections, and rectum resections, quick diagnosis and effective treatment of complications are key. Low mortality centers commonly do not differ from high mortality centers regarding the incidence of major complications but do differ in respect to the success of treating complications. The failure to rescue rate is substantially lower in experienced specialized institutions and is a further parameter of quality. We also observe a proportional correlation between institutional and surgeon-dependent caseload and surgical safety—a fact that remarkably contributed to the political requirement for a minimum caseload in many European countries to permit the performance of high-risk procedures.

Future aspects

Future perspectives include further personalization of multimodal treatment of solid tumors, technical refinements of surgical procedures, such as minimal-access robotic assisted surgery, intraoperative 3D projection of complex structures (i.e., hepatic vessels during hepatic resection), and the influence of big data on daily surgical life. Improvements in procedure simulations will gain a greater place in surgical education, which is a big current issue due to specialization and restrictive rules on maximum working times in hospitals.

Conclusion

The development of drugs used for cancer therapy is an ongoing and developing process, which is discussed in chapter 1.3. At present, despite many new developments, such as targeted therapies and immune therapies, the classical chemotherapies are still the main tools in cancer treatment worldwide, and the new drugs are only available in countries with a significant income.

The toxicity of anti-cancer drugs is a major treatment concern, as hematological side effects and other toxicities seem to be better controlled.

Most of these drugs act on the principles of toxicity, whereas the new area of immune therapies induces delayed and immunological effects.

Surgery is one of the main pillars of cancer therapy. As in all other fields of surgery, not only is the field developing technically, but also multimodal interdisciplinary treatment is increasingly practiced.

With the establishment of new techniques of minimally invasive surgery, rapid recovery strategies are used. Despite the progress made, the awareness of the limits of these methods is also essential.

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CHAPTER 1.5

MANAGEMENT OF ADVERSE EVENTS OF SYSTEMIC DRUG THERAPY AGAINST CANCER

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Abstract

Cytotoxic drugs exert their action by directly reacting with the DNA, by hindering the formation of a mitotic spindle, by reacting with tubulin, or by interfering with protein synthesis and the provoking of tumor cells—and of normal cells. Drug formulation can sometimes achieve the penetration of cytotoxic drugs being targeted towards the tumor; however, the effects of cytotoxic drugs are always unspecific and generally affect the whole organism. This systemic action is a double-edged sword. It is always argued that cytotoxic drugs are effective against circulating tumor cells and micrometastases and thus "downstage" the tumor, or at least slow the metastatic process; thus, damage to all types of dividing tissue with severe complications like neutropenic fever, mucositis and diarrhea, or permanent infertility have to be faced and even damage to postmitotic organs such as nerves and the brain cannot be avoided.

The side effects of cytotoxic drugs are presented and the potential prevention and management is discussed. A thorough evaluation of each patient with his or her organ functions and history taking into account previous diseases helps tailor therapy, heeding the individual risk factors. This should of course always be taken seriously, particularly in elderly individuals. The patient and his or her proxies must be informed about the

planned therapy, its indication, its potential benefits, and its inherent risks to allow informed consent.

Keywords: adverse events, cancer, grading, haematological toxicity, gastrointestinal, fever, central nervous system, peripheral nervous system

Introduction

Due to its unspecific effects against all types of actively dividing cells, adverse effects of antineoplastic chemotherapy are obvious and severe. As the therapeutic window of cancer drug therapies is generally narrow, studies exploring treatment schedules were not only designed to determine the therapy's efficacy against the tumor, but also focused on tolerability, for example, the feasibility and toxicity of the administered drugs.

The first experiences with drug therapy against cancer only date back to 1942; given the relatively short time span, the results and high level of progress are actually a great achievement. So far, a "final breakthrough" has not been achieved in any solid tumor that would allow a metastatic tumor to be cured with chemotherapeutic agents. In consequence, numerous research groups work on developing new drugs or new applications or combinations of approved drugs. New insights are awaited at every convention and the translation from bench to bedside is fast, despite the development of a new compound lasting ten years or more. Most cytostatic drugs are still dosed in relation to the estimated body surface of patients, showing the urge to rapidly apply drugs tested in animal models in humans. Another unique feature of cancer therapies is that they are not tested like other drugs in healthy volunteers but in tumor patients, starting in phase-1 trials in patients with advanced tumors who have no treatment options left.

Given the life threat of any metastatic tumor disease, even the severe side effects of drug therapy are tolerated as soon as the improved efficacy of the therapy is claimed. However, to make therapy side effects comparable, a universally accepted grading system has been elaborated and published by the National Cancer Institute and the National Institutes of Health. It lists all the potential adverse events, whether symptoms, laboratory findings, or functional findings, of any organ or tissue and provides a grading system according to the severity of the adverse event. This terminology, named the Common Terminology Criteria for Adverse Events v.4.0 (CTCAE), was last published as version 4.0 in May 2009.[1] It allows the documentation of each adverse event (AE), any unfavorable and unintended sign, symptom, or disease temporally associated with the

use of a medical treatment procedure that may or may not be considered to be related to the medical treatment or procedure.

The grades refer to the severity of the AE. The CTCAE displays grades 1–5 with unique clinical descriptions following this general guideline:

Table 1.5.1. Grade of toxicity

- Grade 1: Mild

Asymptomatic or mild symptoms, clinical or diagnostic observation only. Intervention not indicated.

- Grade 2: Moderate

Minimal local or noninvasive intervention indicated. May limit age-appropriate IADL.

- Grade 3: Severe or medically significant, but not immediately life threatening.

Hospitalization or prolongation of stay indicated; disabling, limiting self-care ADL.

- Grade 4: life threatening

Urgent intervention indicated.

- Grade 5: death related to AE.

Abbreviations:
IADL: Instrumental activities of daily living, preparing meals, shopping for groceries or clothes, using transport, using the telephone, managing money.[2]
ADL: activities of daily living such as bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden.[3]
Not all grades are appropriate for all AEs. Therefore, not all AEs are listed with all grades. Grade 5 is not an option for all AEs.

However, the CTCAE also has some weaknesses. It is not always easy to use: even for the hematologic toxicities, the grading of granulocytopenia, lymphopenia, and thrombocytopenia are not found in the chapter “Blood and Lymphatic System Disorder” but in “Investigations.” Moreover, neither for white blood cells nor for platelets does the grading severity reflect clinical significance nor the need for intervention. In the absence of bleeding and with a tight controlling schedule, no acute measure or platelet transfusion has to be given even with toxicity grade 4. One could find several such inconsistencies, but this does not affect the acceptance of the whole reporting system.

The most important distinction is that between moderate and severe toxicity, as this defines the need for intervention—and the rates of severe toxicity of a given treatment. Here the consistency of rating from patient to patient and from day to day is of paramount importance.

It is indeed always helpful to seek the written definition in the booklet, to read it to the patient and to ask him or her for the grading to report as much as possible from the patient's view. Reading the exact definition prevents a lot of misreporting—as everybody has his or her own definition of what is severe; however, for AE reporting the grading of CTCAE v.4.0 should be used. One of the toxicities where this is most evidently needed is fatigue.

Symptoms that change over time, like nausea and vomiting or general weakness, are highly dependent on the time of reporting and the actual status of the patient. The advances in technology have provided us with apps for smart phones where trial patients or patients at risk are asked to report some symptom parameters on a daily basis or are monitored for their vital signs to get a more accurate image of their health status and treatment burden.

Hematological toxicity

In the booklet, the AEs are listed according to the affected organ system. For medical oncologists, the most important side effect was hematological toxicity (HT). HT is evaluated with the highest frequency in clinical trials, mostly at every visit by the patient, either to decide about continuation of chemotherapy or to control in case of the need for intervention. The possible interventions are standardized for toxicities of all cell lineages giving the limits of cell counts where red cell or platelet transfusion, the administration of growth factors, or the preventive administration of antibiotics to prevent opportunistic infections are recommended. The severity of the cell-count drop, which lineages are affected, and the timing of the nadir depend not only on the chemotherapeutic regimen and the dose applied, but also on host factors like sex, age, co-morbidities, and the concomitant drugs used. The nadir might be reached as soon as ten days or as long as six weeks after the use of nitrosoureas. Most publications on chemotherapy include a table listing the rates of hematologic toxicities.

Hematologic toxicity is easily reported and graded, as blood counts are near universally available and their results are numbers, which give no room for subjective interpretation. It is mainly the time for recovery from hematologic toxicity that determines the timing of chemotherapy cycles. Most regimens allow cycle durations of three to four weeks. In very rare occasions after the use of DNA-damaging chemotherapeutic drugs, mostly alkylating agents, long-term hematological toxicity occurs as myeloproliferative disorder, refractory anemia, or even as secondary acute leukemia.

Table 1.5.2. hematological toxicity.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia, Hb g/dl	<LLN-10g/dl	<10 g/dl >8g/dl	<8g/dl		Death
Leucopenia					Death
Granulocytopenia	< LLN - 1800/mm3	<1800-1000/mm3	< 1000/mm3-500/mm3	<500/mm3	Death
Lymphocytopenia	<LLN – 800/mm3	<800/mm3-500/mm3	<500/mm3 - >200/mm3	<200/mm3	Death
Platelets	<LLN – 75000/mm3	<75000-50000/mm3	<50000 – 25000/mm3	<25000/mm3	Death

Managing hematologic toxicities includes general measures like providing a "healthy diet" containing enough nutrients, iron, and vitamins to allow blood cell recovery, enough sleep, and avoiding physical and psychological exhaustion.

The management of chemotherapy induced anemia should follow guidelines.[4] Red cell transfusions may be indicated when hemoglobin levels drop below 8g/dl. The use of erythropoietins declined significantly after a shortened survival was related to patients with solid tumors treated with erythropoietin for chemotherapy associated anemia; now, it is again reconsidered for the treatment of symptomatic anemia. Red cell transfusions for cancer patients should be depleted for white blood cells and irradiated to prevent graft-versus-host reactions of white donor blood cells in immune-deficient hosts.

Platelet transfusions are indicated in case of manifest bleeding and according to hematologic and oncologic specific guidelines for patients with platelet counts below 10 000 G/l or 20 000 G/l, respectively.[5] White blood cell counts and differential counts should be monitored to assess the nadir, for example, the lowest counts of cells after a specific drug or regimen. The granulocyte stimulating growth factor (G-CSF) or granulocyte-macrophage growth factor (GM-CSF) may reduce the time with a decreased white blood cell count and the rate of neutropenic infection and should be provided according to international guidelines (Crawford, ESMO guidelines, Annals of Oncology, 2010).[6] This is particularly important for elderly persons undergoing chemotherapy and

should be included in treatment planning.[7] The use of prophylactic antibiotics and antifungal drugs is also part of these guidelines but will probably be modified in the light of newer insights in the function of the gut microbiome and its importance for response to chemotherapy.

Neutropenic fever

Neutropenic fever and neutropenic infections are closely related to hematologic toxicities. These infections occur in relation to the nadir of white blood cells and might be life threatening. They require an adequate and immediate diagnostic work up trying to identify the infectious agent and immediate (within 1–2 hours), empirical broad spectrum antibiotic treatment using antibiotics with or without antifungal treatment, and supportive care addressing cardiac failure, pulmonary and renal insufficiency. Additional antiviral therapy may be indicated. Additional application of G-SCF and GM-CSF has no impact on mortality, but might increase pulmonary complications. In consequence, it is no longer recommended to apply G-SCF and GM-CSF in cases of neutropenic fever.[8]

Prophylaxis against pneumocystis jirovecii pneumonia should be provided to patients showing low lymphocyte counts (CD4 lymphocytes below 200/mm3 or total lymphocytes below 400/mm3) and prophylactic acyclovir to patients with low lymphocyte counts and habitual herpetic eruptions, as well as lamivudine as prophylaxis against hepatitis B reactivation in patients at risk.[9]

Gastrointestinal toxicities

Due to its activity against rapidly dividing cells, the inner lining of the gut is highly affected by chemotherapy, resulting in gastrointestinal toxicities such as anorexia, inappetence, nausea, vomiting, gastro-intestinal cramps, and diarrhea; these affects are present in varying severity in nearly all cytotoxic drug regimens, but also in the newer targeted treatments.

Nausea and vomiting

Nausea and vomiting (N/V) are the most feared gastrointestinal toxicities related to chemotherapy administration. They are caused by systemic drug levels stimulating the “chemoreceptor trigger zone” in the brain stem as well as by direct stimulation in the gastrointestinal tract.

Table 1.5.3. Nausea and vomiting.

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric and/or fluid intake. Tube feeding, total parenteral nutrition, or hospitalization required	-
Vomiting	1–2 episodes separated by at least 5 minutes within 24 hours	3–5 episodes	6 or more episodes, tube feeding, total parenteral nutrition or hospitalization required	Life-threatening consequences urgent intervention required

In the era before setrons, the application of highly emetic drugs such as cisplatine at a dose of 100 mg/m2 was only possible after applying high-dose metoclopramide, corticosteroids and neuroleptics, and benzodiazepines with anti-emetic side effects at the price of deep sedation for several hours.

Setrones, 5 HT serotonine antagonists, and the more recently available NK-1 antagonists are highly effective anti-emetic drugs. Their routine use in emesis prophylaxis has positively changed the practice of chemotherapy administration. In fact, on our wards, the piles of pans for vomit on each bedside table disappeared. A second effect was that patients' nutrition was no longer interrupted for several days during chemotherapy cycles; instead, they could even eat meals on the days of chemotherapy administration. This helps patients maintain their weight and hopefully their muscular mass.

Late nausea and vomiting occur 72 hours or later after chemotherapy administration and are still difficult to treat. The causes of this late toxicity are probably related to tissue damage by the chemotherapeutic drugs. Therefore continuing with anti-emetics, particularly with the neuroleptic drug olanzapine and eating a bland diet for several days after chemotherapy is probably helpful against late emesis.

The third mechanism of N/V is related to negative experiences with chemotherapy or simply the fear of it. Anticipatory nausea and vomiting occur even before drugs are administered and of course needs psychoneural interventions and psychoactive drugs for prevention. Therefore oncologists try to avoid the formation of anticipatory nausea by informing the patients about the management of side effects, supporting them, and by effective anti-emesis medication.

Mucositis

Among the tissues most affected by cytotoxic chemotherapy are the rapidly dividing barrier tissues forming the gastro-intestinal mucosas. This may be mild in most chemotherapeutic regimens used for solid tumors, but might lead to extensive GI ulcerations in regimens used against acute leukemias or in case of radiochemotherapy.[10] Mucositis may be extremely painful and lead to dehydration, malnutrition, and even to GI ulcerations. Adequate pain management, tube feeding, or, more appropriately, total parenteral nutrition, should help overcome this usually short-term but serious toxicity.

Diarrhea

Diarrhea associated with chemotherapy is due to multifactorial damage on the gastrointestinal tract, including epithelial necrosis with accompanying excess mucous secretion, subsequent inflammation of the bowel wall, and a break down of the barrier function, associated with the loss of bodily fluid and proteins that favors infection with gut microflora. Irinotecan can cause delayed diarrhea, occurring more than 24 hours after infusion, which is due to the excretion of the active irinotecan metabolite SN38 into the lumen, causing diarrhea by its effects on the microbiome.

Diarrhea leads to loss of fluid and electrolytes that can rapidly exhaust patients when no adequate substitution is provided. Nausea and vomiting might aggravate the clinical severity of diarrhea, as do sarcopenia and asthenia. Diarrhea according to CTAE. V.4.0.

Table 1.5.4. Diarrhea

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Less than 4 Liquid stools per day; can be managed with **dietary** measures	4–6 liquid stools per day; limits IADL	7 or more liquid stools per day; Incontinence; necessitates hospital admission and iv administration of fluids; limits self care ADL	Life threatening; urgent intervention required	death

Adequate management of course includes giving information to the patient and his or her proxies about the frequency of diarrhea associated with the planned treatment regimen and adequate written information on preventive and therapeutic measures. The substitution of fluid, electrolytes, follows the same steps as for infectious diarrhea, as does medication with loperamide, a local acting opiod drug with minimal absorption. Four milligrams of loperamide are given as a starting dose, followed by two milligrams after every unformed stool. If diarrhea is not managed within 12–24 hours, the patient should be evaluated by a physician and intravenous substitution of fluids, administration of octreotides, and/or antibiotics should be evaluated.[11]

Fatigue

Fatigue is one of the most common and most burdensome symptoms of cancer. Fatigue is defined as tiredness and a feeling of exhaustion that is not adequately relieved by sleep. It affects cancer patients before diagnosis, during therapy, and may persist for years after the successful eradication of the tumor. The biological mechanisms of fatigue are not yet fully elucidated, but fatigue seems to be associated with systemic levels of inflammatory cytokines such as CRP, IL-1, TNF alpha, and Il-6 that may persist after tumor therapy.[12]

As fatigue may be present even before tumor treatment, it would be interesting to record the timing of the individual amount of fatigue in relation to chemotherapy. To achieve this, staying at the exact definition of fatigue grading and using diaries or electronic recordings appear more

reliable than recall after the therapy period. Fatigue grade 2 may impede ADL, whereas fatigue grade 3 might even interfere with ADL, hindering patients dressing or eating. Recording the severity of fatigue in relation to the administration of chemotherapy regimens would allow us to understand how much fatigue is caused by the treatment and how much is related to the tumor burden.

Drug therapies against fatigue—for example methylphenidate—were not convincing in the past; the only successful measure is to increase physical activity to overcome fatigue and reduce the causative levels of inflammatory cytokines at least partly, as demonstrated in patients with a variety of tumors, such as breast cancer, prostate cancer, and colon cancer, and also in primary brain tumors.[13]

Infertility, early menopause

There are acute and potentially permanent effects of cytotoxic drugs on fertility in males and females. The acute effects that last as long as significant levels of chemotherapeutic drugs persist in body fluids can be avoided by safe sex practices and probably cause no distress to patients. Patients need to be informed that pregnancy has to be avoided as long as chemotherapy is given, plus a "safety period" of a few months to allow recovery (seventy days for sperm production, theoretically one menstrual cycle for women).

However, chemotherapeutic drugs may cause permanent infertility. This occurs most frequently with alkylating agents, but may occur with other drugs, often when in relapsing disease several drug regimens are used consecutively or in women approaching the age of menopause. Premature menopause with symptoms of hot flushes, insomnia, and depression may occur.

It is of paramount importance to inform patients about this risk before starting chemotherapy and to offer professional fertility counseling. The preservation of either sperm or oocytes, or even of embryos, should be made available and patients should have enough time to consider these options.

Cardiac toxicity

Some drugs are associated with cardiac toxicity, allowing their use for a limited number of cycles and necessitating monitoring of cardiac function. Cardiac toxicity was first noticed with anthracyclines. Doxorubicine is still the most widely used drug—up to 450mg/m^2 to avoid cardiomyopathy.

Other substances with cardiac toxicity are older alkylating agents like cyclophosphamide and melphalan, docetaxel, the antimetabolite clofarabine, bevacizumab, Her-2 neu-targeting therapy like trastuzumab, to a lesser extent bortezomib, and some targeted agents like dasatinib, lapatinib, and sunitinib.

However, also antibodies targeting Her-2neu and the tyrosine kinase antagonist imatinib may also affect cardiac output negatively. Active surveillance of cardiac function, with measurement of cardiac output before starting the treatment and then in regular intervals, and questioning about cardiac performance are mandatory. Maintaining physical activity or instituting aerobic training during chemotherapy has been successful in many tumor entities to preserve physical performance.

Hepatic toxicity

In rare occasions, chemotherapy induces hepatic toxicity, causing the elevation of liver enzymes and inducing fatigue.[14] When liver toxicity does not resolve within a few days, this toxicity definitely mandates stopping the administration of the drug in question. Hepatic toxicity occurs in a low percentage of patients with alkylating agents, such as procarbacine, nitrosoureas, temozolomide, but also patients with targeted drugs like imatinib, or even with antibodies.

Hand-foot syndrome

Some cytotoxic drugs mainly anthracyclines, antifolates, and taxanes and targeted drugs with anti-VEGF effect may cause hand-foot syndrome or palmar-plantar erythrodysesthesia, manifesting as redness, swelling, and pain on the palms of the hands and soles of the feet, rarely also on the extensor side of the knees and elbows. Hand-foot syndrome may greatly impair the fine motor manipulations of the hands and walking. If not manageable by topical moisturizing exfoliant creams and pain medication with NSAR, dose reduction or the temporary or permanent stopping of the causative agent are needed.

Targeted therapies

With application of tyrosine kinase inhibitors a new spectra of side effects emerged. These small molecules target very selectively their respective target molecule—which usually is highly expressed on cancer cells but in

lower density is expressed in a wide variety of normal tissues. This implies that patients may experience variable multiorgan toxicity.

Imatinib

Imatinib was the first targeted drug to be introduced, in 1998, into clinical use to treat chronic myelogenous leukemia, and later also for gastrointestinal stromal sarcoma. It inhibits the Bcr-abl fusion protein, c-kit, PDGFR alpha and beta, and other tyrosine kinase inhibitors. Most patients tolerate imatinib for long-term use over years and toxicities remain mild and may resolve without dose reduction. But in a smaller proportion of patients, dose reductions, drug holidays, or termination of therapy is required.

The frequent side effects of imatinib include the formation of edemas in up to 60% of patients, which can be ankle edemas or swollen tear sacks, or very rarely pleural effusion, ascites, or brain edema; this is often spontaneously reversible or can be treated with diuretics. Patients may experience nausea (50%), skin rash (40%), fatigue (39%), headache (37%), gastric pain (35%), diarrhea (45%), joint pain (31%), and muscle cramps (47%) that should be treated symptomatically; mostly the toxicities are mild, the rate of severe side effects is usually less than 5%. Nevertheless, these rare, severe side effects may be responsible for stopping therapy with imatinib in affected patients. Rare cases of hepatic and cardiac toxicities have been reported.

Epithelial growth factor receptor targeting therapies

Several classes of blockers of receptors for epithelial growth factors have been developed and are approved for therapy in epithelial growth factor (EGF)–dependent neoplasm. The first TKIs belong to the group of reversible EGFR blockers, mainly gefitinib and erlotinib, whereas newer EGFR TKIS like afatinib and dacomitinib bind irreversibly to the active site of the kinase domain and the third generation EGFR TKI, osimertinib, overcomes resistance related to T790M-related mutation.

The side effects of EGFR TKIs are related to the inhibition of downstream pathways of EGFR, such as the MAPK pathway, inhibition of keratinocyte growth, local inflammation, and immune cell recruitment. This leads to acneiform rashes, which is accentuated with exposure to the sun in the uncovered and upper parts of the body, in the face, and on the scalp, upper chest, and back. Typically it begins with itching and sensory disturbances a few days after the start of therapy, followed by a papular,

then pustular eruption during the second week, with crusting in weeks four to six, and predisposes patients to infections with herpes simplex or with Staphylococcus aureus. Irreversible TKIs lead more than the reversible TKIS to periungual inflammation called paronychia and to involvement of mucous membranes, either oral mucositis alone or the involvement of the entire gastro-intestinal tract with diarrhea. The frequency of acneiform rash is up to 60% in patients treated with reversible TKIs and up to 90% in patients treated with second generation EGFR TKI.[15] Prevention includes protection from sun exposure, ointments with topical steroids, and systemic use of minocycline at 50–100 mg per day. The pruritus induced by EGFR TKI is mediated by substance P and can be inhibited by the neurokinine-1 inhibitor aprepitant.[16]

Anti VEGF directed targeted therapies

Targeting the neovasculature of tumors—one of the hallmarks of cancer—with the intention of reducing the availability of oxygen and nutrients for tumors while also decreasing the elevated intratumoral pressure and normalizing the blood flow within the tumors, thus improving the delivery of drugs, opened a new method of pharmacologic intervention in oncology. For some tumors, antiangiogenic therapy was a major breakthrough, among them most prominently renal cell carcinoma.

Sunitinib was the first targeted agent available from this group. It is a multikinase inhibitor, inhibiting receptors of VEGF2, c-Kit, PDGF-alpha and beta, CSF, and RET. Antiangiogenic treatment increased response and prolonged progression-free survival and overall survival in patients with renal cancer, GIST, and other malignant tumors.

However, antiangiogenic therapy shows a pattern of side effects. Many patients suffer from fatigue that has to be at least partly overcome with increased physical activity. Sunitinib inhibits the uptake of iodine into the thyroid gland and so decreases the synthesis of thyroid hormones, thus contributing to fatigue. Most prominent are the thrombocytopenia, leukopenia, cardio-vascular side effects with arterial hypertension, bleeding, wound dehiscence and hand-foot syndrome, diarrhea, nausea and vomiting, mucosal toxicity, yellow discoloration of skin, hair depigmentation, and xerosis. This impressive list demonstrates that therapy with angiogenic agents requires thorough patient information and skillful, regular monitoring.

The development of systolic hypertension is not yet fully understood but occurs as early as the first month of treatment and requires adequate antihypertensive medication. Urinary proteins and the plasma

level of endothelin-1 increase. Capillary microscopy showed a decrease of the microvascular diameter and increased tortuosity, compatible with a functional lack of nitric oxide. Furthermore, VEGF inhibition was found associated with lower transcription of endothelial nitric oxide synthetase, supporting a pivotal role for NO in this context.[17]

The inhibition of the formation of new vessels is associated with delayed wound healing and wound dehiscence observed in patients with antiangiogenic treatment, which necessitates stopping the drug one week before a planned surgical intervention and restarting it after surgery only after surgical wound healing and approval by the surgeon. In case of emergency surgery, the surgeon has to be informed about the increased risk of bleeding and wound healing.

When bevacizumab, an antibody targeting VEGF is used, the label instructions recommend withholding bevacizumab for at least 6 weeks before elective surgery and to wait 28 days (or until the wound is fully healed) after major surgery before restarting bevacizumab therapy.[18]

Another manifestation of impairment of wound healing is intestinal perforations observed in 1–2% of patients treated with bevacizumab, who require immediate hospitalization and eventually surgical intervention.

Proteinuria might be due to the depletion of VEGF synthesized by podocytes, which maintains the integrity of the glomerular mesangial cells and should be regularly monitored to allow stopping anti-angiogenic therapy before severe renal damage occurs. Moreover, arterial as well as venous thromboembolic events were slightly increased (RR 1.37; 95% CI, 1.10–1.70 [P=0.004] and RR, 1.29; 95% CI, 1.12–1.47 [P<0.001], respectively) in a great meta-analysis that pooled data from a total of 20,050 patients with a broad range of cancer types from 22 studies included in this analysis (10,394 in the bevacizumab group and 9656 in the control group).[19]

Antibodies in cancer therapy

The development of monoclonal antibodies targeting tumor-specific antigens or antigens overexpressed on tumor cell membranes improved the therapy of many malignancies. Anti-CD 20 antibodies like rituximab increased response rates and prolonged survival in B cell lymphomas. To name only a few, Cetuximab targets the epithelial growth factor receptor, and bevacizumab VEGF and trastuzumab target the Her-2neu antigen in breast cancer. Often at the first application of these antibodies, a complication named cytokine release syndrome (CRS), consisting of chills,

fever, hypotension, and tachycardia during or shortly after antibody infusion, is caused by the massive release of IL-6 and other cytokines from damaged cytokine-releasing cells like macrophages and monocytes and lymphocytes. Mostly, CRS can be managed with corticosteroids, antihistamines, and antipyretics as well as with fluid and oxygen support. A few patients (1%) require admission to intensive care and administration of an antibody directed against IL-6, such as tocilizumab, to interrupt the inflammatory process and avoid multi-organ failure.[20]

CRS also presents the main toxicity associated with chimeric antigen receptor T cells (CAR-T cells) that were developed for use in refractory T cell leukemias. Furthermore, patients treated with new bispecific antibodies or with CAR-T cells may develop neurologic toxicities with headache, tremor, seizures, impaired consciousness, and posterior reversible encephalopathy syndrome (PRES). The administration of such antibodies thus necessitates interdisciplinary management for the prevention and therapy of neurologic complications without interfering with the potential benefits of these therapies.

Checkpoint inhibitors

Antibodies targeting immune checkpoints and their ligands whose biological role is to limit immune responses are able "to release the brakes" of the immune system and to enhance the immune response against tumors. Starting with ipilimumab targeting cytotoxic T lymphocyte associated protein (CTLA4), which improved response rates and prolonged survival with the perspective of definite cures in patients with metastasized malignant melanoma, and continuing with antibodies like nivolumab and pembrolizumab, both of which targeted the programmed death receptor-1 (PD-1) that showed unprecedented responses in many solid tumors like melanoma, non-small-cell lung cancer, renal cell cancer, colorectal cancer, bladder cancer, and pharyngeal and laryngeal cancer, to name only a few, cancer therapy entered a new era. The new immune therapies raised the hopes of all patients and their proxies. They also brought a new spectrum of adverse events, inducing inflammatory effects and auto-immunity. Although most patients treated with the new antibodies may experience some auto-immune reactions, the rate of severe adverse events is much lower than with classical cytotoxic chemotherapy. Severe adverse reactions with immune checkpoint inhibitors occur in 10–40% with ipilimumab and less than 5% with anti-PD-1 treated patients, whereas severe hematologic toxicity occurs in more than 50% of treated patients with common cytotoxic schedules.

Nevertheless, the immune related adverse events associated with immune checkpoint inhibitors (IRAE) are different and necessitate thorough monitoring and management, as potential life-threatening situations have to be recognized and prevented.

The most frequent auto-immune reactions are skin toxicities with maculo-papulous exanthemas or vitiligo; most respond to topical ointments and necessitate no interruption of therapy. Steven Johnson syndrome with toxic epidermal necrolysis was observed only exceptionally.

In contrast to adverse events following cytotoxic chemotherapy, after immune checkpoint inhibitors, an extensive diagnostic work-up ruling out bacterial infections or reactivation of viral infections and the eventual administration of adequate anti-infective therapy and of corticosteroids against auto-immunity should be started as well in case of colitis with diarrhea, as in cases of pneumonitis.

Colitis, that is, diarrhea complicated by abdominal cramps, and pain with or without enteral bleeding, occurs typically 5 to 10 weeks after starting mostly ipilimumab therapy and might in rare cases lead to perforation. Symptomatic therapy with i.v. rehydration and careful monitoring is recommended. A fecal calprotectin assay may allow one to distinguish immune-related enterocolitis from infectious causes. Anti-immune therapy starts with oral corticosteroids for grade II colitis, extending to systemic steroids in grade III cases, escalated with the anti-TNF antibody infliximab for refractory cases.

Pneumonitis should be suspected when the patient reports dyspnea and cough. A diagnostic work-up and in cases of hypoxemia, therapy of pneumocystis jirovecii pneumonia with co-trimoxazole, should be initiated immediately. Hepatitis may start after week 7 and may rarely require stopping the therapy.

Autoimmune endocrinologic side effects occur after week 9 in about 20% of treated patients and may involve all endocrine glands. Most frequently, hypothyroidism appears and necessitates adequate hormonal substitution. Hypophysitis is a challenging diagnosis with unspecific symptoms such as fatigue, headache, generalized weakness, hypogonadism, hypotension, and electrolyte disorders. An MRI scan may show swelling of the pituitary gland; eye muscle paresis is less frequent than in pituitary adenomas. Clinical features of an adrenal insufficiency with lack of glucocorticoids and mineralocorticoids may be severe and even require ICU admission, but can be managed with hormonal replacement.

Many other auto-immune events touching other organs may occur in patients treated with checkpoint inhibitors, but less frequently. An awareness that any new symptoms may be due to auto-immune effects and

a thorough diagnostic and therapeutic work-up are essential for the management of the patients.

Contrary to hematological side effects, which can often be clearly defined, and for which several therapies are successfully used, the neurological and neuro-psychiatric side effects of therapy are often more vague, or less well defined, and management is usually symptomatic therapy. Management is often hampered because they seem minor in comparison with the treatment of the oncologic disease; thus, often they may be neglected. The prerequisite for this summary is the exclusion of directly tumor related or metastatic effects. This exclusion will be discussed in subsequent chapters, and emphasis will be given to symptomatic treatment.

As this book is devoted to the side effects of cancer therapies, the management of neurological effects will only be mentioned briefly and will be summarized from the perspective of symptomatic therapy. More detailed information will be contained within subsequent chapters.

Central nervous system (CNS) effects

Cognitive changes

Therapy related cognitive changes cover a wide spectrum from subtle changes, to the ill-defined "chemobrain,"[21] to more severe conditions that appear as either strategic brain lesions or even dementia. These conditions can be confused with fatigue (see above), apathy, and depression. The principles of treatment for seizures respond to the treatment of symptomatic epilepsy. If there seems to be an association with drug treatment, which is rare and unlikely, this will need to considered.

Rapidly developing encephalopathies can be caused by associated cerebrovascular events, infections, and the PRES syndrome, which occurs in "classical" chemotherapies, as well as in targeted therapies. At present, the development of encephalopathies and encephalitis due to immune check-point inhibitors are also a growing concern.[22]

Seizures—treatment

Seizures can be both tumor related and also related to treatment. Certain drugs such as ifosfamide and occasionally others cause encephalopathies and seizures. Non-convulsive seizures[23] can pose a difficult diagnostic issue.

Psychiatric issues

Psychiatric issues such as anxiety, depression, delirious states, and even psychosis can have a number of somatic backgrounds. Psychiatric manifestations, unrelated to somatic changes, can also manifest in any segment of the disease.[24] Relations with partners and caregivers can be at stake and psychiatric crisis can appear.

Psychiatric reactions/manifestations can appear not only in at stages of the disease, but also in all age groups. In particular, elderly persons, often due not only to general circumstances and multimorbidity but also to possible cognitive decline, are the most endangered patient group.

Peripheral nervous system (PNS) effects

Although PNS symptoms are frequent, and can reduce the QL, they are rarely life threatening, contrary to CNS effects.

Neuropathy

Chemotherapy induced neuropathy (CIPN) is usually a dose dependent cumulative neuropathy. It rarely causes motor dysfunction, but more often causes sensory symptoms, coordination difficulties, and pain to a variable degree. The practical effects of sensory loss are often underestimated. The loss of different qualities of perception causes unsteadiness ("trouble with walking"), falls, and clumsiness if the hands are affected. At present, all serious attempts to prevent CIPN have failed and it is very important not only to be aware of the deficits but also to prescribe symptomatic treatment. Physiotherapy and balance and gait training are frequently warranted, as well as counseling on footware, adaptation needs in the home, and awareness of balance and discoordination problems and podiatric interventions.[25]

Muscle cramps are frequent in neuropathies and result in focal muscle pain. Several drugs are used, but the evidence of their effect is low.

Myopathy

Muscle involvement is a far-reaching field. The most common myopathy is steroid-induced myopathy, which causes proximal leg weakness among other symptoms. This can be best avoided by careful administration of steroid therapy. Several drugs, such as gemcitabine and taxanes, cause

myalgia, which usually subsides after treatment. Rarely also rhabdomyolysis and the focal RT recall syndrome appear. The direct effect of RT therapy on muscles is probably underestimated. The addition of RT damage to surrounding (adjacent) tissues is characteristic of radiofibrosis syndrome.[26]

Neuropathic pain

In the management of neuropathic pain the most frequent therapy related issues are painful neuropathies. Their management is dominated by the self-descriptions of patients (several tools are available), discussion of the symptoms, and usually anticonvulsants, antidepressants, and opioids are used. The evidence for the use of combinations is low, and other types of intervention have even lower levels of evidence. Pain, however, is a serious problem, and neuropathic pain needs specific treatment considerations.

Considering deafferentation pain, damage to peripheral nerves, such as the nerve plexus of other large nerve structures, needs to be mentioned. Also, phantom pain after removal of an eye, breast, penis, or limb may occur. Therapies follow the experience and modes of the treatment of neuropathic pain. Increasingly, "surface" drugs are used.[27]

In addition to the drug therapy, local interventions, RT, and neurosurgical interventions are also available.

Immune therapies

There are rare and emerging effects due to immune therapies. This is a rapidly expanding issue, which at present can only be discussed according to individual reports and small series. Immune checkpoint inhibitors can exacerbate pre-existing autoimmune diseases (e.g., myasthenia) as well as induce CNS and neuromuscular autoimmune diseases. The therapies are often immune-modulatory, which can cause conflicts with cancer therapy. Recently, comparisons with the development of immune therapy induced autoimmune diseases and paraneoplastic neurological diseases have also been discussed.[28]

Conclusion

Reading this summary of potential adverse events evidently provokes the question of whether the risks of cytotoxic therapy are worth taking, whether the potential benefits outweigh all the potential adversities; whether these therapies are still the only way out of a clinical situation or

whether there are alternative options. Answering such questions at the level of the "state of the art" is a challenging but near daily situation for medical oncologists. Of course, the information given to the patient will include all options that are "state of the art," including participation in therapeutic trials and present alternatives with targeted therapies or immune therapies whenever such options exist.

Building trust that the team will support the patient to overcome this difficult time and that the therapy has been well chosen is essential. Listening to the patient, answering questions and building a safety network with social support and home care can greatly facilitate tumor therapy.

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CHAPTER 1.6

IS THERE SOMETHING ELSE?

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Abstract

Patients with cancer may develop a wide range of clinical manifestations not directly correlated to growth of the primary tumor or to the development of metastases.

An immune attack on the tumor can trigger an immune response cross-reacting with antigens expressed by the central and peripheral nervous system, thus generating a number of complex paraneoplastic neurological syndromes.

Tumors can also produce many hormonal substances that have a systemic effect and account for a variety of paraneoplastic endocrine syndromes.

Knowledge of paraneoplastic syndromes is fundamental in the clinical approach to patients with cancer and to patients developing complex neurological and endocrine manifestations. Prompt recognition may help the correct management of relevant clinical manifestations and result in the detection of an occult tumor at an early stage.

Keywords: paraneoplastic neurological syndromes, paraneoplastic endocrinological syndromes, onconeural antibodies

Introduction

There are several clinical conditions that can affect patients with cancer, which are usually rare but very disabling; they can often direct an early diagnosis of cancer. These are paraneoplastic neurological syndromes and endocrine syndromes. In 2 out of 3 cases, paraneoplastic neurological syndromes precede the diagnosis of cancer; thus, the detection of onco-neuronal specific antibodies could direct the diagnostic work-up to specific tumors since there is a strict correlation between antibodies and cancer. Furthermore, clinical syndromes deriving from the neoplastic secretion of peptides and hormones may be the first manifestation of a tumor. Their recognition may help the correct management of the relevant clinical manifestations; moreover, a timely diagnosis may result in the detection of an occult tumor at an early stage.

Paraneoplastic Neurological Syndromes

Paraneoplastic neurological disorders (PNS) represent a number of characteristic syndromes that are associated with systemic cancer, but without the invasion of tumor cells into the nervous system or opportunistic infections of the nervous system.[1] They result from an immune response to the tumor which cross-reacts with "onconeural" antigens expressed by the nervous system. However, making a certain diagnosis of PNS is difficult, as at the time of presentation a tumor cannot be found in many patients with possible PNS. A search for the underlying cancer can be frustrating as the tumor mass in most patients is small and hard to detect. Moreover, neuro-imaging or other ancillary techniques for establishing the diagnosis are often normal or non-specific. This combination of factors has made it difficult to establish a reliable diagnosis of PNS. This is all the more important considering that in the majority of cases, these syndromes run a subacute course and may leave the patient incapacitated within weeks, without much hope of neurological improvement later on. Treatment attempts are often initiated once irreversible neurological loss has come about and this inevitably results in the failure of the therapy.

This untoward sequence of events has changed since the detection of anti-neuronal antibodies that are associated with PNS.[2] These antibodies can be identified in serums and provide the opportunity for an early diagnosis of PNS. Since the detection of these auto-antibodies, the field of PNS has evolved rapidly and resulted in the identification of a number of specific auto-antibodies, together with the identification of the genes that

express the corresponding onconeural proteins. Moreover, production of recombinant proteins representing these antigens has enabled routine laboratories to detect auto-antibodies in the serum of patients, leading to improved diagnosis and better patient management. However, it must be recognized that these antigens are all intracellular proteins and the antibodies directed against them are not pathogenic.

It has become clear that some patients with very similar clinical presentations do not have the typical onconeuronal auto-antibodies. These patients instead have autoantibodies against cell-surface antigens, rather than against intracellular antigens, and the patients often respond very well to immunotherapies designed to reduce antibody levels.[3] These antibodies are directed against surface neuronal antigens like leucine-rich glioma inactivated 1 (LGI1), N-methyl-D-aspartate (NMDA) receptors, or glycine receptors.[4–9] Although ovarian tumors are common in patients with NMDAR antibodies, they are not invariable, and many neuronal surface-antibody-positive patients do not have tumors. Some of the diseases are chronic and others are monophasic; however, they often leave the patient with substantial disability if untreated.

We briefly describe the most important syndromes; the diagnostic criteria of PNS have been described by Graus in 2004.[10] For encephalitis associated with neuronal surface antibodies, which in a proportion of cases are paraneoplastic, diagnostic criteria have been established in a consensus paper in 2016.[11]

Paraneoplastic limbic encephalitis

The term limbic encephalitis (LE) is used to describe patients presenting with memory loss, temporal lobe seizures, and psychiatric symptoms, usually running a subacute course. Currently the diagnosis no longer depends on pathological confirmation of inflammation involving the limbic system. It relies on the clinical picture of the subacute onset of working memory deficits, seizures, or psychiatric symptoms combined with the demonstration of MRI or 2-deoxy-2-[F-18] fluoro-D glucose positron emission tomography (FDG-PET) abnormalities in the temporal lobes, and the frequent presence of inflammatory changes in the cerebrospinal fluid or temporal epileptic activity found by electroencephalography. The diagnosis of paraneoplastic LE is aided by detection in the serum and CSF of autoantibodies directed to intracellular antigens (Hu, Ma2, amphiphysin, and CV2/CRMP5) or surface antigens (anti-LGI1, anti-CASPR2, anti-AMPAR, anti-GABAbR).[12] The neurological presentation typically antedates the diagnosis of cancer. The

most commonly associated tumors are SCLC, testicular cancer, thymoma, and breast cancer.[13]

Paraneoplastic encephalomyelitis

In paraneoplastic encephalomyelitis (PEM) more than one part of the CNS is involved, leading to a combination of cerebellar, cerebral, brainstem or spinal cord signs, or dysautonomic or sensory neuropathic signs. In many cases, however, one affected part of the CNS causes the majority of the neurological signs, as limbic or brainstem encephalitis or as a cerebellar syndrome.[14–15] The most frequently associated tumor is small-cell lung cancer (SCLC) which occurs in about three-quarters of patients with PEM or SSN. An anti-neuronal nuclear antibody reacting with a 38–40 kD protein on Western immunoblotting on nuclear extracts, designated anti-Hu, is detected in these patients.[16–17] Detection of this antibody is now used as a specific diagnostic marker for both PNS and underlying malignancy. In about 80% of patients who harbor the anti-Hu antibody, SCLC can be identified.[18–20] In anti-Hu positive patients with PNS and SCLC, 95% of patients have tumor activity limited to the chest. This indicates that the tumor-load of SCLC associated with PNS is smaller than usually seen with SCLC. Neurological asymptomatic patients with SCLC can harbor low-titers of anti-Hu antibodies and smaller tumors are found in these patients as compared with ones with SCLC with no anti-Hu antibodies.[17] Other antibodies have been identified in individual cases, particularly with limbic and other forms of PEM, as anti-CV2/CRMP5[21] and anti-Ta.[22]

Sensory neuronopathy

A paraneoplastic or subacute sensory neuropathy (SSN) may be the only clinical phenomenon of a PNS or may be accompanied by encephalomyelitis. The antibody and tumor profiles are very similar to those of PEM. However, as in most of these syndromes, a tumor may never be found, and evidence is starting to emerge of treatment responsiveness. It will be important to determine whether there are cell surface antigens involved in this painful and debilitating condition, and to begin to diagnose appropriately the non PNS (NPNS) forms for improved treatment.

Subacute sensory neuropathy, first described by Denny-Brown in 1948, is the effect of the destruction of sensory neurons in the dorsal root ganglia by lymphocytes.

The neuropathological hallmark of paraneoplastic SSN is a severe "dropout" of primary sensory neurons in the dorsal root ganglia. Neuronal loss is diffuse but patchy and asymmetric, reflecting patients' clinical presentation. Large-diameter neurons are preferentially lost. Remaining neurons occasionally show nonspecific degenerative changes. There is a highly variable degree of infiltration by T and B lymphocytes, plasma cells, and macrophages, often in a perivascular distribution. Severe depletion of myelinated fibers is present in the dorsal columns, posterior nerve roots, and peripheral sensory nerves, believed to be secondary to the loss of the dorsal root.[23]

Most patients have abnormal cerebrospinal fluid (CSF, including elevated protein, mild mononuclear pleocytosis, elevated IgG index, and/or oligoclonal bands, although at least 10% of patients have normal CSF. Electrodiagnostic studies in paraneoplastic SSN characteristically show a severely reduced amplitude or a complete absence of sensory nerve potentials, with normal or only slightly reduced sensory nerve conduction velocities when a response can be elicited. Most patients show at least some electrophysiological abnormalities in motor nerve conduction studies, with or without symptoms of a mixed sensorimotor polyneuropathy; however, motor conduction studies are almost always less affected than sensory nerve studies.

When considering the differential diagnosis of paraneoplastic SSN it is important to keep in mind that patients generally have severe sensory deficits, areflexia, and sensory gait ataxia. In patients without a known cancer diagnosis, the differential diagnosis of sensory neuronopathy or severe sensory neuropathy includes dorsal root ganglionitis associated with Sjogren's syndrome, idiopathic sensory neuronopathy, and sensory neuropathy associated with anti-disialosyl ganglioside antibodies. In patients with a known neoplasm, the differential diagnosis also includes sensory neuropathy caused by cisplatin or paclitaxel therapy.

Although this type of neuropathy occurs with different tumors, small-cell lung cancer accounts for 70–80% of cases.[20] Most patients have anti-Hu antibodies, which have 99% specificity and 82% sensitivity for the diagnosis of cancer in patients suspected to have SSN.[2]

Paraneoplastic cerebellar degeneration

Paraneoplastic cerebellar degeneration (PCD) can be seen with ovarian and breast cancer, small-cell lung cancer, and Hodgkin's disease.[24–30] It is estimated that at least 50% of all middle-aged patients who develop a subacute cerebellar disorder will go on to harbor a tumor within a few

years. Clinically, the disorder is characterized by subacute development of a pan-cerebellar dysfunction and pathologically by selective loss of Purkinje cells without inflammatory infiltrates. In 1983, an antibody specifically staining the cytoplasm of Purkinje cells and deep cerebellar nuclei was independently found by Greenlee and by Jaeckle and co-workers in patients with gynecological tumors and PCD, but not in control series.[25],[31] On Western immunoblot the auto-antibody reacted with a 34–38 kD and 62–64 kD protein using protein extracts of isolated Purkinje cells.[26] In total, about 40% of patients with PCD would harbor autoantibodies against Purkinje cells, and consequently 60% of patients with clinically proven PCD are Purkinje cells-antibody negative.

Anti-Purkinje cell antibodies were also found in PCD associated with Hodgkin's disease; these react with a different antigen called Tr.[32] It yields a more fine-speckled cytoplasmic staining of cerebellar Purkinje cells on immunohistochemistry. A paraneoplastic cerebellar form of ataxia due to autoantibodies against a glutamate receptor has also been described.[33]

Approximately 50% of patients with PCD and SCLC harbor high titers of anti-Hu antibodies. Those remaining are likely to have anti-VGCC antibodies with associated Lambert-Eaton myasthenic syndrome (LEMS). The P/Q subtype of VGCC has also been described on the Purkinje and cerebellar granule cells of the cerebellum[34] suggesting that anti-VGCC in PCD may be directed against calcium channels on cerebellar cells, but at levels that are not detected by immunofluorescence.

PCD represents the second most frequent paraneoplastic manifestation after peripheral neuropathy. This group encompasses only cases for which the diagnosis of definite PNS can be achieved according to the published criteria.

Opsoclonus-myoclonus syndrome

Opsoclonus is a disorder of saccadic eye movements consisting of involuntary arrhythmic and multidirectional conjugated saccades. The opsoclonus is often associated with truncal ataxia, dysarthria, myoclonus, vertigo, or encephalopathy and may accompany PCD. Opsoclonus-myoclonus syndrome (OMS) occurs primarily in children as a self-limiting disorder and can be the result of a viral infection of the brainstem, but 50% of children have a paraneoplastic form associated with a neuroblastoma.[35] In adults, OMS occurs less frequently as a paraneoplastic disorder. The two most commonly associated tumors are lung and breast cancer, although other tumors can be involved.

In association with breast carcinoma, a specific anti-neuronal nuclear antibody in patients with paraneoplastic OMS has been identified. This antibody was designated anti-Ri and resembles immunohistochemically the Hu antibody by reacting with virtually all neuronal nuclei of the CNS. Western blotting, however, clearly distinguishes it from anti-Hu antibodies by reacting with two separate bands of 53–61kD and 75–84 kD.[36] OMS in adults also has a non-paraneoplastic form. In younger adults (often females between 30–50 years) without evidence of cancer, an acute monophasic condition can occur, likely following from a viral infection. Since breast tumors are an important potential cause of OMS in this age group, it is important to be able to distinguish the non-paraneoplastic forms of both adult types of OMS from those associated with tumors.

Lambert-Eaton myasthenic syndrome

The existence of both PNS and NPNS forms of syndromes is best illustrated by the Lambert Eaton myasthenic syndrome (LEMS). LEMS is an autoimmune disorder of neuromuscular transmission characterized by a reduction in the nerve-stimulated release of acetylcholine from the presynaptic nerve terminal. It associates with SCLC in 60% of patients.[14] The disease is caused by IgG autoantibodies against the P/Q subtype of voltage-gated calcium channels (VGCC) on the presynaptic motor nerve terminals, which is a neuronal membrane ion channel. Since its first discovery in the 1950s, it has been clear that there is a non-paraneoplastic form with the same antibodies to VGCC. Identification of both forms is now made by detection of VGCC antibodies; the test has been made widely available in recent years.

Paraneoplastic endocrine syndromes

A frequent manifestation of cancer is the production of hormonal substances by tumors determining specific clinical syndromes that are termed paraneoplastic endocrine syndromes (PES).[37–38] They comprise a wide range of clinical manifestations and are associated with a large number of hormonal products, especially peptides.

Hypercalcemia

Hypercalcemia is a more common paraneoplastic endocrine syndrome, especially in breast, renal, and lung cancer, and hematologic malignancies like multiple myeloma.[39]

Common clinical manifestations of hypercalcemia include constipation, nausea, polyuria, polydipsia, and neurological symptoms like confusion, weakness, and lethargy.

The mechanisms of hypercalcemia in patients with cancer include the local release of osteoclast-activating factors by bone metastases (especially breast cancer), increased gastrointestinal absorption of calcium determined by the increased production of calcitriol, tumor secretion of a parathyroid hormone-related protein (PTHrP), and, more rarely, by the ectopic secretion of parathyroid hormone itself. The measurement of serum-intact parathyroid hormone (iPTH) and PTHrP permits differentiation between hyperparathyroidism (high-serum iPTH), paraneoplastic hypercalcemia caused by the secretion of PTHrp, and hypercalcemia derived from metastases (low-serum iPTH and low- or normal-serum PTHrP).

Inappropriate secretion of antidiuretic hormone

Hyponatremia due to SIADH is found in 15% of SCLC and has also been reported in other neuroendocrine tumors or other malignancies. Most patients who develop hyponatremia are asymptomatic. In cases where the serum sodium concentration falls rapidly below 120 mEq/L, altered brain edema with mental status and seizures may develop. Fluid restriction associated with the administration of sodium chloride is usually the more effective therapy. Vasopressin receptor antagonists are also available for chronic SIADH.

Paraneoplastic Cushing's syndrome

Ectopic ACTH production is found mainly in association with small-cell lung cancer (SCLC); the less-frequent neoplasms are pulmonary carcinoid, thymoma, medullary thyroid carcinoma, islet cell malignancy, and pheochromocytoma. More rarely, ACTH production can be determined by tumor production of a corticotropin-releasing hormone (CRH).

Patients develop clinical features of Cushing's syndrome, such as centripetal obesity, muscle atrophy, hypertension, and diabetes. Hypokalemia and hypochloremic alkalosis are also frequent findings.

Laboratory diagnosis is based on high ACTH levels, non-suppression of morning cortisol after a dexameathasone suppression test, and elevated 24-hour urinary cortisol levels.

Human chorionic gonadotropin production

Production of human chorionic gonadotropin (HCG) is found in trophoblastic tumors (e.g., choriocarcinomas, testicular embryonal carcinomas, and seminomas) and more rarely in lung and pancreatic cancer.

Clinical manifestation depends on the age of the patient. In younger children, precocious puberty can be found whereas in adult males gynecomastia is common.

Hypoglycemia

Paraneoplastic hypoglycemia is due to the secretion of the insulin-like growth factor II (IGF-II) (a peptide activating the insulin receptor) in extra-pancreatic tumors, especially sarcomas. Hypoglycaemia occurs especially in the fasting state with diaphoresis, confusion, and lethargy.

Another mechanism of hypoglycaemia consists in overproduction of insulin in islet-cell malignancy especially when hepatic metastasis develops.

Other hormones

A variety of other hormones can be produced by cancer resulting in several syndromes. Growth hormone (GH) and growth-hormone-releasing hormone-determining acromegaly is a rare finding that has been reported especially in pancreatic endocrine tumors and SCLC. Prolactin ectopic secretion determining galactorrhea has been reported in carcinoma of the lung and kidney. A variety of peptides, like insulin (see above), gastrin, glucagon, and vasoactive intestinal peptide (VIP), usually secreted by pancreatic endocrine tumors, are rarely also produced by non-endocrine neoplasms.

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PART 2

CHAPTER 2.1

TOOLS AND METHODS TO ASSESS THE FOCAL EFFECTS OF CHEMOTHERAPY ON THE CENTRAL NERVOUS SYSTEM

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Abstract

Chemotherapy can be toxic to the central nervous system (CNS), as the systematical or intrathecal administration of several widely used antineoplastic agents commonly results in the development of central neurotoxicity. The clinical dysfunction can be presented with more generalized symptoms, such as a decline in cognition, fatigue, and mood changes, or with focal CNS damage, including, among others, seizures, stroke, motor symptoms, and cerebellar dysfunction. Increasingly, late focal effects, such as the SMART, ALERT, and PIPG syndromes have been noted. The assessment of damage to the function of the CNS as a result of chemotherapy administration remains a challenge. On the basis of the patients' symptoms and needs, series of tests can be chosen to provide an optimal tool. Available data show that the proper assessment of chemotherapy-induced focal CNS dysfunction is a daily practice challenge, since its early recognition is mandatory to limit its severity through appropriate treatment modification and other specific interventions. However, the accurate evaluation of temporary and long term chemotherapy-induced central

neurotoxicity has not been comprehensively addressed, and its grading still represents an unmet clinical need.

Keywords: assessment, CNS neurotoxicity, chemotherapy, focal effects, outcome measures

Introduction to neurological assessment scales in neuro-oncology

Neurological assessment scales are useful tools to try to reliably and accurately quantify the severity of a neurological disease as well as its progression. Their immediate objective is to translate the set of neurological alterations present in each patient into an overall score that quantifies the deficit, in order to objectively and dynamically assess the intensity of the neurological deficit at a specific moment and allow comparisons to be made, assess the effectiveness of interventions or treatments, and try to predict the evolution of a neurological situation (prognosis). In addition, transforming clinical language into numerical data allows the statistical management of data and the exchange of information with other professionals. A neurological scale must be specific to the pathology it evaluates, incorporating in a balanced way the neurological signs with the greatest effect on the prognosis and the signs of functionality and cognitive alteration that can best be correlated with functional recovery or patient autonomy.

The assessment instruments must comply with adequate psychometric properties, including in particular *validity* (it really measures what it intends to measure) and *reliability* (the results obtained are repeatable and similar when used by different researchers, with little intra- and inter-observer variability). Measures of the degree of consistency or concordance can always be expressed by a *correlation coefficient*, *responsiveness* (important when performing an intervention starting from a baseline), *feasibility* (ease of administration), and *comfort* (using it should be brief, without the need for special training, and it should be applicable inside and outside the hospital).

In neuro-oncology, the development of scales and their application have gone hand in hand with the development of clinical trials and the emergence of new treatments. The variables traditionally used on the effectiveness of treatments have been tumor size, overall or progression-free survival, or the physical toxicities (adverse effects) associated with these. In recent years, other objectives such as preservation or improvement of the quality of life or the maintenance of patient

functionality have been gaining ground; specific measures are required for their evaluation. The scale types most commonly used are functional assessment scales and quality of life questionnaires.

Functional scales

Functional scales inform us of the patients' ability to relate to the environment in which they operate, trying to measure what patients are able to do in daily life to compare it with what they were or could be able to do. Although, in general, these are simple and intuitive scales regarding patients' functional condition, they all share the same basic limitation, which is the subjectivity to which they are subject given that the scores require the clinical practitioner to interpret the activities that the patient can or cannot do.

Quality of life questionnaires

Health-related quality of life defines the impact of the disease on the life and well-being of the individual, from the personal and unique perspective of the affected person. In neuro-oncology, specifically, the morbidity associated with the brain neoplasm itself, the therapeutic techniques, and the palliative nature of most chemotherapy and radiotherapy treatments used in these patients makes the study of the quality of life a fundamental aspect in daily clinical practice for the treatment of these tumors. In this way, the guidelines of the different oncological societies[1] recommend the incorporation of quality of life tests or questionnaires in the assessment of patients and the efficacy of neuro-oncological treatments.

Neurological assessment scales

Neurological assessment scales are a more objective index that aim to measure the magnitude of the neurological deficit, being of greater utility to evaluate or monitor the recovery or compensation of a neurological deficit with a given treatment. In neuro-oncology, general scales have been used, such as the Neurological Performance Scale (NPS) designed by the MRC (Medical Research Council) (www.mrc.ac.uk).[2–3]

Among the limitations of all these scales, the imprecision of the definitions of many items stands out, as well as the inherent subjectivity in scoring the intensity of symptomatology, resulting, in our opinion, in an assessment that is always insufficient and not discriminative enough to correctly evaluate this type of patients. In addition, patients have a variety

of degrees of neurological as well as functional damage at the cognitive level due to the brain tumor itself and to oncological or symptomatic treatments (anticonvulsant drugs, corticosteroids).

The Neurologic Assessment in Neuro-Oncology (NANO) scale

The NANO scale is a standardized tool designed to measure neurological function in neuro-oncology, which was drafted by an international and multidisciplinary panel of physicians including neurologists, medical oncologists, radiation oncologists, and neurosurgeons with expertise in neuro-oncology as an objective and quantifiable metric of neurologic function evaluable during a routine office examination in brain tumor patients. The scoring assessment is based on direct observation and testing performed during clinical evaluation and is not based on historical information or reported symptoms. The NANO scale is conducted and reported by a trained health care professional who evaluates the patient, and include 9 neurologic function domains likely to be affected by supratentorial, infratentorial, and brainstem lesions, selected on the basis of the most common clinical features identified in patients with brain tumors: gait, strength, upper-extremity ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior. Each domain is subdivided into 3 or 4 levels of function with scores that range from 0 to 2 or 0 to 3. A score of 0 indicates normal function, while the highest score indicates the most severe level of deficit for that domain.[4–5]

Importantly, the numerical cumulative score obtained in the NANO scale can be compared over time to determine neurological response, stability, and progression according to whether the clinical patient status is stable, better, or worse as part of the overall response assessment. Neurologic response is defined as a ≥2 level improvement in at least one domain without worsening in other domains from a baseline or best-level of function that is not attributable to change in concurrent medications or recovery from a comorbid event. Neurologic stability indicates a score of neurologic function that does not meet any of the following criteria: neurologic response, neurologic progression, non-evaluable, or not assessed. Neurologic progression is defined as a ≥2 level worsening from a baseline or best-level of function within ≥1 domain or worsening to the highest score within ≥1 domain that is felt to be related to underlying tumor progression and is not attributable to a comorbid event or change in concurrent medication. Of note, an assessment of neurologic progression does not require evaluation of a minimum number of domains of the NANO scale if any of these conditions is met. Importantly, “non-

evaluable" should be selected if it is more likely than not that a factor other than underlying tumor activity contributed to an observed change in neurologic function. Such factors may include changes in a concurrent medication, such as corticosteroids, sedatives, narcotics, or anti-epileptic agents; acute or chronic adverse events related to therapeutic interventions; or a comorbid event such as a toxic-metabolic encephalopathy, post-ictal state, stroke, and so on.

One of the main advantages of the NANO score is that it can be performed easily and rapidly, with a median assessment time of 4 minutes: most patients (75%) can be assessed in less than 10 minutes, and therefore be routinely assessed using this scale during an office examination. In a prospective international multicenter, multidisciplinary pilot study, the NANO scale was reported to have a high interobserver (>90%) agreement when used in prominent neuro-oncology centers where clinicians have significant experience caring for brain tumor patients.[4–5] Increasing experience in general community practice is being reported,[6–7] especially in the setting of works focused on investigating the role of the NANO scale in predicting the prognosis of patients with glioblastoma. Despite the favorable results suggesting the superiority of the NANO score compared with standard prognostic scores (KPS, ECOG) in predicting the survival of glioblastoma patients, the retrospective nature of these studies, which also assessed the NANO score retrospectively, precludes establishing its prognostic role at the moment.

Unfortunately, the currently designed NANO scale was developed specifically for adults (≥18 years of age) and no pediatric population was included in the inter-reliability study to validate it. As has been said, the NANO scale was specifically developed to assess brain tumor patients. The RANO leptomeningeal metastases (LM) working group has modified the NANO scale for patients with LM to be used as part of the response assessment. Ten domains are included: gait, strength, sensation, vision, eye movements, facial strength, hearing, swallowing, level of consciousness, and behavior. Similarly, each domain is scored from 0 to 3 or 0 to 2 on the basis of the level of function.[8]

Tools and methods to assess specific focal CNS neurotoxicities

Aphasia

Language impairment may be seen in patients with CNS toxicity due to anticancer-treatment, in the setting of several problems such as seizures,

stroke, and/or encephalopathy.[9] Dysphasia and aphasia result in difficulty in understanding or producing language (words, sentences, conversation), which also includes reading and writing. Usually the term dysphasia describes difficulty and the term aphasia describes impossibility, but in many neuro-oncologic works both terms are used indistinguishably. Intubated patients would be requested only to read and write for assessing language impairment.

- The assessment of language disorders includes the ability of the patient to understand and express that understanding, mainly by evaluation: fluency, nomination, repetition, and comprehension. Numerous questionnaires and scales to evaluate aphasia are available in the literature. To perform a comprehensive assessment of aphasia, the most commonly examination employed is the Boston Diagnostic Aphasia Examination (BDAE), currently on its third edition,[10] which was designed to diagnose aphasia and related disorders as a comprehensive assessment that could provide a basis for the diagnosis and typology of aphasias and for inferring the cerebral localization of neural damage. The BDAE evaluates language skills based on perceptual modalities (auditory, visual, and gestural), processing functions (comprehension, analysis, problem-solving), and response modalities (writing, articulation, and manipulation). Administration time ranges from 20 to 45 minutes for the shortened version but it can last up to 120 minutes for the extended version. Other comprehensive tests exist, such as the revised version of the Western Aphasia Battery (WAB-R™).[11]
- The above-mentioned scales, despite being very useful in providing detailed information regarding aphasia, are not useful in daily clinical practice in the outpatient and inpatient assessment of patients developing CNS toxicity. Alternatively, the gradation offered by non-specific general scales can be very useful for the early detection and daily follow-up of aphasia. For example, in the Scandinavian Stroke Scale, speech is graded in four grades as follows: (1) no aphasia, (2) limited vocabulary or incoherent speech, (3) more than yes/no, but no longer sentences, and (4) only yes/no or less.[12] Similarly, also in four grades, in NIHSS (see the stroke section) the item aphasia is graded according to severity: no aphasia; mild-moderate aphasia (some obvious changes, without significant limitation); severe aphasia (fragmentary expression, inference needed, cannot identify materials); mute/global aphasia (no usable speech/auditory comprehension). In the toxicity scale

CTCAEv5, the impairment of verbal communication skills is termed as dysphasia. Three scores according to severity based mainly on the ability to communicate are defined: grade 1, awareness of receptive or expressive characteristics, ability to communicate not impaired; grade 2, moderate receptive or expressive characteristics, ability to communicate spontaneously impaired; grade 3, severe receptive or expressive characteristics, ability to read, write, or communicate intelligibly impaired (CTCAEv5).[13]

- The NANO scale, previously described, divides language disturbance into four well-defined grades, a score of 0 describes normal and 1–3 describe abnormal language; 1 point is given when the patient easily conveys meaning to the examiner; 2 points are given when there is difficulty conveying meaning to the examiner, and 3 points are given when the patient is mute or has global aphasia or is unable to convey meaning to the examiner. Examples of level 1 include word-finding difficulty and minor paraphasic errors/neologisms/word substitutions; however, the patient is able to form sentences. Level 2 includes the inability to form sentences, limited word output, or fluent language but empty speech.[5]

Ataxia and cerebellar dysfunction

Ataxia means an inability to coordinate voluntary muscular movements, which is symptomatic of some CNS disorders and injuries, and is not due to muscle weakness. Neuro-oncologic patients with acute or chronic CNS toxicity can present with ataxia of the eyes, upper or lower extremities and/or trunk, and can be explored by showing dysmetria by the undershoot or overshoot of the intended position with the hand, arm, leg, or eye, and gait ataxia. Traditionally, in neuro-oncology trials and daily clinical practice, ataxia is usually graded and reported according to oncological scales (CTCAEv5), the same as for most symptoms or signs, in three rates: grade 1. asymptomatic ataxia based on clinical or diagnostic observations only; grade 2, moderate symptoms limiting instrumental ADL; and grade 3, severe symptoms, limiting self-care ADL, and symptoms that require mechanical assistance.

However, in neurology, several rating scales have been defined to better evaluate the impairment of coordination of movements, balance, and gait. Among them is the International Cooperative Ataxia Rating Scale (ICARS), which is an outcome measure created in 1997 by the Committee of the World Federation of Neurology with the goal of standardizing the quantification of impairment due to hereditary ataxia.[12] The scale is scored

out of 100 with 19 items and 4 subscales of postural and gait disturbances, limb ataxia, dysarthria, and oculomotor disorders. Higher scores indicate higher levels of impairment. The estimated time a trained physician or technician will take to administer the test is 15–30 minutes. It has been validated for use in patients with focal cerebellar lesions. Some locations have recently employed it in brain tumor patients, especially in the pediatric population.[14] Unfortunately, ICARS is long and time-consuming and it becomes impractical in a wider clinical-practice context. Other alternative scales with fewer assessment items than the ICARS that are more useful for the daily assessment of ataxia have been developed. These include the Assessment and Rating of Ataxia (SARA) and the Brief Ataxia Rating Scale (BARS). Both have shown to be reliable and valid measures in determining the severity of ataxia in children with posterior fossa tumors. SARA is a clinical scale based on a semi-quantitative assessment of cerebellar ataxia on an impairment level. SARA has 8 items that are related to gait, stance, sitting, speech, the finger-chase test, the nose-finger test, fast alternating movements, and the heel-shin test. Each item ranges from 0, normal, to 4, up to 8 points, depending on the item, meaning at worst the inability to perform the function.[15] A Brief Ataxia Rating Scale (BARS) based on a modified form of the ICARS was performed in an attempt to both reduce redundancies of the ICARS and shorten and simplify the administration of ataxia outcome measures. The BARS provides a quantitative measure of the neurological examination and includes the assessment of 5 items: gait, the knee-tibia test, the finger-to-nose test, dysarthria, and oculomotor abnormalities; the total points are out of 30. Testing in both takes fewer than 15 minutes, approximately.[16]

In the NANO scale, ataxia is specifically addressed in two of the nine domains. The gait domain is recommended to be assessed by walking at least 10 steps and is scored as 0, normal; 1, abnormal but walks without assistance; 2, abnormal and requires assistance (companion, cane, walker, etc.); and 3, unable to walk. Ataxia of upper extremities ranges from 0, able to touch finger to nose without difficulty; 1, able to touch finger to nose with difficulty; and 2, unable to touch finger to nose. The score is based on the best response of at least 3 attempts. Falls and poor balance have been shown to be associated with chemotherapy toxicity in older patients with cancer, frequently associated with sensory ataxia. The American Society of Clinical Oncology (ASCO) guidelines for geriatric oncology recommend screening for falls in all community-dwelling older adults aged 65 and over by a simple one-item screening tool: “How many falls have you had in the previous 6 months (or since your last visit)?”[17]

Hearing loss

Hearing loss is a potential complication of platinum-based chemotherapy or radiation therapy.[9] Usually, assessed by the CTCAEv5, in addition to the subjective impairment noticed by the patient and limitations due to hearing loss, this gradation includes an objective assessment according to the changes in the audiogram. This text is scored as follows: when the patient shows a threshold shift of 15–25 dB (grade 1); >25 dB (grade 2), averaged at 2 contiguous test frequencies in at least one ear; >25 dB averaged at 3 contiguous test frequencies in at least one ear (grade 3); and a decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above) (grade 4). Obviously, this gradation requires a baseline assessment with an audiogram. When absent, severity gradation is based on the subjective perception and/or the need for intervention.

In elderly people, many instruments are available to identify the impact of hearing loss on daily life and carrying out hearing-dependent activities, including the Hearing-Dependent Daily Activities Scale, which is a clinically useful scale designed for use in primary care to easily identify hypoacusia,[18] and the Hearing Handicap Inventory for the Elderly (HHIE), which has been developed as a self-assessment tool to assess the impact of hearing loss on the emotional and social adjustment of older patients. It consists of a 13-item subscale based on emotional side effects and a 12-item subscale exploring social and situational consequences. The HHIE score ranges from 0 to 100 with a cut-off score of ≥43 indicating a significant perceived handicap. Scores ranging from 17 to 42 indicate a mild to moderate perceived handicap. The HHIE is available in many languages and may be completed in a few minutes, making it a good tool to be considered in neuro-oncologic patients for screening hypoacusia when suspected.[19] The Whispered Voice Test is another simple and accurate test for detecting hearing impairment, which, joined to the HHIE, has been recently employed in one study of cancer patients undergoing a comprehensive geriatric assessment.[20]

Myelopathy

Toxic myelopathy is among the most devastating complication in the setting of oncologic treatment, usually as an early- or late- delayed complication of radiation therapy, or intrathecal administration of chemotherapy.[9] The American Spinal Injury Association (ASIA) Impairment Scales (AIS) is a universal and gold-standard classification tool for spinal cord injury based on a standardized sensory and motor

assessment with the most recent revised edition published in 2011.[12] It is a standardized examination consisting of a myotomal-based motor examination, dermatomal-based sensory examination, and an anorectal examination. On the basis of the findings of these examinations, an injury severity or grade and level are assigned. The exam is based on neurological responses, touch, and pinprick sensations tested in each dermatome, and the strength of the muscles that control key motions on both sides of the body. Muscle strength is scored on a scale of 0–5 according to the MRC, and sensation is graded on a scale of 0–2: 0 is no sensation, 1 is altered or decreased sensation, and 2 is full sensation. Each side of the body is graded independently. The AIS further classifies injuries into complete or incomplete spinal cord injuries. A complete spinal cord injury is defined as the absence of all motor and sensory functions, including sacral roots, distal to the site of injury. These injuries are designated as being Grade A on the AIS. Incomplete injuries are defined as those with some degree of retained motor or sensory function below the site of injury. These are graded B through E on the AIS. Patients with AIS Grade B injuries have some sensory function but no motor function. AIS Grade C injuries have a motor grade less than 3 below the neurologic level of injury while AIS Grade D injuries have a motor grade of at least 3 below the neurologic level of injury. Patients with Grade E injuries have normal motor and sensory examinations, but still may have abnormal reflexes or other neurologic phenomena. The Frankel Grade scale is a five-grade system of classifying traumatic spinal cord injury used in some oncologic works that does not include the level of neurologic injury in its classification, and which was replaced in 1992 by the ASIA Impairment Scale (AIS).

In neuro-oncology practice, the ASIA scale is mostly employed in the evaluation of neurological impairment and prognosis due to epidural spinal cord compression[21] or spinal tumors; however, it might also be a useful tool to rate spinal cord toxicity, instead of the less specific gradation in the CTCAEv5 scale that scores “myelitis” in five severity grades: grade 1, asymptomatic, mild signs (e.g., Babinski’s reflex or Lhermitte’s sign); grade 2, moderate weakness or sensory loss, limiting instrumental ADL; grade 3: severe weakness or sensory loss, limiting self-care ADL; grade 4: life-threatening consequences, urgent intervention indicated; grade 5: death due to spinal cord toxicity.

Myoclonus

In a cancer patient, a wide variety of drugs can cause myoclonus, including opiates, some chemotherapy agents (i.e., chlorambucil, ifosfamide), and antibiotics (i.e., β-lactams).[9] Recently, it has been described in the setting of novel therapies in hematology like CAR-T cell therapy. Myoclonus can appear isolated, focal, or generalized, and, frequently, in the clinical picture of encephalopathy.

Usually, no systematic gradation of myoclonus is performed in the neurological exam. However, typically in the setting of investigation or clinical trials, the main tool for assessing myoclonus is the Unified Myoclonus Rating Scale (UMRS).[22] It assesses the severity and characteristics of the disorder and the associated disability. The UMRS has 73 items, grouped into five sections: patient's questionnaire (12 items, scored from 1 to 5); myoclonus at rest (8 items for frequency and amplitude, scored from 0 to 4); stimulus sensitivity (17 items, dichotomous); myoclonus with action (10 items, scored for frequency and amplitude on a 5-point scale); and functional tests (5 items, scored from 0 to 4). It also includes a global disability scale, scored from 0 (normal) to 4 (severe), and two items assessing the presence (yes/no) and severity (from 0 to 3) of negative myoclonus. Components for evaluation of myoclonus-related sleep disorders are not included in this scale. The UMRS has satisfactory internal consistency and inter-rater reliability and is responsive to changes due to treatment. Another scale is the Myoclonus Evaluation Scale, which scores from 0 to 4 the abnormality and presence of myoclonus in several movements and in sustained posture.[23]

Parkinsonism

Parkinsonism is probably among the less frequent CNS toxicities. It has been described anecdotally with some chemotherapy agents like hexamethylmelamine, intravenous ARA-C, vincristine, 5-Fluorouracil (5-FU), and post-encephalitis VEB infection in hematopoietic cell transplantation.[9] Patients with radiation-induced dementia with leukoencephalopathy may develop gait ataxia, incontinence, and sometimes a phenotype of akinetic mutism with extrapyramidal signs resembling a parkinsonism.

In neurology, many scales have been developed during the past several decades to measure this kind of movement disorder. The Unified Parkinson's Disease Rating Scale (UPDRS), originally developed in the 1980s, has become the most widely used clinical rating scale for

Parkinson's disease (PD)[24] and it has also been applied for mass screenings for parkinsonism, that may include drug-induced parkinsonism.[25] UPDRS includes four subscales which cover mentation, behavior, and mood (subscale 1), activities of daily living (subscale 2), motor manifestations (subscale 3), and complications of therapy (subscale 4). Data for subscales 1, 2, and 4 are elicited from patients and caregivers, whereas data for subscale 3 is examination-based. The UPDRS subscale 3 has been shown to have good sensitivity and specificity for screening for toxic parkinsonism.[25]

The Hoehn and Yahr (H&H scale) staging is probably the most widely known evaluation of people with PD.[12] It is really a simple staging from 1 (unilateral involvement only) to 5 (wheelchair bound or bedridden unless aided) of the motor manifestations of PD, based upon examination of the patient, intended to reflect the degree of progression, which combines features of motor impairment and disability. However, the scale is not linear and may not even be ordered in rank, with some people having greater disability with stage 2 (with substantial bradykinesia but good stability on the pull test) compared with some that have been ranked as stage 3 (which fall on the pull test but have relatively mild bradykinesia and rigidity).Work focused on long-term CNS toxicity due to prophylactic cranial irradiation in SCLC have used the H&H scale for assessing the extrapyramidal symptoms and signs of radiation-induced parkinsonism.[26]

Seizures

Seizures are a frequent complication of brain tumor patients and/or are related with toxicity due to systemic and intrathecal chemotherapy, or radiation therapy, typically in the setting of radiation necrosis.[9] Seizure assessment may be defined according to: (a) diagnosis and classification, (b) severity, and (c) quality of life impact (QoL). The International League Against Epilepsy (ILAE) has proposed several systems of classifying seizures and epilepsy syndromes,[27] despite the fact that in neuro-oncology dividing seizures into secondarily generalized or focal (partial) is considered to be the most pragmatic.[28] Several QoL questionnaires have been developed to gradate the functional effect of epilepsy and its treatment(s).[12] In neuro-oncology, the presence of seizures is poorly addressed in the several HRQoL and symptom-burden scales commonly employed, including FACT-Br (questions: I have had seizures [rating 0–4]]; I am afraid of having a seizure [rating 0–4]); BN20 (Do you have seizures [yes/no]), and MDASI-BT (Your seizure at its worst [rating 0–10]).[28]

In daily clinical practice, the epilepsy burden is usually based on seizure severity, meaning frequency, intensity, and duration, and need for antiepileptic drug (AED) use. Until now, there has been no universally accepted standard scale for grading seizure severity in neurology practice. This is because most existing scales are limited by their lack of psychometric evidence.[29] Examples of these scales include the Veterans Administration Seizure Frequency and Severity Rating Scale, the National Hospital Chalfont Seizure Severity Scale, the Liverpool Seizure Severity Scale, and the Seizure Severity Questionnaire,[29] which differ on seizure frequency, duration, warning, and impaired function.[28] In neuro-oncology there is very limited evidence supporting clinical scales that assess the severity of seizures due to their lack of psychometric evidence, except for the Engel Epilepsy Surgery Outcome Scale. The Engel scale was developed to compare seizure outcomes in patients who have undergone surgical resection of an epileptic focus, including patients with brain tumor–related epilepsy.[28] Overall, Engel's scale classifies seizure postoperative outcome as follows: class 1, free of disabling seizures; class 2, disabling seizures rare ("almost seizure free"); class 3, worthwhile improvement; class 4, no worthwhile improvement. It is noteworthy that this classification has highly subjective components. It is based on the term "disabling seizure," which can vary in definition from person to person. Additionally, the determination of worthwhile improvement versus no worthwhile improvement is subjective and would likely differ from patient to patient or physician to physician. Importantly, this scale is reserved only for patients who have undergone surgical procedures and it may prove difficult in view of some of the ambiguous terminology, specifically regarding Engel classes 3 and 4.[28]

On the basis of these limitations, a new classification of seizure outcome following epilepsy surgery was proposed by the ILAE. The ILAE Epilepsy Surgery Outcome classification scale classifies the outcome after epilepsy surgery as: class 1, completely seizure free, no auras; class 2, only auras, no other seizures; class 3, one to three seizure days/year, ± auras; class 4, four seizure days/year to 50% reduction of baseline seizure days, ± aura; class 5, less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days, ± auras; and class 6, more than 100% increase of baseline seizure days, +/1 auras. This scale has been used in brain-tumor epilepsy.[30]

The CTCAEv5 score graduates the severity of seizures in 5 grades, with grade 1 including only partial seizures and grade 5 corresponding to death. The in-between grades 2 to 4 include generalized seizures where an increase in severity corresponds to an increase in the

frequency or duration of the seizures without treatment response, reaching up to the point of threatening the patient's life.

Recently, a Seizure Assessment Tool for Brain Tumor Trials has been proposed for capturing seizure data in patients undergoing brain tumor treatment, based on (1) seizure classification, (2) seizure frequency (number of seizure days from last visit), (3) seizure outcome (using the ILAE outcome scale), and (4) seizure severity (using the seizure-specific questions in the existing brain tumor HRQoL or symptom-burden scale).[28] Despite the current lack of data regarding the validity of the scale in brain tumor patients, the implementation of this tool could be tested in the future in the setting of highly epileptic lesions due to CNS neurotoxicity, such as radiation necrosis or SMART syndrome, with the aim of improving the assessment of a very common reason for consultation in neuro-oncology.

Status epilepticus (SE) is considered when a seizure persists for a sufficient length of time or repeats frequently enough that recovery between attacks does not occur, which can sometimes be non-convulsive. SE can occur associated with some chemotherapy agents like cyclosporine or ifosfamide, among others.[9] Two validated, well-established scales available for the assessment of the generalized SE could be considered in this setting: the Status Epilepticus Severity Score (STESS) and the Epidemiology-Based Mortality Score SE (ESME).[31] Recently, the addition of the modified Rankin scale to STESS has been proposed, leading to a modified STESS (mSTESS),[32] as it is a useful tool in predicting mortality in patients with SE at admission. The mSTESS classification is based on five outcome descriptors: age, aetiology, semiology, consciousness pre-treatment, and modified Rankin scale. An overall mSTESS score of 0–2 is defined as a favorable outcome (low risk of death), a score of 3–4 is defined as intermediate (medium risk of death), and a score of >4 is defined as an unfavorable outcome (high risk of death). The Epidemiology-Based Mortality Score SE (ESME) predicts the outcome at admission on the basis of four outcome descriptors (derived from a total of 45 items). The four outcome descriptors are: age, aetiology (12 categories covering drug therapies, and brain tumors), comorbidities (4 categories including any tumor), and electroencephalogram findings. An overall ESME score of ≥64 predicts an unfavourable outcome of death (high risk of death) and a score <64 predicts a favorable outcome (low risk of death). For an outcome prediction in generalized SE, there is evidence supporting the use of two scales in neuro-oncology patients: the STESS and the ESME and mESME. STESS is a rapid assessment tool that predicts a better negative outcome. When compared to STESS and mSTESS, ESME takes more time to perform but has a better predictive power, for both

positive and negative outcomes. Beside, in its aetiology descriptor ESME includes drug therapies and brain tumors, and not just the previous history of seizures like STESS. This inclusion helps improve the assessment of individual outcomes and makes ESME more representatives to our population of interest. Its use in anticancer therapy-induced SE could also be considered.

Somnolence or insomnia

The clinical presentation of CNS toxicity due to acute radiation or chemotherapy-induced encephalopathy typically includes somnolence, a striking feature in the so-called somnolence syndrome described as an early or delayed complication (1–6 months) after brain radiation therapy. Furthermore, therapy with agents like thalidomide is generally associated with various degrees of somnolence as a very common manifestation.[9] Furthermore, many neuro-oncologic patients receive antiepileptic drugs that induce somnolence as a frequent adverse event. In CTACEv5 somnolence is graded according to the following scores: grade 1, mild but with more than usual drowsiness or sleepiness; grade 2, moderate sedation, limiting instrumental ADL; grade 3, obnubilation stupor; grade 4, life-threatening consequences, urgent intervention indicated; grade 5, death. However, specific scales have been designed to better assess the sleepiness experienced by patients who are increasingly used in clinical oncological practice. The Stanford Sleepiness Scale (SSS) is a quick and easy self-report 7-point scale to assess how alert patients are feeling. Patients may record their "degree of sleepiness" at different times throughout the day.[33] Another subjective measure of sleepiness is the Epworth Sleepiness Scale (ESS), which is used to determine the level of daytime sleepiness. ESS is a simple, self-administered, validated questionnaire designed to provide a measure of the propensity for daytime sleep. Patients are asked to rate how likely they are to fall asleep during different, routine, daytime situations. The test is a list of eight situations in which the subject rates his or her tendency to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing. The total score is based on a scale of 0 to 24. Scores > 8 are considered to be abnormal.[34]

Insomnia is a very common complication of glucocorticoid use, probably the most commonly employed agent in neuro-oncology. Besides, insomnia is a well-known CNS toxicity in patients under treatment with hormonal agents like megestrol, Gonadotropin-Releasing Hormone (GnRH) Agonists, and tamoxifen.[9] In CTCAEv5, insomnia is defined as difficulty in falling asleep, staying asleep, or waking up early, ranging

from grade 1 (mild) to grade 3 (severe). Additionally, insomnia is an item included in many general questionnaires. Of note, the Insomnia Severity Index (ISI) is a brief screening assessment tool designed to evaluate insomnia; it became one of the most widely used assessment instruments in clinical and observational studies to identify potential cases of insomnia and assess the perceived severity of insomnia. ISI measures the patient's perception of both nocturnal and diurnal symptoms of insomnia. The ISI comprises 7 items assessing the perceived severity of difficulties involving initiating sleep, staying asleep, and early morning awakenings, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. The psychometric properties of the ISI in cancer survivors have been very recently reported, supporting the reliability of the scale in this population.[35]

Spasticity and strength

Spasticity is a clinical sign usually seen in many chronic neurological conditions, notably head injury, spinal cord injury, or stroke, which can be the result of therapy inducing damage to CNS. Clinically, it is manifested as an increased, involuntary, velocity-dependent muscle tone that causes resistance to a passive change in a joint angle at the neurological exam. One of the most widely used measures for spasticity is the Asworth Scale. The original Ashworth Scale tests resistance to passive movement around a joint with varying degrees of velocity. Scores range from 0 to 4, with 5 choices. A score of 1 indicates no resistance, and 5 indicates rigidity. The Modified Asworth Scale is similar to Ashworth but adds a 1+ scoring category to indicate resistance through less than half of the movement; it scores from 0 to 4 with 6 choices.[12]

Impairment of strength can result from central neurotoxicity in a given cancer patient, developing for example myelopathy or stroke. The Medical Research Council (MRC) Scale is the most commonly accepted method of the assessment of muscle strength.[12] This method involves testing key muscles from the upper and lower extremities against the examiner's resistance and grading the patient's strength on a 0 to 5 scale accordingly: 0, no muscle activation; 1, trace muscle activation, such as a twitch, without achieving a full range of motion; 2, muscle activation with gravity eliminated, achieving a full range of motion; 3, muscle activation against gravity, full range of motion; 4, muscle activation against some resistance, full range of motion; 5, muscle activation against the examiner's full resistance, full range of motion. The MRC testing method

is very common, easy to perform, and does not require any specialized equipment. Widely employed also in neuro-oncology practice, it has some well-known limitations. Scoring is subjective based on the examiner's perception. There is variability between examiners for the maximal resistance they are able to apply, as some examiners are stronger than others. Importantly, the test does not account for musculoskeletal conditions that may make testing painful or difficult to tolerate, such as tendonopathy or arthritis. The test is dependent on patient effort, which may be poor in some patients, owing to pain, proper comprehension of instructions, psychological causes, or secondary gain.

Stroke

Stroke in cancer patients can be a treatment-related complication. Patients receiving antiangiogenic agents VEGF and VEGFR inhibitors are thought to have an increased risk of arterial thromboembolic events, including ischemic stroke. Tamoxifen has been associated with an increased risk of stroke. In children, strokes from chemotherapy itself have been associated with asparaginase and methotrexate. Furthermore, treatments seem to predispose hematopoietic stem-cell transplantation (HSCT) patients to premature cardiovascular disease. In this setting, the DMSO-related stroke was a classical complication in the infusion period. On the other hand, radiation therapy is known to be a risk factor for having a stroke. Radiation therapy may induce injury to large vessels, such as the carotid artery, or small vessel, leading to stroke. Stroke-like migraine attacks after radiation therapy (SMART) syndrome is characterized by prolonged and usually reversible episodes of headache and focal deficits including seizures, which can resemble stroke. The attacks are usually subacute and involve stroke-like neurological deficits like hemiparesis, aphasia, homonymous hemianopsia, hemisensory deficits, and transient visual loss, with or without seizures.[9]

In a neuro-oncologic patient with a stroke or stroke-like syndrome, the clinical presentation depends on the location and extent of the lesion. Ischemic strokes usually present with focal neurologic deficits, although patients who develop multiple bilateral strokes from an embolic shower typically present with confusion. Hemorrhages may present with a variety of symptoms including altered consciousness, headaches, focal deficits, and seizures.

In CTCAEv5, strokes are considered per se and at more than grade 3 severe toxicity requiring urgent intervention, highlighting the

strong limitation of this scale for grading this type of CNS toxicity, which can be long-lasting and requires a continuous follow-up.

A large number of stroke-assessment scales are described, including the Canadian Neurologic Scale, the European Stroke Scale, the Hemispheric Stroke Scale, the Mathew Stroke Scale, the National Institutes of Health Stroke Scale (NIHSS), the Orgogozo Scale, the Scandinavian Stroke Scale, the Toronto Stroke Scale, and Unified Neurologic Stroke Scale, among others.[12] The NIHSS was developed through a robust consensus approach, taking the most informative measures from existent stroke-examination scales (Toronto Stroke Scale, Oxbury Initial Severity Scale, and Cincinnati Stroke Scale) and creating a composite scale that was further reviewed by a panel of stroke researchers and amended (further items were added to ensure the assessment was as comprehensive as possible). The resulting scale is the most commonly used in clinical acute-stroke practice, which can be performed during the bedside neurologic examination. The NIHSS is a widely validated 15-item scale that standardizes and quantifies the basic neurological examination, paying particular attention to those aspects most pertinent to stroke. The NIHSS provides an ordinal, nonlinear measure of acute stroke-related impairments by assigning numerical values to various aspects of neurological function. The scale incorporates assessment of language, motor function, sensory loss, consciousness, visual fields, extraocular movements, coordination, neglect, and speech. It is scored from 0 (no impairment) to a maximum of 42. Scores of 21 or greater are usually described as "severe." The test takes approximately 5 minutes to administer and another 5 minutes to record the proper scores.[12] Of note, the NIHSS shows the weakness of all neurologic scores in that changes in the examination and therefore in the score, may not accurately reflect meaningful changes in the patients' status. Growing experience of the usefulness of this scale in the cancer population is available in the literature.[36–37]

Tremor

Tremor is a frequent complaint of cancer patients receiving corticosteroids, thalidomide, chlorambucil, arsenic trioxide, Ceritinib, IFN-alfa, and blinatumomab. It can be isolated or in the setting of encephalopathy (i.e, patients treated with CAR-T cell). Patients receiving calcineurin inhibitors (tacrolimus, cyclosporine) to prevent graft-versus-host-disease GVHD following allogeneic transplants frequently develop tremor. Brain tumor patients receiving valproate may present hand tremor as a side effect.[9]

Tremor is graded according to CTCAEv5, as follows: grade 1, mild symptoms; grade 2, moderate symptoms, limiting instrumental ADL; grade 3, severe symptoms, limiting self-care ADL. However, a more detailed examination can be done by the employment of specific neurological clinical rating scales that have been developed to measure tremor. For example, the Essential Tremor Rating Assessment Scale (TETRAS), which contains nine performance items that rate action tremor in the head, face, voice, limbs and trunk from 0 to 4 in half-point intervals, has been reported to be a reliable tool for the clinical assessment of essential tremor.[38] In mild tremor, it may be more useful for the assessment of tremor to ask the patient to write his or her name or a sentence (writing test) or to draw an Archimedes spiral with each hand while ensuring that the patient keeps his or her writing arm off the table. In this line, currently, regulatory agencies (i.e. EMA) recommend that a neurological examination must be performed in patients before starting blinatumomab therapy and those patients should be clinically monitored for signs and symptoms of neurologic events, including the writing test.[39]

Visual loss

Problems of vision in a cancer patient may be the consequence of therapy, which can present as a transient and reversible symptom, in most cases, or, less frequently, as a chronic irreversible visual impairment from radiation-induced optic neuropathy. Patients under treatment with crizotinib or retinoids may have visual complaints that consist mainly of blurred vision, abnormal color vision, transient visual loss or visual obscuration, diplopia, photopsia, chromatopsia, impaired vision, and vitreous floaters. PRES usually manifest with blindness or homonymous hemianopsia, in addition to headache and seizures.[9]

In the neurological exam, the visual fields are tested by confrontation, and the examiner compares the patient's visual field to their own and assumes that theirs is normal. Both the NIHSS and NANO scales incorporate the assessment of visual loss on its gradation with 4 levels. In NIHSS, gradation includes 1 point for partial hemianopsia, 2 points for complete hemianopsia and 3 points for bilateral hemianopsia or complete blindness. However, in NANO scale, 1 point is rated for equivocal or inconsistent partial hemianopsia, whereas unequivocal partial hemianopsia is rated as two points. Complete hemianopsia is rated as 3 points, and no specific gradation is considered for those patients with complete blindness.

Visual acuity (VA) is usually measured using the Snellen Scale. The patient covers one eye and reads aloud the letters on a chart, beginning at the top and moving toward the bottom. The smallest row of letters that the patient reads accurately determines VA in the uncovered eye. CTCAEv5 needs a baseline assessment and the Snellen eye chart to check VA. Gradation of blurred vision is as follows: grade 1, intervention not indicated; grade 2, symptomatic, moderate decrease in VA (best corrected VA 20/40 and better or 3 lines or less decreased vision from known baseline), limiting instrumental ADL; grade 3, symptomatic with a marked decrease in VA (best corrected VA worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200), limiting self-care ADL; grade 4, best corrected VA of 20/200 or worse in the affected eye.

Papilledema, defined as swelling and elevation of the optic disc, is typically observed when there is markedly elevated intracranial pressure and can be graded according to the Modified Frisén scale (MFS).[40] This scale uses visual features of the optic disc and peripapillary retina to stage optic disc edema in 5 grades, from grade 0 (normal disc optic) to grade 5 (severe degree of edema). Recently, MFS has been incorporated in the neurological monitoring of patients receiving CAR-T cell therapy.

In the SMART (stroke-like migraine attacks after radiation therapy) syndrome, patients have headaches, which are typically described as migraines and may be accompanied by visual aura. The Visual Aura Rating Scale (VARS) is helpful for the diagnosis of migraine with aura. The VARS score is the weighted sum of the presence of five visual symptom characteristics: duration 5–60 minutes (3 points), develops gradually > or = 5 minutes (2 points), scotoma (2 points), zigzag lines (2 points), and unilateral (1 point). The maximum score is 10 points.[41]

Conclusion

In our opinion, we still lack the best neuro-oncological scale for the evaluation and follow-up of patients with focal CNS dysfunction due to oncologic treatment. It is necessary to bear in mind that although the assessment instruments are measures that can facilitate the evaluation process and expand the information about the patient's situation, they can never replace the clinical interview.

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CHAPTER 2.2

SCORES AND SCALES IN CNS GLOBAL DYSFUNCTION ASSESSMENT

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Abstract

The assessment of function damage to the global central nervous system (CNS) remains a challenge as there is limited evidence from the scales being used by patients receiving cancer therapies. This lack of accuracy leads to heterogeneity in assessments between physicians. To date, the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) is the main tool available to grade the severity of CNS toxicity in relation to cancer treatment. Conversely, in neurology and psychology, hundreds of different clinical scales exist to evaluate specific neurological disturbances. On occasions, these disease-specific tools have been used and sometimes even validated in cancer patients. However, the tools employed for clinical assessments must be reliable and accurate in quantifying the severity of a neurological symptom as well as its evolution. The proper assessment from its early recognition is mandatory in order to limit its severity through appropriate modification to treatment.

This chapter revises the background and the main characteristics of the most widely used methods to grade the more frequent non-focal CNS symptoms in patients receiving cancer therapies, from headache, encephalopathy and a disturbed level of consciousness, cognitive impairment, and psychiatric disorders, to fatigue.

Keywords: National Cancer Institute Common Terminology Criteria for Adverse Events, headache, Six-Item Headache Impact, Visual Analogue Scale, level of consciousness, Glasgow Coma Scale, encephalopathy,

CAR-T cell therapy associated toxicity score, immune effector cell-associated encephalopathy score, cognitive impairment, mini-mental state examination, Hopkins Verbal Learning Test Revised, Trail Making Test, Controlled Oral Word Association, Rey-Osterrieth Complex Figure, apathy, Apathy Evaluation Scale, psychiatric disorders, Distress Thermometer Test, Hospital Anxiety and Depression Scale, Patient Health Questionnaire-9, Beck Depression Inventory, fatigue, Brief Fatigue Inventory, Cancer Fatigue Scale

Introduction

In oncology, traditionally the main parameters or measures used to assess the benefit and efficacy of treatments are the changes observed in tumor volume and overall survival or progression-free survival. An extensive body of literature has been published validating and assessing the value of these measures in patient outcome.[1] Moreover, new treatment efficacy assessments are in active development. These assessments will aim to evaluate the challenge represented by new immunomodulatory therapies (like the pseudoprogression effects). To the contrary, less attention has been paid to the assessment of treatment tolerability and the evaluation of adverse events. The appraisal and grading of some treatment-related secondary effects is still controversial, especially for neurological adverse events.

Since 1982, the most commonly used score in the examination and grading of adverse events is the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE)[2] (see table 2.2.1) for further details on CNS global grading of adverse events. These criteria are used to manage treatments, either in trials or in daily practice, and have been very useful in providing standardization and consistency in the definition of treatment-related toxicities across the world. However, despite the unquestionable advance that the NCI-CTCAE has made to homogenize medical practice, the bases for the definition of the severity grades in some adverse events are too simple and sometimes ambiguous. This is the case for most neurological treatment complications. Adverse events of ≥ grade 3 are those leading to life-threatening situations or limiting self-care, whereas grade 2 are those that interfere with the age-appropriate instrumental activities of daily living, and grade 1 are mild symptoms. The definitions for each grade are not very concrete. For neurologic assessment, the NCI-CTCAE grading system is mostly based on patient-reported outcomes and is therefore inherently more subjective. This lack of accuracy leads to heterogeneity in assessments between

physicians and/or centers, preventing not only the impact assessment of a determined adverse event, but also the efficacy of the measures and treatments applied to prevent or ameliorate the condition. One remarkable and widely studied example of this situation is the problem with the assessment of chemotherapy-induced peripheral neuropathy,[3] addressed in chapter 4.4. Other examples are stroke, only graded in categories 1 and 2, despite its potentially devastating effects, and the clear simplification that this grading system provides in the assessment of the most complex central nervous system function, cognition. Furthermore, other treatment related neurological complications are not included in the NCI-CTCAE, like the spectrum of syndromes related to the long-term side effects of brain irradiation, such as the SMART syndrome (stroke-like migraine attacks after radiotherapy).

On the other hand, in neurology and psychology, hundreds of different clinically used scales exist to evaluate specific neurological disturbance. These disease-specific tools can offer added value in the assessment of cancer-related neurological complications beyond the more simplistic approach provided by the NCI-CTCAE scale. However, most of these scales have not been designed for cancer patients; furthermore, they so not take into account their particularities. In addition, specialists have not reached a consensus on the usefulness of all these scales, and some have not been properly assessed in terms of clinicometric properties.

Neurologic assessment scales must be useful tools in order to reliably and accurately quantify the severity of a neurological disease as well as its evolution. Its immediate objective is to transfer the set of neurological alterations present in each patient to an overall score that quantifies the deficit, in order to objectively and dynamically assess the intensity of the neurological deficit at a specific time. This kind of assessment allows comparisons to be established, and permits assessment of the incidence, severity, and effectiveness of the adverse event measured, as well as providing for evaluation of the medical intervention's outcome, to prevent the event. In addition, the transformation of clinical language into numerical data is what makes the statistical management of data and the objective exchange of information with other professionals possible.

A neurological scale must be specific to the evaluated disturbance. It must incorporate in a balanced way the neurological signs and symptoms putting the greatest emphasis on prognosis and functionality. This evaluation instrument must comply with adequate psychometric

properties:[1]* *validity* (actually measures what it intends to measure) and *reliability* (the results obtained are repeatable and similar when used by different physicians, with little intra- and interobserver variability). Moreover, a scale ideally must also have a measure of the degree of *consistency* (extent to which items within a questionnaire assess the same characteristics), it must be *sensitive* to change, *feasible* (easy to administrate), and *comfortable* (brief, without requiring special training and applicable inside and outside the hospital).[4]

However, despite the unquestionable usefulness of the scales and scores for both the evaluation process and the increased amount of information collected on patient status, we should not forget that these tools can never replace a clinical interview and examination.

In this chapter and the next, we will review the neurological scales currently used and those that could potentially be used to assess the main treatment of cancer-related complications in the central nervous system. In the first chapter, we will focus on the non-focal neurological complications, and in the subsequent chapter we will look at the focal neurological disturbances induced by treatments.

1. Headache

All patients undergoing oncological treatment or with brain tumors are at risk of suffering headache, which is one of the main complications of global CNS dysfunction. The physio pathological mechanisms involved in headache are still unknown, but the disruption of the blood brain barrier (BBB) seems to play a relevant role.[5] See table 2.2.2, a summary table of cancer therapies that have been associated with headache.

1.1. Scales and scores

Established scales in oncology

The CTCAE system graduates the severity of headache attacks in 3 grades (see table 2.2.1). Neither grade 4 nor grade 5 are included in this scale because a headache is not considered a neurological symptom that could threaten life or cause death by itself, although it can be a symptom of intracranial hypertension.

[1]* For each scale described in the different chapters, we will report the reliability measurement parameters that are either most relevant or are available in the literature. Thus, these may be subject to variation between scales.

General neurology practice scales

In neurology practice, the clinical scales used in headache assessment are divided into four main areas: (a) diagnosis and classification, (b) functional impairment, (c) severity of attacks, and d) quality of life. In this section, we will not describe scales used for (a) diagnosis and classification, as headache in relation to treatment does not have an exclusive signature of symptoms and its diagnosis is made by exclusion; and (b) quality of life, as scales are validated only in migraine patients and do not consider any other type of headaches (see table 2.2.3 for further details).

1.2. Functional impairment scales

To assess functional impairment generated by headache we have two principal scales, the Six-Item Headache Impact Test (HIT-6) and the Migraine Disability Assessment Questionnaire (MIDAS).

HIT-6 was designed in 2003 to provide a global measure of the impact of headaches in patients' lives.[6] The 6 items of this scale were selected from a group of 89: of these, 54 items were taken from an existing headache-impact item pool validated by Item Response Theory methods, and 35 items were proposed by physicians. The resulting 6 selected items evaluate (1) frequency of severe headache, (2) the impact generated by the headache in limiting daily activities, (3) necessity to lie down, (4) fatigue, (5) irritability, and (6) difficulties in concentrating.

Each of the 6 items is scored according to its frequency (never = 6 points, rarely = 8 points, sometimes = 10 points, very often = 11 points, always = 13 points). This generates an overall score from 36 to 78 points. On the basis of this score, the impact of headache in patients is classified as having little or no impact (grade 1 = score 36–49), moderate impact (grade 2 = score 50–55), substantial impact (grade 3 = score 56–59), and severe impact (grade 4 = score 60–78).

It can be used as an indicator of treatment response, in general terms; a reduction of 2.3 points indicates a clinically significant improvement**.** HIT-6 has demonstrated good psychometric properties, with a high intra-rater reliability of Cronbach's α (α) = 0,78 and a high inter-rater reliability intra-class correlation coefficient of (ICC) = 0.80.[7]

MIDAS was designed in 1999 to quantify headache-related disability.[8] Despite being developed to assess migraine, the test is highly reliable across the spectrum of headaches. It is based on a 5-item questionnaire about disability associated with headache in the last 3

months. The items were selected from the Headache Impact Questionnaire (HImQ) as well as from an expert advisory committee opinion. The score is calculated as the sum of days lost or productivity reduced due to headache (work, school, household work, and non-work activities). The overall level of disability score ranges from 0 to 270 days.

On the basis of this score, patients' headache-related disability is classified as little or no disability (grade 1 = 0–5 days), mild disability (grade 2 = 6–10 days), moderate disability (grade III = 11–20 days), and severe disability (grade 4a = 21–40 days; grade 4b ≥41 days). It is only administered every 3 months or less frequently. MIDAS also has demonstrated high intra-rater reliability (α =0,83) and a high inter-rater reliability score estimated by Spearman's correlation (ρ =0.84).[9]

1.3. Pain intensity scales

Pain intensity headache scales are classified into four main groups: (a) categorical scales with the Verbal Rating Scale (VRS) (which shows similarities to the CTCAE system in categories 1 to 3); b) linear scales with the Visual Analogue Scale (VAS); c) the Numeric Rating Scale (NRS); and (d) the Faces Pain Scale (FPS). With their distinct particularities, none of them was consistently shown to be superior to the others when it came to assessing general pain in cancer patients, they were also used in some brain tumor clinical trials but have yet to be validated. However, when it focuses on headache, the International Headache Society (HIS) guidelines recommended the use of either VRS or VAS.[10] The VRS-4 is a categorical four-level rating scale established by the early triptan clinical trials. It comprises a list of adjectives used to denote increasing pain intensities. A number is assigned for each of these adjectives: 0 (absent), 1 (mild), 2 (moderate), 3 (severe). In addition, there is a larger version, VRS-6, which adds the following categories: 4 (very severe) and 5 (most severe pain imaginable). VRS has demonstrated a good intra-rater reliability score and acceptable inter-rater reliability score with a cohen's kappa coefficient (k) of 0.65 and 0.54, respectively.[11]

The VAS is a linear rating scale where the assessment involves visualization of the pain intensity in relation to a 100-mm horizontal line anchored by the endpoints defining the extreme limits as "no pain" and the "worst imaginable pain." The limit defines the subject's pain. The score is measured from the zero anchor to the patient's limit. The following cut points are recommended: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm). VAS has also

demonstrated acceptable intra-rater and inter-rater reliability scores (of k= 0,70, k=0,61, respectively).[11]

2. Encephalopathy and level of consciousness

Encephalopathy represents one of the most-common global CNS cancer treatment side effects (see table 2.2.4). In acute encephalopathy, the clinical spectrum of symptoms ranges from slight disturbances of mental state to severe unconsciousness, and it is occasionally accompanied by myoclonus and seizures. It is mostly associated with drugs that cross the BBB and with cranial radiotherapy (especially hours/days after the course of irradiation and particularly in patients receiving large fractions of radiation). Chronic encephalopathies, appearing month to years after cancer treatment, have a distinct clinical presentation pattern, with mild disturbances of consciousness (not severe) and predominantly of cognition and mood dysfunction, which are consequences of established structural changes in the brain.

While encephalopathy is accompanied by other neurological symptoms, this section focuses on global encephalopathy assessment scales.

2.1. Scales and scores

Established scales in oncology

CTCAE system

The CTCAE system grades the severity of encephalopathy in 5 grades according to the impairment of ability to perform the activities of daily living (see table 2.2.1 for further details). The term encephalopathy can be overlapped with other poorly defined CTCAE adverse-event terms such as cognitive disturbance, somnolence, depressed level of consciousness, confusion, and delirium,[12] hence complicating the grading of neurological toxicity.

Cellular (*Chimeric antigen receptor T cell therapy*) immunotherapy scales

It is important to highlight the current and future role of Chimeric antigen receptor T (CAR T) cell therapy, one of the most promising therapies for hematologic malignancies. Besides cytokine released syndrome (CRS),

neurotoxicity in the form of encephalopathy has emerged as the dominant feature of the neurologic condition termed Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). Since the assessment and grading varied considerably across clinical trials and institutions, specific assessment tools for grading ICANS have been created. In particular, for addressing encephalopathy, two scales have been designed (see table 2.2.5).

The *CAR-T cell therapy associated TOXicity score* (CARTOX-10) incorporates 10 key elements of the Mini-Mental State Examination (MMSE) to evaluate alterations in speech, orientation, handwriting, and concentration—symptoms highly suggestive of encephalopathy. It considers orientation (5 points), naming (3 points), writing (1 point), and attention (1 point). The scoring is as follows: 10 points, no impairment; 7–9 points, grade 1 ICANS; 3–6 points, grade 2 ICANS; 0–2 points, grade 3 ICANS; 0 points, grade 4 ICANS (unarousable/unable to perform the scale); death: grade 5 ICANS. However, the psychometric proprieties are not yet available.[13]

Very recently, a slightly modified version of the CARTOX-10 screening tool, termed the Immune Effector Cell-Associated Encephalopathy (ICE) Score, was developed. It provides objectivity to grade multiple overlapping encephalopathy terms currently included on approved CAR-T products. The updated encephalopathy screening tool includes the assessment of several domains: orientation (4 points), naming (3 points), following commands (1 point), writing (1 point), and attention (1 point). ICE adds an extra item when compared to CARTOX-10: following commands. This item assesses receptive aphasia, a clinical manifestation frequently seen in these patients. The rest of the items and the scoring system remain the same as for CARTOX-10. Psychometric proprieties are not yet available for either of these scales.

The ICE score is useful for screening adult encephalopathy; its use in children may be limited to those who are >12 years with enough level of cognitive abilities to perform the ICE. Encephalopathy assessment for Children <12 years should be done by using the Cornell Assessment of Pediatric Delirium (CAPD).

Importantly, the grading of ICANS requires the assessment of the CARTOX-10/ICE score as well as the evaluation of several other neurological domains, such as level of consciousness, motor symptoms, seizures, and signs of raised ICP/cerebral edema, which may occur with or without encephalopathy.[13–14]

General neurology practice scales

In neurology practice, the clinical scales used in encephalopathy assessment are based on the outcome/prognosis of post-anoxic patients, newborns in perinatal asphyxia, and adults with hypoxic–ischemic brain injury after cardiac arrest. For oncology patients, neither of the above-mentioned scales is of relevance. The reason for excluding post-anoxic adults' scales is that most of the studies are carried out on comatose patients, and this is not a representative clinical state of patients suffering from encephalopathy secondary to cancer treatments, as these patients exceptionally reach a coma state and the physiopathology differs completely.

The clinical evaluation of impaired consciousness in patients affected by encephalopathy can be assessed using the Glasgow Coma Scale (GCS), which, despite its limitations that have led to the development of other new scales, is still the most used among specialists.

Additionally, apart from encephalopathy, there are other relevant non-focal neurologic symptoms that may be present with impaired consciousness: this is the case with chemical meningitis, the most common acute adverse event of intra-CSF chemotherapy.[15] The diagnostic challenge of chemical meningitis lies in the fact that its clinical manifestations and cerebrospinal fluid characteristics can mimic other aetiologies, such as infectious meningitis or leptomeningeal disease progression. Precisely because of that, chemical meningitis has to be a diagnosis of exclusion. Microbiological culture, viral PCRs, CFS cytology, and tumoral markers are additional recommended tests. Furthermore, the temporal relationship with the administered drug, the improvement after withdrawal, and the re-challenge (often unintentionally) are clinical aspects that may support the diagnosis.

While several scores for the differential diagnosis of infectious aetiologies (bacterial versus viral) have been published, there are no universal guidelines that determine the scales to be used for the assessment of the severity of meningitis.

In the best-case scenario, chemical meningitis presents mild symptoms, except in some cases where it can compromise consciousness. In these situations, general scales that assess the level of consciousness can be used as a measure to assess the severity of the meningitis.

An overview of the principal level of consciousness scales is presented in table 2.2.6.

The Glasgow Coma Scale (GCS) was the first grading scale for the assessment of level of consciousness. It provides a structured method

to assess the depth and duration of impaired consciousness and coma, by evaluating three components: motor, verbal, and eye responses. Most studies that led to the development and validation of this scale were conducted in an intensive care unit (ICU), thereby including mostly traumatic brain injury patients, but also a proportion of brain cancer patients.[16]

The GCS was originally a 14-point scale, and did not distinguish between "normal" and "abnormal flexion (decorticate)" in the motor response component. In 1976, the revised score converted the GCS into a 15-point scale by adding a category in the motor response subscale for ''withdrawal from painful stimulus (normal).''

The actual ranging score of the GCS includes a minimum score of 3 and a maximum score of 15, classifying as severe scores ≤8, moderate scores of 9 to 12, and mild scores of 13 to 15.

Special mention must be made of the Glasgow Coma Scale—Pupils Score (GCS-P) a recently described score derived from the GSC in response to the lack of assessment of brainstem integrity, which is a pivotal structure in maintaining consciousness.

Systematic review of GCS reliability has demonstrated adequate inter-rater reliability scores with an ICC range from 0.39–0.79. Focused only on neuro-oncology studies, the inter-rater reliability score was k=0.91; however, no conclusions can be drawn for intra-rater reliability scores due to the poor quality of the studies.[16] Further improvement in the assessment of this point is advisable.

GCS does have its limitations. First, it is only a three-item scale. Second, it is not applicable in cases of aphasia or in situations where testing the verbal or eye response is not possible (tracheal intubation or facial/eye swelling). Last, it is not designed to identify subtle changes in alteration of consciousness. While these limitations have led to the development of other scales, this is still the most widely used scale in the evaluation of conscious impairment.[17]

Despite the available grading tools, encephalopathy still remains sometimes challenging to diagnose and is often not regarded as an important medical condition. In this clinical setting, electroencephalography (EEG) can be a useful tool to support the diagnosis when diagnostic questions still exist and there are doubts between true encephalopathy or an epileptic state. The advantage of this tool is that it is quick to use and available in the majority of hospitals. In most cases, the outcome will be expressed as either diffuse nonspecific non-epileptiform background slowing, with or without triphasic waveforms (TWs), and frontal intermittent rhythmic delta activity (FIRDA). Reflecting that cortical and

subcortical dysfunction produce a variety of EEG findings. Synek, Young, et al.[18–19] proposed a potentially useful prognostic EEG classification for comatose patients, but, once more, the most valid and reliable data on the predictive value of EEG comes from post-anoxic patients.

3. Cognitive impairment

Cancer-related cognitive impairment (CRCI) represents one of the main complaints during cancer treatment and has been overlooked many times. CRCI can be presented as a delayed onset complication and/or be progressive even years after cessation of therapy. Its evaluation is often challenging. This is because multiple variables are involved in its development, which makes it difficult to delineate the precise contribution of each factor on cognition impairment. These factors can include the administered treatment of brain irradiation or chemotherapy agents (also called "chemobrain"), the cancer homeostatic changes by itself, personal intrinsic factors like cognitive reserve, mood disorders, nutritional deficiencies, endocrinopathies, comorbidities, or other neurological complications like seizures.

In literature, different oncologic treatments have been related to different levels of cognitive impairment[2]* (see table 2.2.7): around 15 to 70% with conventional chemotherapy agents,[20] 50 to 90% with conventional radiotherapy,[21] and up to 50% in prophylactic cranial radiotherapy.[22] With regard to hormonal agents, fewer studies have been conducted examining the impact of endocrine therapy on cognition. This cognitive impairment linked to hormonal agents is observed mostly in breast cancer patients. Two recently published studies[23] show the potential deleterious effects on various cognitive domains. Moreover, heterogeneity in assessments, patients' characteristics, and small sample sizes, among other design weaknesses, in the different studies are the main limitations on extrapolating results. For supportive therapies and other novel drugs (e.g., angiogenesis inhibitors, immunotherapy) the precise impact on cognition of these therapies is still unknown, with the exception of antiepileptic drugs.

[2]* These differences are due to variations in patient characteristics and methods used in these studies, therefore making comparability difficult.

3.1. Scales and cognition tests

A formal standardized evaluation of cognitive impairment requires the use of scales and psychometric tests. As the field of cognition is extensive, we have divided this section into three main subsections: "3.1.1. Screening tests" for Global cognitive evaluation used in cancer patients; "3.1.2. Specific cognitive evaluation domains tests" in cancer patients; and "3.1.3. Other scales."

3.1.1. Screening tests: global cognitive evaluation

Due to the vast number of tests available for the detection of global cognitive impairment, a selection of those considered of greatest interest has been made. These have been differentiated into two main categories depending on the time it takes to complete the test: brief tests, which are useful in daily office clinical practice, but are susceptible to producing false negatives (FN), especially when the cognitive alteration is mild or in patients of a high educational level or intelligence, and false positives (FP), in illiterate subjects or patients with low educational levels. Large tests are commonly used in neuropsychological evaluation or research and have a lower risk of FPs or FNs; however, they are too lengthy for realization during daily medical clinical practice and require a specialized neuropsychology office (see table 2.2.8).

Furthermore, as a first initial step of the cognitive evaluation, it is also important to screen for mood disorders. They may interfere in the cognition assessment where true cognitive disability is not present.

Among the huge number of scales mentioned in table 2.2.8, the most relevant for the general cancer population are the Mini-Mental State Examination (MMSE) and Mattis's Dementia Rating Scale (DRS). Furthermore, a special recommendation for cognitive assessment scales in elderly cancer patients is also proposed by some authors, highlighting the use of Mini-Cog, the Blessed Orientation-Memory-Concentration (BOMC) test, and the Montreal Cognitive Assessment (MoCA).

It is important to highlight that all these tests are screening tools that are no substitute for a complete diagnostic work-up.

The Mini-Mental State Examination (MMSE) is an extremely well-known test, originally created in 1975 to evaluate the mental state of hospitalized psychiatric patients.[24] It is still the most widely used brief screening test for the detection of global mental deterioration, the estimation of the severity of mental state at a given point in time, to follow-up cognitive changes in an individual over time, and to document an individual's response to treatment. Its main advantage is its wide

dissemination of use and its extensive empirical evidence support. Because it was not designed specifically for the detection of dementia, most of its score is dominated by the cognitive functions of orientation and language and only serves to evaluate memory, which happens to be the cognitive domain that is primordially affected in the most common dementias. The executive functions are also underrepresented, which makes it an instrument that is not very sensitive to frontal dysfunction or to the type of cognitive impairment related with cancer treatments.

The results of the only meta-analysis available on the diagnostic utility of MMSE, which includes 34 quality studies, shows that the diagnostic utility of MMSE for dementia is acceptable with a sensitivity of 79.8% and a specificity of 81.3%, in specialized media. Limited studies have evaluated the diagnostic utility for cognition impairment. The results of the five studies included in the meta-analysis referred to above show that the diagnostic utility is limited with a sensitivity of 62.7% and a specificity of 63.3%.[25]

On the other hand, the Mattis Dementia Rating Scale (MDRS-2) is a large test initially designed to diagnose Alzheimer's disease; however, afterwards its use spread to the early detection and staging of other dementias. MDRS-2 was also adopted for clinical cancer trials in CNS lymphoma and lung cancer.

The scale includes 36 tasks that are grouped into five subscale cognitive domains: attention, initiation/perseveration, construction, conceptualization, and memory. Items are arranged hierarchically, so that more difficult items are presented first. If a patient performs adequately on the initial items within a given section, full credit is given for the rest of the items in that section. Compared to previous iterations of the MDR, the MDR-2 adds age and education factors that greatly enhance the normative data. Cognitive impairment was defined as a MDRS-2 raw score <123.[26]

To screen for cognitive impairment in elderly cancer populations, the recommended tests include the Mini-Cog or the Blessed (BOMC) test. The Min-Cog is a 3-minute test with two components: a 3-item recall test for memory and a clock-drawing test. It has high sensitivity and specificity for identifying cognitive impairment when compared with longer tools. An abnormal test is defined by zero words recalled or one to two words recalled plus abnormal clock-drawing results.[27]

On the other hand, the BOMC test is a screening tool that evaluates orientation, registration, and attention. Scores from each of the six items are normalized in a weighted score. The higher the total weighted score, the more likely the patient is to present cognitive disability. Weight scores totaling greater than 10 are generally accepted as

an indication of clinically meaningful cognitive impairment. Finally, the Montreal Cognitive Assessment (MoCA) is also used by geriatricians in oncology, but is considerably longer than the Mini-Cog and BOMC.

Finally, the CTCAE system also provides a severity gradation of cognitive impairment, categorized in 3 grades (for further details see table 2.2.1), although in comparison with the aforementioned tests it is much less widely used.

3.1.2 Specific cognitive evaluation domains tests in cancer patients

Neuropsychological studies have contributed to better characterize cognitive impairment secondary to cancer treatments (see table 2.2.9). In 2011, the ICCTF[3]* published recommendations to unify the neuropsychological tests carried out in studies with oncologic patients. These recommendations were focused on three neurocognitive domains: (a) verbal memory, (b) information processing speed, and (c) executive function.[28] Also, based on clinical practice and other post-hoc analysis, (d) visuospatial abilities and visual memory should also be explored.[22,29] Although the guide was published for studies of patients with systemic cancer, these same tests have been used in clinical trials with patients with brain tumors (see table 2.2.10).

Neurocognitive testing battery recommended in oncological patients' assessment

1. Verbal memory: The Hopkins Verbal Learning Test-Revised (HVLT-R) is a quick test that contains a list of 12 words that are repeated 3 times. After 20 minutes, the patient has to remember the list without prompting and also recognize the original 12 words when mixed in a list with other additional words. It has 6 different versions, which makes it a very suitable test for any longitudinal study, avoiding the learning effect by repeating tests over time. The reliability of the HVLT has been demonstrated in patients with head injuries, schizophrenia, and dementia. The intra-rater reliability score varied from r=0.39–0.74 depending on the studies. No inter-rater reliability score is available.
2. Information processing speed: The Trail Making Test (TMT) is a test that requires attention, processing speed, and executive functions (shifting). It has 2 parts: part A: patients have to join

[3]* International Cognition and Cancer Task Force Conference.

circles that contain numbers from the smallest to the largest; part B: patients have to join circles by inserting numbers and letters, the numbers from the smallest to the largest and the letters in alphabetical order. The intra-rater reliability score of TMT A and B was between 0.76 and 0.89 and between 0.86 and 0.94, respectively. Time for administration: TMT part A and B (5–10 min).

3. Executive function: in the Controlled Oral Word Association (COWA) test, based on verbal fluency, patients have to say as many words as possible inside a minute that begin with a given letter. Administration: COWA (3 min). Presents an intra-rater reliability score of COWA r=0.74.
4. In addition to the recommendations of the ICCTF, Simó et al. suggest adding the Rey-Osterrieth Complex Figure (ROCF), both the first and second copy, because it is a quick test that completes the neuropsychological study adding information on visuospatial perception, apraxia, and visual memory. Administration: first copy of ROCF (3–5 min); second copy of ROCF (ensure 20 minutes have already passed from the first copy of ROCF). Results have revealed excellent intra-rater reliability scores with an ICC of 0.94 for the first copy and an ICC of 0.95 for the remembered copy; and also, excellent inter-rater reliability scores with an ICC of 0.93 for the first copy and 0.96 for the remembered copy.

3.1.3. Other scales: Apathy

Apathy is described as a state of primary motivational impairment not attributable to a diminished level of consciousness, an intellectual deficit, or emotional distress. It is seen in several conditions of acquired brain damage, including Parkinson's disease, stroke, dementias, and traumatic brain injury. It is also frequently observed in brain tumor patients, especially in those whose frontal brain structures are affected, for examples, where the anterior cingulate cortex (a recognized key structure in the generation of motivation) is affected, and by patients undergoing cranial radiotherapy. Although the CTCAE system does not include "apathy" as an adverse event, other grading systems have been developed and they are summarized in table 2.2.11. Special mention should be made of the Apathy Evaluation Scale (AES) as it is a unique scale that has been tested in neuro-oncology patients**.** It was developed in 1991 to quantify and characterize apathy in adult patients.[30] It is an 18-item scale available in three versions: self-rated (AES-S), informant (AES-I; family member,

friend, or professional caregiver), and clinician (AES-C), the last two versions (informant and clinician) are very useful as apathy is often associated with impaired insight. It has been validated in acquired brain injury patients (stroke, hypoxic brain damage, Alzheimer's disease, traumatic brain injury), depression, and healthy controls. The averaged administration time for the AES is about 10 to 20 minutes. AES has demonstrated both high intra- and inter-rater reliability scores with an α value of 0.86–0.94 and an ICC of 0.94, respectively.

Psychiatric disorders

The prevalence of psychiatric disorders is significantly higher in cancer patients than it is in the general population. A meta-analysis reported that up to 30–40% of cancer patients present mood disorders.[31] The presence of psychiatric disorders is influenced by multiple factors and many times by a combination of such factors, such as the reaction to the acceptance of the diagnosis, the consequences of cancer treatments or supportive therapies, and in the case of cerebral tumors the localization in eloquent areas. The principal therapies that have been associated with psychiatric disorders are summarized in table 2.2.12.

4.1. Scales and scores

Established scales in oncology

The CTCAE system classifies the spectrum of psychiatric disorders according to various descriptors. However, psychiatric disorders can be expressed in many ways and subjectivity in the self-evaluation of these symptoms may be implicit in their assessment. A selection of the most relevant descriptors for the assessment of psychiatric disorders is presented in table 2.2.1. Psychiatric disorders had not been considered an aspect of cancer's quality of care until the publication of *Cancer Care for the Whole Patient* in 2007 from the Institute of Medicine (IOM). Since then, the National Comprehensive Cancer Network (NCCN) has been recommending screening for psychiatric disorders in cancer patients as a new standard of care.

A recommended distress[4]* screening tool in guidelines is the "Distress Thermometer." It is based on a self-administered single-item

[4]* Multifactorial unpleasant experience of a psychological social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer,

questionnaire, which identifies distress arising from any cause. The patient circles the number that best describes his or her distress level experienced during the past week. The final scores range from 0 (no distress) to 10 (extreme distress). A punctuation of ≥4 is considered of clinical significance and should be followed up with a second screening tool, the "Problem List." This questionnaire is based on a 39-item scale classified in 5 major categories: practical, family, emotional, spiritual/religious, and physical.[32] The "Distress Thermometer" has demonstrated good psychometric properties with high intra-rater reliability (α =0.90);[33] no inter-rater reliability data is available. It has been validated in different types of cancer, and also in primary brain tumor patients.

Another more general and simplistic approach can be achieved through the recent validated scale used to evaluate neuro-oncology patients, the NANO scale.[34] It is a general scale that provides an overall assessment for neuro-oncology patients (see next chapter) and includes "behavior" as one of the principal domains to be explored. This is graded as normal, mild/moderate, and severe alteration, understanding behavior exclusively as a conduct disorder.

General neurology practice scales

In daily neurology practice, it is not unusual to evaluate patients with primary neurological disorders who suffered secondary psychiatric complications to their brain disease or its chronic therapy. Because an extensive arsenal of neuropsychiatric scales exists, this section will focus on the most relevant and ready to implement scales in routine clinical practice. While specific scales to evaluate psychiatric symptoms in specific neurological diseases are available in neurodegenerative diseases like dementia—for example, the Neuropsychiatric Inventory Questionnaire (NPI-Q), Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), Behavior Rating Scale for Dementia (BRSD), Cornell Scale for Depression in Dementia (CSDD) or Parkinson's Disease: Non-motor Symptoms in a subsection of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS UPDRS), Parkinson Psychosis Questionnaire (PPQ), Parkinson Psychosis Rating Scale (PPRS), and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's

its physical symptoms, and its treatment (extract from the latest version of the NCCN Guidelines Distress Management).

Disease-Rating Scale (QUIP-RS)—others are not related to a specific disease.

Among the most notable neuropsychiatric scales, none is specifically designed for the evaluation of cancer patients. However, there are several oncologic studies where neuropsychiatric scales have been validated, some of them including neuro-oncology and cancer patients.

To select the most relevant neuropsychiatric scales, the emphasis will be on scales that: (1) have good psychometric proprieties; (2) are validated in oncologic patients; and (3) are based on the most frequent mood disorders, focusing on anxiety, depression, delirium/psychosis, and suicide risk.

4.1.1. Anxiety

Table 2.2.13 presents scales for the detection of generalized symptoms of anxiety. The Hospital Anxiety and Depression Scale (HADS) has been specifically used in neuro-oncology studies and has shown optimal psychometric proprieties. More details on HADS will be explained in the next section ("4.1.2. Depression").

4.1.2. Depression

Table 2.2.14 presents scales for detection of generalized symptoms of depression. The Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI-II), Patient Health Questionaire-9 (PHQ-9), and Geriatric Depression Scale (GDS) are the main scales that are also validated in neuro-oncologic patients.[35]

The Hospital Anxiety and Depression Scale (HADS) was designed to detect both anxiety and depression disorders. It consists of a 14-item scale (7 items related to anxiety and 7 items related to depression). Each item is scored from 0 to 3 meaning that each patient can score between 0 to 21 for either anxiety or depression. The cut off points for each symptom (anxiety or depression) are the following: 0–7 (normality), 8–10 (borderline), and 11–21 (abnormal). Average administration time is estimated at around ≤10 minutes.[36]

HADS presents good psychometric proprieties, with high intra-rater reliability (α=0.82), also including cancer patients in its assessment, and high inter-rater reliability ($k = 0.86$),[37] although this last property was not determined using neuro-oncology patients.

On the other hand, the Beck Depression Inventory Second Edition (BDI-II) is the most recent version of the BDI, one of the most widely

used self-report measures of depression in both research and clinical practice. BDI-II is a 21-item self-report inventory measuring the severity of depression in adolescents and adults, who are asked to respond to each question over a two-week time period. BDI-II assesses 21 symptoms and attitudes which include mood, pessimism, sense of failure, lack of satisfaction, guilty feelings, sense of punishment, self-dislike, self-accusation, suicidal ideation, crying, irritability, social withdrawal, indecisiveness, distortion of body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido. The BDI-II is scored by adding up the highest ratings for each of the 21 symptoms. Items are organized according to their severity, rating each symptom on a 4-point scale from 0 (absent) to 3 (severe). A score of 0–13 indicates minimal depression, 14–19 mild depression, 20–28 moderate depression, and 29–63 severe depression. The BDI has reported high intra-rater reliability ($\alpha>0.75$). Its inter-rater reliability was not reported.

In addition, the Patient Health Questionnaire (PHQ-9) is a brief measure designed exclusively to detect depression severity at a point in time and to monitor changes over time. It is a self-administered questionnaire consisting of 9 items in relation to symptoms of depression having occurred in the previous two weeks. The proposed cut-off points are: 1–4 (minimal depression), 5–9 (mild depression), 10–14 (moderate depression), 15–19 (moderately severe depression), and 20–27 (severe depression). The average administration time estimated is about ≤10 minutes. There is another shorter version in existence, the PHQ-2 questionnaire, which is validated in cancer but not yet in neuro-oncology patients. The internal consistency of the PHQ-9 has been shown to be high (α=0.85 -0.89), specifically in neuro-oncology patients it is α=0,85. Its inter-rater reliability was not reported.[37]

Finally, special mention should be made of the Geriatric Depression Scale (GDS), which was recently recommended for screening for depression in elderly cancer patients on chemotherapy.[38] The GDS Long Form is a brief, 30-item questionnaire in which participants are asked to respond by answering “yes” or “no” in reference to how they have felt over the past week. Another shorter version of GDS consisting of a 15-item questionnaire is also available. Items were selected from the Long Form GDS (the ones with the highest correlation with depressive symptoms in validation studies). From the 15 items, 10 indicated the presence of depression when answered positively, while the rest (question numbers 1, 5, 7, 11, and 13) indicated depression when answered negatively. Scores of 0–4 are considered normal, depending on age,

education, and complaints; 5–8 indicate mild depression; 9–11 indicate moderate depression; and 12–15 indicate severe depression. The Short Form is easier to perform in mildly to moderately demented patients who have short attention spans and/or feel easily fatigued. It takes about 5 to 7 minutes to complete. It is a useful screening tool in a clinical setting to facilitate assessment of depression in older adults especially when baseline measurements are compared to subsequent scores. The short form of GDS, in cancer patients, has an acceptable inter-rater reliability (α=0.749).

4.1.3. Delirium and psychosis

Delirium is one of the most common complications seen in cancer patients. It is defined as a disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.[2] Improving the recognition and treatment of this condition would reduce morbidity and mortality rates, as well as health-care costs and prolonged hospital stays among other factors. Several delirium assessment tools, also tested in cancer patients, have been designed to assess delirium severity: the Memorial Delirium Assessment Scale (MDAS), the Delirium Rating Scale-Revised 98 (DRS-R-98), the Delirium Observation Screening (DOS) Scale, and the Confusion Assessment Method (CAM) (see table 2.2.15).

The Delirium Rating Scale (DRS), currently on its revised version (DRS-R-98) is considered the gold standard. Recently, it has been validated for the new DSM-5 criteria.[39] The DRS-R-98 consists of a 13-severity item score ranging from 0 (not present) to 3 points (severely present). It includes an extra 3-item score (to differentiate delirium from other disorders), all rated over the previous 24 hours. Severity scores range from 0 to 39, and total scores range from 0 to 46. Scores $\geq$15 are indicative of delirium. The DRS-R-98 takes about 10 to 15 min to complete and it has demonstrated good psychometric proprieties, with a high intra-rater reliability score (α =0.87). Compared with the previous DRS test, DRS-R98 does not yet provide data in cancer patients.

The Memorial Delirium Assessment (MDAS) is a validated 10-item scale that was initially designed to quantify the severity of delirium in medically hospitalized cancer and acquired immunodeficiency syndrome (AIDS) patients. The items assess disturbances in arousal and level of consciousness, as well as cognitive impairment: reduced level of awareness, disorientation, short-term memory impairment, impaired digit span, attention disorder, and disorganized thinking, perceptual disturbance, delusions, psychomotor activity, and sleep–wake cycle disturbance. Each

item is scored from 0 to 3 for a maximum total score of 30 points. Scores ≥13 indicate the presence of delirium as revealed in the validation study. The average estimated administration time estimated is about 10 minutes. MDAS has demonstrated good psychometric proprieties, with high intra-rater reliability (α =0.91) and high inter-rater reliability (ICC= 0.92) in the group of cancer patients.[40]

The Delirium Observation Screening Scale (DOS) is a brief 13-point screening tool based on observation and designed for nurses to use. Responses are dichotomous. Scores ≥3 are considered positive delirium screens. The DOS was developed to achieve fast, early recognition of delirium during routine clinical care, and it has recently been shown to be an accurate screening tool for delirium in patients with advanced cancer, including patients with brain metastasis. DOS has demonstrated good psychometric proprieties, with an intra-rater reliability score of α=0.772, also including brain cancer patients,[41] no inter-rater reliability is available yet.

Finally, the Confusion Assessment Method (CAM) is a brief diagnostic test designed to allow non-psychiatric clinicians to identify delirium. The CAM is based on 9 delirium features: acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation and an altered sleep–wake cycle. The diagnostic algorithm is based on 4-cardinal features of delirium (the ones that have the greatest ability to distinguish delirium from other types of cognitive impairment): (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. A diagnosis of delirium according to the CAM requires the presence of features 1, 2, and either 3 or 4.[42] The estimated average administration time is about 5 minutes.

There is also a CAM-ICU version for use with non-verbal mechanically ventilated patients, and CAM-S to assess delirium severity.

CAM has demonstrated good psychometric proprieties with a high inter-rater reliability score assessing the 4- CAM features (k = 0.81)[43] also including brain cancer patients. No data of intra-rater reliability is available.

Psychosis is defined as a disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia or bipolar disorder, or a symptom induced by a brain tumor.[2] There are no existing specific scales that evaluate psychosis in neuro-oncologic patients. However, it is worth mentioning the Positive and Negative Syndrome Scale (PANNS), which is designed to evaluate the presence, absence, and severity of positive, negative, and

general psychopathology symptoms of schizophrenia. Of the 30-items included, 7 constitute a positive scale, 7 a negative scale, and the remaining 16 a general psychopathology scale. The scores for these scales are obtained by adding the ratings across component items. In terms of psychometric proprieties, PANNS-Positive has an intra-rater reliability score of α=0.64, PANNS-Negative of α=0.81, and the General Psychopathology Scale of α =0.77.[44] The data for inter-rater reliability was obtained from the Swedish version validation, where PANNS-Negative ICC has an intra-rater reliability score of 0.83–0.90, PANNS-Positive ICC of 0.98–0.99, and the General Psychopathology Scale ICC of 0.95–0.98.[45]

4.1.4. Suicide

Suicide is unfortunately not infrequent in neurological diseases, and the neuro-oncologist has the responsibility to foresee it and try to prevent it. The most renowned psychiatric scales to evaluate suicide risk are presented in table 2.2.16. Thus far, there is no validated scale for neuro-oncological patients. The Hopelessness Scale (HS) has been explored in general cancer patients, without specifying the type of tumor, but with a reduced implementation due to its psychometric limitations.[46]

5. Fatigue

Most cancer patients are at risk of suffering from fatigue, which is greatly detrimental to their quality of life. Its treatment requires a multidisciplinary approach, as multifactorial causes can be involved in its pathogenesis. Factors that play a role in fatigue development are the cancer itself, oncologic treatments conditioning medical comorbidities and endocrine dysfunction, supportive therapies, untreated mood disorders, and physical conditions. In the general cancer population, the prevalence at the time of diagnosis is about 50–75%, reaching 93–95% during oncologic treatments. Moreover, fatigue can persist years after ending treatments in around 30% of patients.[47] Table 2.2.17 presents a summary table of cancer and supportive therapies that have been associated with fatigue.

5.1. Scales and scores

Established scales in oncology

The CTCAE system graduates the severity of fatigue into 3 grades (see table 2.2.1). Neither grade 4 nor 5 are included because fatigue could not threaten life nor cause death by itself.

Various published clinical practice guidelines,[5]* recommend screening for fatigue in cancer patients (in pre-treatment, during active treatment, and post-treatment), thereby becoming an important aspect of oncologic supportive care.

On the other hand, there are several scales designed to evaluate fatigue, but there is no standard consensus of which ones should be used, mainly due to the absence of agreement on the definition of fatigue. As an example, the NCCN defines fatigue as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Another example is the definition provided by CTCAE that describes fatigue as a disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.

The principal and more extended unidimensional scales (providing information only about severity) and multidimensional scales used in fatigue studies including neuro-oncology patients are reviewed below (table 2.2.18).[48]

The Brief Fatigue Inventory (BFI) is a short 9-item numeric scale designed in 1999 for measuring the severity of fatigue and fatigue-related impairment in cancer patients. It was based on the Brief Pain Inventory (BPI) scale, and it has been validated in several cancer types, including brain tumors. It graduates the severity of fatigue in a numerical scale from 0 to 10 and it can be used both during treatment and after treatment.[49–50] The items analyzed are general activity, mood, walking ability, normal work (includes work outside the home and housework), relations with other people, and enjoyment of life. Among psychometric proprieties, the

[5]* National Comprehensive Cancer Network Clinical Practice Guideline (NCCN Guidelines) in Oncology for Cancer-Related fatigue (lasted version 1.2019), NCCN Guidelines for Survivorship (lasted version 1.2019), Pan-Canadian Guideline for Screening, Assessment (lasted version 4.2015), and Management of Cancer-Related Fatigue in Adults and American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Adaptation (4.2014).

BFI presents high intra-rater reliability (k=0.73), although no data on its inter-rater reliability is available.[49]

The Cancer Fatigue Scale (CFS) is a 15-item scale designed in 2000 for measuring three dimensions of fatigue (physical fatigue, cognitive fatigue, and activity-related fatigue subscales). This scale has been validated in several cancer types, including brain tumors.[50] Among psychometric proprieties, the CFS has an intra-rater reliability of α=0.88. No data on its inter-rater reliability is available.[49]

Discussion

Our desire to take into account the objective of providing a supportive tool for neuro-oncologists has led us to discuss the applicability of the current scales validated for the assessment of non-focal neurological symptoms in cancer patients.

Headache

The majority of cancer patients have functional impairments that are a consequence of the cancer itself, but are also the result of comorbidities associated with advanced age. The CTCAE evaluates the severity of headaches according to only one descriptor, activity. The inconvenience of measuring headache severity according to activity in oncologic patients is how to distinguish which spectrum of functional impairments are directly related to the neurological symptom. Taking into consideration these observations, the Six-Item Headache Impact Test (HIT-6) could be recommended as the most appropriate scale to measure the functional impairment of headaches in cancer patients (in terms of impact). Its reliability and brevity and the non-interference of confounding factors facilitate its implementation; however, a validation on cancer patients has not yet been performed. The Migraine Disability Assessment Questionnaire (MIDAS) is less applicable since the disability in oncologic patients may be influenced by multiple external factors. When it comes to severity scales, we do suggest the use of either CTCAE or the Visual Analogue Scale (VAS), both already validated in our group of interest. Other pain intensity scales (VRS, NRS, and FPS), despite having been widely used in oncologic clinical trials, have yet to be validated.

Encephalopathy and level of consciousness

There are no existing validated scales for encephalopathy assessment, except those specifically developed for encephalopathies derived from CAR-T cell therapies. In this case, the ASBMT group provides a uniform consensus grading system (ICANS) recommending the use of either the CAR-T Cell Therapy Associated Toxicity Score (CARTOX-10) or the Immune Effector Cell-Associated Encephalopathy (ICE) Score, both currently being validated.

CARTOX-10 and ICE scores try to give a response, attempting to better define encephalopathy and the other neurological symptoms that accompany the medical condition. However, CARTOX-10, is less complete than ICE because it does not consider receptive aphasia, a symptom frequently present in those patients.

If our focus on encephalopathy assessment is impaired consciousness, the Glasgow Coma Scale (GCS) is still the most widespread choice among specialists.

The use of the CTCAE system for grading encephalopathy is more limited due to the overlap of symptoms with other adverse neurological events and also for the way in which severity is measured and defined (based on the limits on daily living activities when we are considering hospitalizing patients).

Cognitive impairment

In terms of cognitive assessment, the principal recommendation is the use of the neurocognitive battery tests proposed by the ICCTF (HVLT-R, TMT forms A-B, and COWA) as they have been validated in cancer and neuro-oncologic patients. The cognitive domains explored consider verbal memory, information processing speed, and executive functions. The application of the ROCF (first and second copies) is also recommended as it will complement the neuropsychological study by adding information about visuospatial perception, apraxia, and visual memory. For the elderly cancer population, the Mini-Cog and the Blessed Orientation-Memory-Concentration (BOMC) are considered useful tools for a global cognitive assessment.

Finally, in terms of apathy evaluation, the use of the Apathy Evaluation Scale (AES) is recommended. Although this scale has not been validated in neuro-oncology patients, it has been widely used in brain tumor clinical trials.

Psychiatric disorders

Often the limited visitation time and the stigma related to mood disorders leads to these issues being overlooked in daily clinical practice. Except for the selected anxiety/depression scales—Hamilton Depression Rating Scale (HADS), Beck Depression Inventory (BDI-II), Patient Health Questionnaire (PHQ-9), and Geriatric Depression Scale (GDS)—and delirium scales—Delirium Rating Scale (DRS-R-98), Memorial Delirium Assessment Scale (MDAS), Delirium Observation Screening (DOS), and Confusion Assessment Method (CAM)—there are no other validated screening tools for a particular psychiatric symptom in cancer patients. The CTCAE system is the recommended tool for evaluating the severity of specific psychiatric symptoms. Furthermore, as the first initial step of the psychiatric evaluation and following NCCN guidelines, it is recommended that each patient visit start with the Distress Thermometer Test, which has been validated in oncologic patients, and later on graduate the severity of the symptoms with the CTCAE system.

Fatigue

When it comes to fatigue, the use of either the CTCAE or the Brief Fatigue Inventory (BF) could be recommended for the assessment of fatigue severity as a unidimensional domain. However, for a more detailed assessment, we recommend using a multidimensional scale such as the Cancer Fatigue Scale (CFS). This may be a more appropriate approach for the assessment of cancer patients, as fatigue is associated with other cancer symptoms.

Finally, we would like to note that due to the disposal of specific tools for the assessment of fatigue in neuro-oncology patients, this chapter does not include fatigue scales used in general neurology practice, like the Neurological Fatigue Index, validated in multiple sclerosis (NFI-MS), stroke (NFI-stroke), and motor neurone disease (NFI-MND). Also, the Fatigue Severity Scale (FSS), the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F), the Parkinson Fatigue Scale (PFS), and the visual Analog Fatigue Scale (VAFS) are scales widely used in the assessment of fatigue in Parkinson's disease.

Table 2.2.1. Extract from CTCAE v5.0

CNS global symptom	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life - threatening consequences; urgent intervention indicated	Death
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	-
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self-care ADL; inconsolable; medical or psychiatric intervention indicated	-	-
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid, extreme disorganization); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self-care ADL; urgent intervention indicated; new onset	Life-threatening consequences, threats of harm to self or others; urgent intervention indicated	Death
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Suicidal attempt	-	-	Suicide attempt or gesture without intent to die	Suicide attempt with intent to die which requires hospitalization	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	-	-

Table 2.2.2. Causes of headache in cancer patients.

Headache	
Cancer	**Brain primary tumors and brain metastases**
Systemic therapies	**Conventional chemotherapy agents**: Procarbazine, Methotrexate, 5-Fluorouracil, Ara-C, Temozolomide, Etoposide, Hydroxyurea, Nitrosoureas, L- Asparaginase, Cisplatin, Gemcitabine, Cladribine, Capecitabine, Fludarabine, Nelarabine, Topotecan **Anti-hormonal therapy**: Tamoxifen **Cytokines**: Interferons, Interleukins, Tumor necrosis factor, OKT3, levamisole **Differentiation agents**: Retinoid acid **Monoclonal antibody**: Rituximab, Trastuzumab, Ipilimumab, Bevacizumab **Small molecules inhibitors**: Tyrosine kinase inhibitor (Imatinib); mToR inhibitors (Everolimus); Histone deacetylase inhibitors (Panobinostat); Serine/threonine kinase inhibitors (Vemurafenib) **Chimeric Antigen Receptor (CAR) T Cells**
Intrathecal chemotherapy	**Any** (Methotrexate, Ara-C, Topotecan, Thiotepa)
Radiotherapy	**Acute**: radiation encephalopathy **Subacute**: demyelinating encephalopathy **Chronic**: Radiation necrosis, Smart syndrome
Supportive therapies	**Corticosteroids, cimetidine, metoclopramide, ondansetron, opioids** (withdrawal)

Table 2.2.3. Functional impairment and severity headache scales most used in neurology practice.

Measure	Test	Reference
Functional Impairment **IMPACT**	Six-Item Headache Impact Test (HIT 6)	Kosinski et al., *Qual Life Res* 12 (8): 963–74, 2003
Functional Impairment **DISABILITY**	Migraine Disability Assessment Questionnaire (MIDAS)	Stewart et al., *Cephalalgia* 19: 107–14, 1999; Stewart et al. *Pain* 88: 41–52, 2000; Blumenfeld et al., *Cephalalgia* 31 (3): 301–15, 2011
INTENSITY	Verbal Rating Scale (VRS)	Jensen et al., *Pain* 27: 117–26, 1986
	Visual Analogue Scale (VAS)	Huskisson et al., *Lancet* 2: 1127–31, 1974
	Numerical Rating Scales (NRS)	Hartrick et al., *Pain Pract* 3 (4): 310–16, 2003
	Faces Pain Scale (FPS)	Bieri et al., *Pain* 41 (2): 139–50, 1990; Wong et al. *Pediatric Nursing* 14: 9–17, 1988
*Note: none of the headache scales have been validated in neuro-oncology patients		

Table 2.2.4. Causes of encephalopathy secondary to cancer treatments.

Encephalopathy	
Systemic therapies	**Conventional chemotherapy agents**: L-Asparaginase, 5-Azacytidine, Cisplatin, Cytarabine, Etoposide, Fludarabine, Methotrexate, Mitomycin C, Nelarabine, Nitrosoureas, Procarbazine, Tamoxifen, Thiotepa, Gemcitabine, Ifosfamide, Vincristine, Cyclophosphamide, Cyclosporine **Small molecule inhibitor**: Bortezomib **Antiangiogenic agents**: Bevacizumab, Sorafenib, Sunitinib **Biological agents**: Rituximab, Interferonα, interleukin-2, Ipilimumab, Chimeric Antigen Receptor (CAR) T Cells **Immunomodulatory agents**: Sirolimus, Tacrolimus
Intrathecal chemotherapy	**Any** (Methotrexate)
Radiotherapy	**Acute**: encephalopathy **Subacute**: demyelinating encephalopathy **Chronic**: Radiation necrosis, Smart syndrome
Supportive therapies and others	**Anticonvulsants**: carbamazepine, gabapentin, levetiracetam, lamotrigine, phenytoin, valproic acid **Antibiotics**: cephalosporins, penicillin, metronidazole **Ondansetron, morphine** **Intravenous immunoglobulins**

Table 2.2.5. CAR-T cell neurotoxicity scales.

Measure	Test	Reference
Encephalopathy	CAR-T-cell-therapy-associated TOXicity score (CARTOX-10)	Neelapu et al., *Nat Rev Clin Oncol* 15: 47–62, 2018
	Immune Effector Cell-Associated Encephalopathy score (ICE score)	Lee et al., *Biol Blood Marrow Transplant* 25, 2018

Table 2.2.6. Level of consciousness scales most used in neurology practice.

Measure	Test	Reference
Level of consciousness	Glasgow Coma Scale (GCS)*	Teasdale et al., *Lancet* 2(7872): 81–84, 1974; Teasdale et al., *Acta Neurochir* 34: 45–55, 1976
	Reaction Level Scale (RLS85) *	Starmark et al., ICRAN, Edinburgh, 1982; Starmark et al., *Acta Neurochir* 90 (3–4): 73–80, 1988
	Comprehensive Level of Consciousness Scale (CLOCS)	Stanczak et al., *J Neurosurg* 60 (5): 955–60, 1984
	Full Outline of Unresponsiveness score (FOUR score) *	Widjicks et al., *Ann Neurol* 58: 585–59, 2005
* validated in Neuro-oncology patients		

Table 2.2.7. Causes of cognitive impairment secondary to cancer-directed therapies.

Cognitive impairment	
Cancer	**Systemic Tumor by itself** and brain areas involved in **primary or metastatic lesions**
Cancer therapies	**Conventional chemotherapy agents**: Nitrosureas, Cisplatin, Cyclophosphamide, Ara-C, Dacarbazine, Fludarabine, 5-FU, Ifosfamide, Methotrexate, Vincristine **Anti-hormonal therapy:** Tamoxifen **Cytokines:** INF α, levamisole **Molecular targeted- therapies**: Antiangiogenics agents, check-points inhibitors **Chimeric Antigen Receptor (CAR) T Cells** **Radiation therapy** **Surgery**
Supportive therapies	**Corticosteroids, analgesics, anti-epileptic drugs**

Table 2.2.8. Global cognitive evaluation scales (brief and large tests).

Measure	Test	Reference
Global mental impairment/deterioration **(Brief Test)**[1]	Mental Status Questionnaire (MSQ)	Kahn et al., *Am J Psychiatry* 117 (August): 120–24, 1960
	Orientation-Memory-Concentration Test (OMC)	Katzman et al., *Am J Psychiatry* 140 (6): 734–39, 1983
	Abbreviated Mental Test Score (AMTS)	Hodkinson, *Age Ageing* 1 (4): 233–38, 1972; *Occas Pap R Coll Gen Pract* (59): 28, 1993
	Short Portable Mental State Questionnaire (SPMQ)	Pfeiffer, *J Am Geriatr Soc* 23 (10): 433–41, 1975
	Blessed Orientation-Memory-Concentration (BOMC)*	Katzman et al., *Am J Psychiatry* 140: 734–39, 1983
	The 7-minute Screen	Solomon et al., *Fam Med*, 30 (4): 265–71, 1998
	Memory Impairment Screen (MIS)	Buschke et al., *Neurology* 52 (2): 231–38, 1999
	Mini- Cog*	Borson et al., *Int J Geriatr Psychiatry* 15: 1021–27, 2000
	Short Test of Mental Status	Kokmen et al., *Mayo Clin Proc* 62 (4): 281–88, 1987
	Mini-mental State Examination (MMSE)*	Folstien et al., *J Psychiatr Res* 12 (3): 189–98, 1975

[1] ≤10–15 minutes.

Global mental impairment/deterioration **(Large Test)**[2]	Clifton Assessment Procedures for the Elderly (CAPE)	Pattie et al., *Br J Psychiat* 133: 457–60, 1978
	Mattis Dementia Rating Scale (MDRS-2) *	Mattis, *Dementia rating scale: professional manual*, 1988; Jurica et al., *Psychological Assessment Resources*, 2001
	Halsted-Reitan Test Battery (HRNB)	Golden et al., in Grune & Stratton, New York, 1980
	Cognitive Abilities Screening Instrument (CASI)	Teng et al., *Int Psychogeriatr* 6 (1): 45–58, 1994
	High Sensitivity Cognitive Screen (HSCS)	Faust et al., *J Nerv Ment Dis* 177 (1): 25–31, 1989
	Montreal Cognitive Assessment (MoCA)*	Nasreddine et al., *J Am Geriatr Soc* 53 (4): 695–99, 2005
*studies included oncological patients		

[2] ≥10–15 minutes

Table 2.2.9. Specific domains cognitive evaluation.

Neurocognitive Domain	Localization	Test	Reference
Intelligence	Verbal intelligence	Subtest vocabulary WAIS-IV	Wechsler, in *The Psychological*, New York, 1955; Wechsler, in *The Psychological Corporation*, San Antonio, TX, 2008
	Non-verbal intelligence	Subtest matrix reasoning WAIS-IV	
Verbal Memory	Left hippocampus	Hopkins Verbal Learning Test Revised (HVLT-R)	Brandt, *Clinical Neuropsychologist* 5: 2: 125–42, 1991
Visual Memory	Right hippocampus	Rey-Osterrieth Complex Figure (ROCF): 1st copy	Osterrieth, *Archives de Psychologie* 30: 206–356, 1944
Attention and information processing speed	Frontal lobe	Trail Making Test A Digit symbol subtest of the WAIS-IV	Reitan, *Perceptual and Motor Skills* 8 (3): 271–76 Wechsler, in *The Psychological*, New York, 1955; Wechsler, in *The Psychological Corporation*, San Antonio, TX, 2008
Working memory		Digit span subtest of the WAIS-IV	Wechsler, in *The Psychological*, New York 1955; Wechsler, in *The Psychological Corporation*, San Antonio, TX, 2008
Executive functions		Controlled Oral Word Association (COWA) Trail Making Test B Rey-Osterrieth Complex Figure (ROCF): 1st copy	Benton et al., in *AJA Associates*, Iowa City, IA, 1994 Reitan, *Perceptual and Motor Skills* 8 (3): 271–76, 1958

Visuospatial perception	Parietal- occipital right lobe	Rey-Osterrieth Complex Figure (ROCF): 1st copy Block design subtest of WAIS-IV	Osterrieth, *Archives de Psychologie* 30: 206–356, 1944 Wechsler, in *The Psychological*, New York, US, 1955; Wechsler, in *The Psychological Corporation*, San Antonio, TX, 2008
Language	Left hemisphere: Broca's area- Arcuate fasciculus-Wernicke's area	Boston Naming Test Category Fluency Test Vocabulary subtest of WAIS-IV	Kaplan et al., in Lea & Febiger, Philadelphia, 1983 Lezak et al., in New York: Oxford University Press, 2004 Wechsler, in *The Psychological*, New York, 1955; Wechsler, in *The Psychological Corporation*, San Antonio, TX, 2008

Table 2.2.10. Neurocognitive testing battery recommend in Oncological patients' assessment.

Neurocognitive Domain	**Test**
Verbal Memory	Hopkins Verbal Learning Test Revised (HVLT-R)*
Attention and information processing speed	Trail Making Test (TMT)*
Executive functions	Controlled Oral Word Association (COWA)*
Visuospatial perception and Visual Memory	Rey-Osterrieth Complex Figure (ROCF): 1st and 2nd copy
*recommendations of ICCTF (**76**)	

Table 2.2.11. Apathy scales most used in neurology practice.

Measure	Test	Validation groups	Reference
Apathy	Apathy Evaluation Scale (AES)*	Acquired brain injury (stroke, hypoxic brain damage, Alzheimer's disease, traumatic brain injury), depression, healthy controls	Marin et al., *Psychiatry Res* 38 (2): 143–62, 1991
	Starkstein Apathy Scale (SAS)	Parkinson's disease	Starkstein et al., *J Neuropsychiatry Clin Neurosci* 4 (2): 134–39, 1992
	Apathy inventory (AI)	Alzheimer's disease, Parkinson's disease and non-demented elderly subjects	Robert et al., *Int J Geriatr Psychiatry* 17 (12): 1099–105, 2002; Leone et al., *La revue de gériatrie* 33 (9): 777–83, 2008
	Lille Apathy Rating Scale (LARS)	Parkinson's disease and healthy controls	Sockeel et al., *J Neurol Neurosurg Psychiatry* 77 (5): 579–84, 2006; Dujardin et al., *Mov Disord* 28 (14): 2014–19
	Non-motor Symptoms Scale (NMSS) from MDS-UPDRS[3]	Parkinson's disease	Chaudhuri et al., *ACNR* 4 (4): 20–25, 2004
*studies included Neuro-oncological patients			

[3] Movement Disorders Society, Unified Parkinson's Disease Rating Scale.

Table 2.2.12. Causes of Psychiatric disorders related to cancer patients.

Psychiatric Disorders	
Cancer	**Tumor and brain areas involved**
Cancer therapies	**Conventional chemotherapy agents** **Biological agents:** Interferonα, interleukin-2, Ipilimumab, Chimeric Antigen Receptor (CAR) T Cells **Hormonal therapy** **Radiation therapy**
Supportive therapies and others	**Anticonvulsants:** levetiracetam **Antibiotics**: voriconazole, cefepime, ceftazidime **Corticosteroids** **Benzodiazepines** **Opioids**
Comorbidities	**Other systemic diseases, sleep disorders, psychosocial factors**

Table 2.2.13. Generalized anxiety scales most used in Neurology practice.

Measure	**Test**	**Reference**
Anxiety	Hamilton Anxiety Scale (HAM-A)	Hamilton et al., *Br J Med Psychiat* 32: 50–55, 1959
	State-Trait Anxiety Inventory (STAI)	Spielberger et al., Consulting Psychologists Press (1970, 1983)
	Hospital Anxiety and Depression Scale (HADS-A)*	Zigmong et al., *Acta Psychiatr Scand* 67: 361–70, 1983
	Brief Scale for Anxiety (BADS)	Tyrer et al., *J Neurol Neurosurg Psychiatry* 47: 970–75, 1984
	Beck Anxiety Inventory (BAI)	Beck et al., *J Consult Clin Psychol* 56: 893–97, 1988
	Anxiety Scale	Goldberg et al., *Br Med J* 97: 897–99, 1988
* validated in neuro-oncology patients		

Table 2.2.14. Depression scales most used in Neurology practice

Measure	Test	Reference
Depression	Hamilton Depression Rating Scale (HAM-D)	Hamilton, *J Neurol Neurosurg Psychiatry* 23: 56–62, 1960
	Beck Depression Inventory (BDI-II)	Beck et al., *Arch Gen Psychiatry* 4: 561–71, 1961; Beck et al., San Antonio, TX: Psychological Corporation, 1996
	Montgomery-Asberg Depression Rating Scale (MADRS)	Montgomery et al., *Br J Psychiatr* 134: 382–89, 1979
	Geriatric Depression Scale (GDS)*	Yesavage et al., *J Psychiatr Res* 17 (1): 37–49, 1982–83; Mohile et al., *J Clin Oncol*, 36 (22): 2326–47, 2018
	Hospital Anxiety and Depression Scale (HADS-D)*	Zigmong et al., *Acta Psychiatr Scand* 67: 361–70, 1983
	Patient Health Questionare-9 (PHQ-9)*	Kroenke et al., *J Gen Intern Med*, 16 (9): 606–13, 2001
* validated in neuro-oncology patients		

Table 2.2.15. Delirium and psychosis scales.

Measure	Test	Reference
Delirium **SEVERITY**	Delirium Rating Scale (DRS*-R-98)	Trzepacz et al., *J Neuropsychiatry Clin Neurosci* 13: 229–42, 2001
	Memorial Delirium Assessment Scale (MDAS)*	Breitbart et al., *J Pain Symptom Manage* 13: 128–37, 1997
	Delirium Observation Screening (DOS) Scale*	Schuurmans et al., *Res Theory Nurs Pract* 17: 31–50, 2003
	Confusion Assessment Method (CAM)*	Inouye et al., *Ann Intern Med* 113: 941–48, 1990
Psychosis	Positive and Negative Syndrome Scale (PANNS)	Kay et al., *Schizophr Bull* 13 (2): 261–76, 1987
* validated in neuro-oncology patients		

Table 16. Psychiatry scale most used to evaluate suicide risk.

Measure	Test	Reference
Suicide **RISK**	Scale for Suicide Ideation (SSI)	Beck et al., *J Consult Clin Psychol* 47 (2): 343–52, 1979
	Hopelessness Scale (HS)	Beck et al., *J Consult Clin Psychol* 42 (6): 861–65, 1974
	Risk Suicide (RS)	Plutchik et al., *Prog Neuropsychopharmacol Biol Psychiatry* 13 Suppl: S23–34, 1989

Table 17. Causes of cancer-related fatigue.

Fatigue	
Cancer	Tumor and brain areas involved
Cancer therapies	Conventional chemotherapy agents Biological agents Molecular targeted-therapies Hormonal therapy Radiation therapy Surgery
Cancer-associated conditions	Endocrine dysfunction, anemia, electrolyte imbalance, and infections
Comorbidities	Other systemic diseases, sleep disorders, psychosocial factors, and pain
Supportive therapies	Opioids, antiepileptic drugs, anxiolytics, hypnotics, and analgesics

Table 2.2.18. Fatigue scales most used in oncology practice.

Measure	Test	Reference
Unidimensional **Severity**	Profile of Mood State-Fatigue (POMS-F)	McNair et al., Educational and Testing Service, 1971
	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ C30)	Aaronson et al., *J Natl Cancer Inst*. 85: 365–76, 1993
	Fatigue Questionnaire (FQ)	Chalder et al., *J Psychosom Res* 37 (2): 147–53, 1993
	Functional Assessment of Cancer Therapy- Fatigue (FACT-F)	Yellen et al., *JPain Symptom Manage* 13 (2): 63–74, 1997
	Brief Fatigue Inventory (BFI)*	Mendoza et al., *Cancer* 85 (5): 1186–96, 1999
Multidimensional	Checklist Individual strength (CIS)	Vercoulen et al., *J. Psychosom Res* 38: 383–92, 1994
	Multidimensional Fatigue Inventory-20 (MFI-20)	Smets et al., *J Psychosom Res* 39 (3): 315–25, 1995
	Schwartz Cancer Fatigue Scale (SCFS-6)	Schwartz et al., *J Nurs Meas* 7: 35–45, 1999
	Cancer Fatigue Scale (CFS)*	Okuyama et al., *J Pain Symptom Manage* 19 (1): 5–14, 2000
	Daily Fatigue Cancer Scale (DFCS)	Baussard et al., *Eur J Oncol Nurs* 2017 26: 42–48, 2000
	Piper Fatigue Scale-12 (PFS-12)	Reeve et al., *Breast Cancer Res Treat* 136 (1): 9–20, 2012
*validated in neuro-oncology patients		

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CHAPTER 2.3

EVALUATION OF SPINAL CORD FUNCTION IN CANCER TREATMENT-ASSOCIATED TOXICITY

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Abstract

Neurotoxicity to the spinal cord in association with cancer therapy may occur in several different treatment settings, according to surgical, radiotherapeutic, chemotherapeutic, immunologic, or combined treatment approaches. The onset of neurological signs and symptoms from cancer treatment-associated spinal toxicity, as well as their evolution over time, is heavily entangled with the treatment applied.

The clinical identification and evaluation of spinal cord dysfunction in association with cancer treatment mostly depends on the experience of the treating physician. As these side effects are generally rare, specially trained Neurologists or clinical Neurooncologists would generally be required. In clinical routine, the possibility for quantification of spinal cord signs and symptoms, using validated scales and scores, is limited as there are no clinical studies available.

However, while there a numerous scores and grading systems that focus on spinal cord function reported in the literature, there is no specific evaluation system established to quantify cancer treatment-associated spinal toxicity. Most applied spinal grading systems are focused on prognosis and treatment outcome after surgical and/or radiotherapeutical intervention. For study purposes, the evaluation of treatment-related spinal dysfunction may best be documented by using one of the frequently used grading systems. For clinical routine, close clinical neurological monitoring is recommended.

In order to prevent further neurological damage, preserve gait function, and maintain quality of life, knowledge of cancer treatment-associated spinal toxicity is essential for clinicians engaged in the management of cancer patients.

Keywords: spinal cord toxicity, chemotherapy, radiotherapy, surgery, spinal cord toxicity scales, spinal toxicity scores, spinal toxicity grading, Frankel classification grading, Nurick's classification system, Ranawat classification, American spinal injury association, McCormick grading system, Tokuhashi score, NCI Common Terminology Criteria for Adverse Events, European myelopathy score, Cooper scale

Introduction

The association between spinal cord toxicity and cancer treatment has already been extensively elaborated in Part 2. The basis for diagnosis of spinal cord dysfunction due to cancer treatment is the knowledge concerning different cancer treatment modalities including surgical, radiotherapeutic, systemic, and immunological approaches and their potential side effects.

Although the occurrence of spinal toxicity during cancer treatment is generally rare, it may have an impact on the prognosis and it will definitely affect neurological function and quality of life in those patients. The quantification of cancer-associated spinal cord toxicity according to a grading system remains a challenge, as there is a clear lack of evidence.

Therefore, the diagnosis of treatment-associated spinal cord toxicity in cancer patients is very much up to the clinicians engaged in the patient care. The first hints of spinal cord dysfunction associated with cancer treatment are neurological signs and symptoms occurring during the course of treatment, such as back pain, gait dysfunction, sensory deficits affecting the limbs, and bladder and bowel dysfunction, or an occurrence on a sensory level. Most of the toxicities are cumulative, which means an increase of neurological signs and symptoms during the course of treatment.

In the literature, there is no dedicated scale or score for quantification of cancer-associated spinal cord dysfunction. As most reported treatment-associated spinal toxicities in cancer patients result from cases with different tumors and different treatment regimens, there is—to date—no evidence for a grading system. Moreover, the broad spectrum of possible causal relationships between cancer treatment and spinal toxicity, as well as the various differential diagnostic considerations,

seems to hamper a structured approach (Dornbos et al. 2019; Pinnix et al. 2017; Alberti et al 2016; Alsdorf et al. 2016). However, several scales and scores are used to quantify spinal cord dysfunction to document the extent of spinal cord injury and their possible implications on prognosis and neurological recovery.

As spinal toxicity associated with cancer treatment is very uncommon, other more frequent causes should be considered for patients who develop spinal cord dysfunction during the course of the disease. First, metastases to the spine with spinal cord compression or neoplastic meningitis must be ruled out (Oberndorfer et al. 2012). Second, inflammatory causes, such as viral (VZV) infections in immunocompromised patients, need to considered, as must degenerative spine diseases such as disc disease, spondylitis, or spondylarthrosis.

Besides the clinical neurological work-up, the application of a grading system in spinal cord dysfunction due to cancer treatment may not only be of help in the setting of a clinical study, but may also provide useful and structured information for caregivers in everyday practice (Dornbos et al. 2019).

Scale and score used for spinal cord injury

The following scores and grading systems that are discussed were selected due to their appearance and application in cancer treatment studies, as well as in case reports with a focus on spinal cord toxicity. The order of appearance is alphabetical:

The American Spinal Injury Association (AISA) Score was an advancement of the Frankel Classification grading system; it allowed accurate characterization of incomplete and complete spinal cord injuries and became the gold standard in this indication (Davies et al 2017; Fontes et al. 2016; Roberts et al. 2017). Detailed motor and sensory function according to each dermatome and myotome can be documented. The AISA classification grading system has never been applied in cancer treatment associated spinal toxicity.

The Cooper Scale combines grading of upper (grade 0–4) and lower extremity (grade 0–5) function. The higher the grade, the more severe the deficit. Upper and lower extremities are analyzed separately and the grades are not summarized. This score was mainly designed to monitor the outcome of surgical interventions to intramedullary spine tumors and myelopathiesn (Cooper et al 1985; Dalitz et al. 2019). Despite surgery, there are no data on cancer treatment-associated spinal toxicity.

The European Myelopathy Score (EMS) represents a scoring method (total score, 5–18: the lower the score the more severe the deficits), and includes a wide spectrum of spinal functions such as upper motor neuron, gait function, bladder and bowel function, lower motor neuron, hand function, posterior column, proprioception and coordination, paresthesia, and pain. Although this score evaluates spinal cord function in more detail, it has only been applied in a few surgical studies so far (Miscusi et al. 2015; Herdmann et al. 1994). No data on cancer treatment associated spinal toxicity is available.

The spinal cord injury Frankel Classification Grading System, running from grade A (no spinal cord function) to grade E (normal to mild symptoms), has been evaluated in patients with acute spinal injury due to trauma and for prognostic evaluation of malignant spinal cord compression after surgery (Ditunno et al. 1997; Lo et al. 2017). This score has also been integrated in the modified Tokuhashi classification, in order to gain pre-treatment prognostic information in patients with malignant spinal cord compression for consecutive treatment planning (Mattana et al. 2015; Oberndorfer et al. 2000). Radiological characteristics on MRI scans were investigated in patients with epidural spinal cord compression in association with motor deficits using the Frankel Classification Grading System. MRI features such as lamina involvement and the retropulsion of the posterior wall are correlated with motor deficits graded by the Frankel System (Liu et al. 2015). Also, the Frankel Classification Grading System has never been applied in cancer treatment-associated spinal toxicity.

The McCormick Grading System and the modified McCormick Scale (grade 1, neurological intact minimal dysesthesia, to grade 5, paraplegia or quadriplegia) was used to evaluate postoperative spinal cord function in order to classify risk factors for postoperative recurrence of spinal tumors and to analyze prognostic factors in meningioma (Zhang et al. 2017; Kalamarides et al. 2018; Wostrack et al. 2012; Arima et al. 2014). Beside the extent of tumor resection, and intramedullary localization of the tumor, the McCormick grade turned out to also generate a risk factor for the recurrence of spinal tumors and may also be used to evaluate neurotoxicity in surgical treatment of intradural metastases (Zhang et al. 2017; Wostrack et al. 2012). Further, the outcome of surgical treatment of spinal ependymoma in NF2 was compared with a conservative approach using the McCormick Grading System. A modified McCormick Outcome Score showed that selected patients with growing/symptomatic ependymoma may benefit from a surgical approach (Kalamarides et al. 2018). The McCormick Grading System is mostly used for surgical treatment stratification in different spinal tumors but has never

been applied in order to investigate cancer treatment-associated spinal toxicity (besides surgical neurotoxicity) (Alberti et al. 2016).

Another tool for the quantification of spinal toxicity is the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (grade 1, asymptomatic or mild, to grade 5, death), which is presented in the nervous system disorders section (https://www.nih.gov/). However, there is no special section for spinal toxicity within the NCI-CTCAE. Therefore, neurological signs and symptoms from spinal dysfunction have to be quoted in a rather unspecific way. The assessment of spinal toxicity using the NCI-CTCAE, has been used in some radiotherapy trials (Ryu et al. 2013, Sharma et al. 2017). For chemotherapy associated spinal toxicity, there are several case reports and literature reviews available for different kinds of drugs (methotrexate, cytarabine, nelarabine, etoposide), different tumors, and different routes of application (intravenous, intrathecal). This literature is mostly based on case reports, and there is no evidence that the NCI-CTCAE would be a preferable neurological grading system for spinal toxicity. However, assessment in hematooncological trials is mostly based in the NCI-CTCAE.

Nurick's Classification Grading System for myelopathy was introduced in order to quantify neurological disability in patients with degenerative spine disorders, such as spondylotic myelopathy (Nurick S. 1972). Studies on postsurgical outcome according to the degree of preoperative spinal cord compression and ambulatory status were performed in spinal meningioma and extramedullary spinal tumors and spinal metastases (Davies et al. 2017; Fontes et al. 2016; Kim et al. 2011). Nurick's Classification Grading System has never been applied in cancer treatment-associated spinal toxicity.

The Ranawat classification of neurological deficits was introduced for patients with rheumatoid arthritis undergoing spinal fusion for deformity of the cervical spine (Ranawat et al. 1979). Studies were done mostly in patients suffering from rheumatoid myelopathy and have never been applied in cancer patients (Nannapaneni et al. 2005).

The Tokuhashi score is used as a prognostic score for patients with spinal metastases and malignant spinal cord compression. Studies indicated that the implementation of the score helps tailor treatment to either conservative care, including radiotherapy or surgery, or supportive care (Mattana et al. 2015; Oberndorfer et al. 2000; Tateiwa et al. 2019; Ito et al. 2018; Morgen et al. 2018). Most studies using this score are focused on the surgical management of metastatic spinal cord disease. The Tokuhashi Score Grading System, including its modifications, is used for treatment stratification, mostly evaluating surgical approaches in

metastatic spinal disease but it has never been applied to investigate cancer treatment associated spinal toxicity (Andre-Obadia et al. 2016; Alberti et al. 2016).

The clinical approach

For the management of side effects from cancer treatments in the clinical routine, outside the scope of study protocols, physicians are more focused on everyday function and quality of life—as patients are. Spinal cord toxicity due to cancer treatment is one of the rare side effects, which lies somewhat out of the box for clinicians engaged in patient care, even for neurooncologists.

To detect spinal cord dysfunction in cancer patients one should screen for:

- Gait dysfunction
- Back pain
- Ascending sensory deficits
- Bladder or bowel dysfunction

These red flags may initiate a more detailed investigation towards spinal cord pathology using clinical neurological examination, MRI of the spine, or even CSF analysis. Once spinal cord dysfunction has been identified, and causes other than cancer treatment association have been ruled out, the neurological signs and symptoms should be documented in detail. Grading systems and scales as mentioned above can provide a useful monitoring tool; however, no clear recommendation for a single grading system can be given. Once spinal cord toxicity occurs, the neurologist should be involved in order to monitor the course of the toxicity in detail and to provide advice with respect to symptomatic treatment, for treatment modification, or even termination of anti-cancer treatment. Evidence-based toxicity criteria on the assessment of spinal toxicity due to cancer treatment are still missing.

Additional diagnostic tools

Beside the clinical neurological assessment, additional diagnostic tools may be useful, such as MRI of the spine, CSF analysis, nerve conduction velocity studies, or somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP) by transcranial stimulation. Biopsy of an unclear spinal lesion is a difficult procedure, with a wide range of inflammatory,

infectious, and neoplastic diseases as possible causes, and is often inconclusive or even leads to misdiagnosis in up to 30% of cases (Obandia et al. 2017).

SSEP and MEP are often applied in the operating room in order to prevent neurological damage during spinal cord surgery. However, these methods are primarily important to rule out causes other than cancer treatment-related causes for spinal cord dysfunction.

The golden standard for the diagnosis of cancer treatment-associated spinal cord toxicity would be, besides clinical neurological investigation, MRI of the spine—possibly combined with CSF analysis (Dua et al. 2015; Dormegny et al. 2018; Pinnix et al. 2017; Alsdorf et al. 2016).

Conclusion

Spinal cord toxicity due to cancer treatment can lead to significant impairment of neurological function and quality of life. As a consequence, the modification, reduction, or discontinuation of the anti-cancer treatment is necessary. In the clinical routine, awareness and early diagnosis of side effects from anti-cancer treatment to the spinal cord are challenging and the evaluation using a grading system is not established. Experienced and trained neurologists and neuro-oncologists are mandatory for the management of spinal cord dysfunction in cancer patients, especially when dysfunction is suspected to be associated with anticancer treatment.

Scales and scores for spinal cord dysfunction in cancer patients are primarily used for surgical and radiotherapeutic treatment stratification and outcome measurement. For newer treatment approaches such as targeted therapies using antibodies or small molecules or immunological approaches (checkpoint inhibitors, CAR-T cell therapy), which may also induce spinal toxicity in some selected cases, no grading system has been applied so far.

In case of spinal cord dysfunction in cancer patients, a clinical neurological evaluation and diagnostic workup, including MRI of the spine and CSF analysis in particular, is highly recommended. The application of grading systems, discussed in this chapter, may be useful for pre- and post-therapeutic interventions in the proximity of the spinal cord or in the frame of clinical studies on anti-cancer treatment.

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CHAPTER 2.4

SCALES: PERIPHERAL NERVES

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Abstract

Chemotherapy Induced Peripheral Neurotoxicity (CIPN) is a common side effect of different drugs widely used to treat patients with cancer, the most common being platinum-drugs, taxanes, proteasome inhibitors, vinca alkaloids, epothilones, and thalidomide. There is no gold standard for CIPN assessment and no tool has yet been proved to be ideal to detect and grade CIPN. Many different outcome measures, among which are different scales, have been proposed in different oncological trials. They can be divided into toxicity scales (mainly devised in an oncological setting), physician-based scales (mainly devised in a neurological setting), and Patient-Reported Outcome (PRO) measures. In this chapter we summarize the evidence of their clinimetric properties. CIPN evaluating tools were mainly developed for adults, but we also address the search for the ideal outcome measure in children. International multicentre clinimetric studies are warranted to determine the gold standard for CIPN assessment and find an answer to this unmet clinical need.

Keywords: chemotherapy induced peripheral neurotoxicity, clinimetrics, childhood cancer survivors, adulthood cancer survivors, quality of life, pain, neuropathy

General clinimetric issues

Patients affected with cancer may develop peripheral nervous system (PNS) dysfunctions due to several conditions. There can be a direct spreading of cancer to the PNS itself and/or secondary processes (for example, paraneoplastic syndromes) (Briani et al. 2019), but the most common PNS damage is iatrogenic. This most common one is related to systemic treatments (Cavaletti, Alberti, and Marmiroli 2015), even if radiation can also sometimes determine PNS alterations in the radiation field (Delanian, Lefaix, and Pradat 2012). Thus, since the majority of cases are due to medical intervention, an increasing need to monitor these side effects is required.

We will focus mainly on iatrogenic PNS alterations due to their epidemiological predominance. Chemotherapy Induced Peripheral Neurotoxicity (CIPN) is, in fact, a common side effect of widely used agents to treat cancer: platinum-drugs, taxanes, proteasome inhibitors, vinca alkaloids, epothilones, and thalidomide (Cavaletti and Marmiroli 2015). The increasing relevance of CIPN is due to two main reasons. First, cancer patients may survive for a long time and CIPN is a long-lasting, or even permanent, condition (Battaglini et al. 2018, Miaskowski et al. 2018, Kidwell et al. 2012, Dalla Torre et al. 2016, Briani et al. 2014); thus, CIPN has become an intolerable condition due to the increased survival. Second, there is no treatment for CIPN (Hershman et al. 2014, Albers et al. 2014, Marmiroli and Cavaletti 2016). We still have an incomplete knowledge of CIPN pathogenesis in the lab (Cavaletti and Marmiroli 2015) and there are also relevant clinimetric issues with patients. The latter is our concern in this chapter since it is a crucial pitfall in trial designs. There is no gold standard for CIPN assessment (Cavaletti et al. 2010, Alberti 2017): no tool has yet proved to be ideal to detect and grade CIPN. Therefore, there are no solid epidemiological data on which a sound trial design could be built; moreover, the appropriate endpoint to use is yet to be defined. Many different outcome measures, among which are different scales, have been proposed. They can be divided into toxicity scales (mainly devised in an oncological setting), physician-based scales (mainly devised in a neurological setting), and Patient-Reported Outcome (PRO) measures.

The relevance of the “clinimetric” issue can be perceived by observing the course of action taken at an international level to fulfill this scientific lack. In 2017, the National Cancer Institute Symptom Management and Health-Related Quality of Life Steering Committee Clinical Trials Planning Meeting (CTPM) was established to look for an adequate solution. The work of the committee resulted in a commentary

published in 2019; Dorsey and colleagues (Dorsey et al. 2019) concluded that given the absence of a valid gold standard, working groups were needed and were thus created to unravel this issue. In the same period, the Analgesic, Anaesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials (CONCEPPT) published guidelines; even with the lack of a gold standard, they made suggestions on eligibility criteria, outcome measures, endpoints, and sample size estimation. They proposed that a combined set of outcome measures should be followed: physician-based ones and PROs (Gewandter et al. 2018).

In the next section we will address some basic concepts regarding clinical scale properties and present the currently used toxicity scales, physician-based scales, and PROs. Finally, we will address toxicity scales in the pediatric population.

Definition of outcome measure properties

When approaching clinical scales, or in general-health-status instruments, some basic psychometric concepts should be known in order to critically approach the literature.

Reliability

The broad definition of reliability is related to the degree of being free of random error (Aaronson et al. 2002). The two main approaches to evaluate reliability are internal consistency reliability and reproducibility. *Internal consistency reliability* is usually defined with Cronbach's coefficient α; thus, the instrument should be administered once to be evaluated. This approach is suitable for multi-item scales since it estimates reliability, testing all possible split-half correlations. *Reproducibility* is obtained either with multiple testing of the instrument (at least twice), assessing its stability over time—among respondents who are assumed to be unchanged for the condition of interest (test-retest)—and with the inter-rater agreement at one time point.

Validity

Validity refers to the degree to which a given instrument measures what it is intended to (Aaronson et al. 2002). This specific characteristic can be empirically tested at different levels, termed content related, construct

related, and criterion related. *Content-related* validity refers to the evidence that the content domain of the selected scale is appropriate for what concerns its intended use. Validity can be explored either by a panel of experts or, more often, by the population experiencing the tested condition. A technical description, often encountered, related to content-validity is "face validity": this indicates whether the tool appears effective in terms of its stated aims. *Construct-related* validity means the instrument we are examining is able to produce scores that match what is expected, given what the instrument is measuring; this property is usually explored by testing the logical relations between the tested scale and others that are known to differ on relevant variables related to the condition of interest. *Criterion-related* validity refers to the evidence that the score of the selected tool is related to a criterion measure. Criterion measures are measure of a certain condition that is regarded as valid. In regard to PROs, this property is rarely tested or assessed, even if it is possible to compare a shorter version of one tool against a longer one (i.e., thus becoming the gold standard). It is appropriately assessed in the area of screening instrument testing: in this case, the new outcome measure is compared against a criterion measure, evaluating sensitivity, specificity, and receiver-operating properties.

Responsiveness

The responsiveness of a selected tool is related to its sensitivity to change; thus it is evaluated and it is valuable in longitudinal monitoring. A scale/instrument is responsive, ideally, if it can detect a difference in the selected outcome, even when the change is small. More notably, this property should be regarded as assessing the actual change over time: it is the signal–noise ratio, given that the former is the actual change over time and the latter is the variability in the score not associated with a variation in the variable or status of interest. Of course, when considering minimal changes, they should still be meaningful for people affected by the condition, their significant others, or their health care providers.

Interpretability

Interpretability is defined as the degree to which one can assign easily understood meaning to a tool's quantitative scores (Aaronson et al. 2002). This is a relevant characteristic to keep in mind in order to use and administer instruments that have an actual chance of being understood by the person who is being addressed. To enhance interpretability, it is

appropriate to provide information that translates scores in qualitative terms and/or into measures more easily understandable by the subject.

Toxicity scales

Given that we are primary evaluating an iatrogenic oncological side effect, it is appropriate to first address toxicity assessment instruments that were devised to collect adverse events: the Eastern Cooperative Oncology Group (ECOG) scale, the World Health Organization (WHO) scale, the Ajani scale and the National Cancer Institute–Common Toxicity Criteria Adverse Event (NCI-CTCAE).

The ECOG scale was developed in 1974 to define standardized toxicity criteria. It was then used in all ECOG studies and its last revision dates back to 1982 (Oken et al. 1982). It explores three domains—sensory, motor, and autonomic—on a 0–4 scale for motor and autonomic items and on a 0–3 scale for sensory disturbances. The motor neuropathy score is assigned as normal (0), mild objective weakness (1), severe weakness (3), and respiratory dysfunction secondary to weakness/paralysis confining patient to bed/wheelchair (4). Sensory neuropathy is rated as normal (0), decreased DTR or mild paresthesias (1), absent DTR, severe paresthesia (2), and disabling sensory loss, severe neuropathic pain (3). Autonomic alterations are rated as normal (0), mild constipation (1), severe constipation (2), bladder dysfunction/obstipation (3), obstipation requiring surgery (4). Compared to the WHO scale, it shows a broader exploration of PNS dysfunction, assessing also autonomic disturbances and introducing the crucial and "novel" concept of "disabling sensory loss," giving primary importance not only to positive but also to negative symptoms.

The WHO scale was developed in 1979, with the objective of monitoring multiple parameters for cancer patients, as well as adverse events (Oken et al. 1982). There is a section dedicated to PNS alterations subdivided into sensory and motor items. They allow a 0–4 score for motor assessment and a 0–3 score for sensory ones. For the motor testing, a 0 score means "normal," 1, "subjective weakness," 2, "mild objective weakness," 3, "marked weakness," and 4, "paralysis." For the sensory testing, 0 means "normal," 1, "decreased deep tendon reflexes (DTR) or paresthesias," 2 "severe paresthesias," 3 "intolerable paresthesias," and 4 "paralysis." This tool, even if endorsed by multiple international organizations, never achieved widespread use (Miller et al. 1981).

The Ajani scale (Ajani et al. 1990) is the product of a committee of the Houston Cancer Centre—the Chemotherapy Working Group and

the Department of Medical Specialties and Neuro-Oncology—that elaborated specific criteria adapting the WHO scale with an unpublished internal scale. The substantial difference of the Ajani scale is that each score is intended to correspond to a morbidity range to drive future therapy. Not only was health-care professionals' points of view considered, but also interviews were performed in order to evaluate patients' and their relatives' opinions. For CIPN, a motor and sensory neuropathy score was presented on a 0–4 scale. Motor status is defined as normal (0), mild or transient muscle weakness (1), persistent moderate weakness but ambulatory (2), unable to ambulate (3), and complete paralysis (4). Sensory assessment is summarized as normal (0), paraesthesias/decreased deep tendon reflexes (1), mild objective abnormality/absence of DTR/mild to moderate functional abnormality (2), severe paraesthesias/moderate objective abnormalities/severe functional abnormalities (3), complete sensory loss/loss of function (4).

However, the most widely used scale is the NCI-CTCAE Cavaletti et al. 2010). Its first version dates back to 1983, and it was the result of an agreement between the Cooperative Oncology groups in North America and Canada. Originally it was called simply the Common Toxicity Criteria (CTC); it comprehended neuro-sensory and neuro-motor parameters to assess patients' status with a focus on interference with function. This scale was the first to take into account function. In 1998 the NCI proposed a revised and expanded version renamed NCI-CTC v2.0 (Cavaletti et al. 2019), which has now reached its fifth version—NCI-CTCAE v5.0 (NCI.)—released in 2017. Neuropathy-related items comprise the "sensory" and "motor" neuropathy score, on a 5-rating point scale. Motor status is assessed as asymptomatic/clinical or diagnostic observations only (grade 1), moderate symptoms/limiting instrumental ADL (grade 2), severe symptoms/limiting self-care ADL (grade 3), life-threatening consequences/urgent intervention indicated (grade 4), and death (grade 5). Sensory one, instead, is graded as asymptomatic (grade 1), moderate symptoms/limiting instrumental ADL (grade 2), severe symptoms/limiting self-care ADL (grade 3), life-threatening consequences/urgent intervention indicated (grade 4).

The NCI-CTCAE, as with all the toxicity scales reported so far, has a major flaw in that it includes only patients' subjective evaluation without a formal neurological examination. Another major limitation of this tool is its ceiling effect, which is also worsened by a significant inter-observer disagreement (Postma et al. 1998) leading to the underestimation of CIPN rates of incidence and severity (Griffith et al. 2010). However, it has been demonstrated that intensive training can enhance NCI-CTCAE

reliability (inter-observe, r=0.71–0.80). Concerning validity, there are some differences between the sensory and motor scale. The sensory subscale was demonstrated to have constructed validity; in fact, the sensory scores were higher in subjects who received higher cumulative dosages (Lavoie Smith et al. 2011). Instead, the motor subscale did not show the same validity profile, and the motor subscale has been demonstrated to incorrectly estimate motor impairment when compared with a formal strength assessment (Lavoie Smith et al. 2011). It relys only on patients' points of view, when, in fact, self-reported weakness can mirror many other conditions that are quite common in cancer patients, such as sensory ataxia (Cavaletti et al. 2019), fatigue, depression, or muscular waste (Spence, Heesch, and Brown 2010).

Physician-based outcome measures

In order to increase the clinimetric performance of the assessment tools, scales based on a formal neurological examination were also proposed, with the development of so-called composite scales (i.e., clinical and instrumental scales). They are used both in a clinical and in a research setting and were mainly developed by neurologists, in contrast with toxicity scales, which were mainly developed in an oncological setting.

One of the most widely used scales is the Total Neuropathy Score (TNS©) which incorporates detection of sensory, motor, and autonomic symptoms, a formal neurological assessment of sensibility (both superficial and deep), strength, and deep tendon reflexes (DTR), and semiquantitative vibration threshold evaluation and nerve conduction studies (Cornblath et al. 1999). It was originally devised and validated for diabetic neuropathy (Cornblath et al. 1999), but it was then tested in patients with toxic neuropathies (Chaudhry et al. 2003, 1994). The original version comprised 10 items that can be rated on a 0–4 scoring system (thus, the maximum score is 40), as follows:

1. Sensory symptoms: none (score 0), symptoms limited to fingers or toes (1), symptoms extend to ankle or wrist (2), symptoms extend to knee or elbow (3), symptoms above knees or elbows, or functionally disabling (4).
2. Motor symptoms: none (score 0), slight difficulty (1), moderate difficulty (2), requires help/assistance (3), paralysis.
3. Autonomic symptoms: none (score 0), 1 symptom (1), 2 symptoms (2), 3 symptoms (3), 4 or 5 symptoms (4).

4. Pin sensibility: none (score 0), reduced in fingers or toes (1), reduced up to ankle or wrist (2), reduced up to knee or elbow (3), reduced above knees or elbows (4).
5. Vibration sensibility: none (score 0), reduced in fingers or toes (1), reduced up to ankle or wrist (2), reduced up to knee or elbow (3), reduced above knees or elbows (4).
6. Strength: normal (score 0), mild weakness (1), moderate weakness (2), severe weakness (3), paralysis (4).
7. DTR: normal (0), ankle reflex reduced (1), ankle reflex absent (2), ankle reflex absent, other reduced (3), all reflexes absent (4).
8. Vibration sensation (Quantitative sensory testing [QST]): normal to 125% of upper level of normality (ULN) (score 0); 125–50% of ULN (1); 151–200% of ULN (2); 201–300% (3); > 300% (4).
9. Sural amplitude: normal/reduced up to <5% of lower level of normality (LLN) (score 0); 76–95% of LLN (score 1); 51–75% of LLN (score 2); 26–50% of LLN (score 3); 0–25% of LLN (score 4).
10. Peroneal amplitude: normal/reduced up to <5% of lower level of normality (LLN) (score 0); 76–95% of LLN (score 1); 51–75% of LLN (score 2); 26–50% of LLN (score 3); 0–25% of LLN (score 4).

In 1999, Cornblath et al. (Cornblath et al. 1999) demonstrated the validity of the scale, as well as its high intra- and inter-rated reliability. The first study using TNS© in CIPN patients dates back to 1994 (Chaudhry et al. 1994): the authors concluded that the scale was suitable for monitoring CIPN patients and suggested its use in longitudinal monitoring. Shorter versions of TNS© were subsequently developed. The rTNS© differs from the original one in not including the QST testing for vibration threshold; thus, it is less time consuming and applicable also in settings where the specialized device is not present. The cTNS© differs from the rTNS© since it does not include neurophysiological assessment of the sural and peroneal nerves, thus being applicable in a "clinical" setting without requiring specific equipment such as EMG apparatus.

TNS© was first tested in a CIPN setting by Cavaletti et al. (Cavaletti et al. 2003), in a study aimed at determining whether the scale and/or the reduced version was able to assess the presence and severity of CIPN. Sixty consecutive women treated with paclitaxel and cisplatin or paclitaxel and ifofosfamide, enrolled in a single center, were examined during treatment and data were compared with 50 age-matched healthy control subjects. In this population, a single experienced examiner tested

both TNS© and rTNS© and compared it with several oncological scales: the NCI-CTCAE v2.0, Ajani, and ECOG scales. TNS© was found to be reliable since it reflected the overall changes of oncological scales. Moreover, rTNS© was demonstrated to be as informative as the full version, thus, the authors concluded that the use of the TNS shorter version should be suggested given its faster applicability. Cavaletti et al. in 2006 (Cavaletti et al. 2006) performed a multicenter study, thanks to the constitution of the Italian NETox group, testing not only rTNS© but also the even shorter version cTNS©, with the aim of assessing the severity of CIPN and comparing the results with those obtained from oncological scales (ECOG, NCI-CTCAE v 2.0). They assessed 428 (218 females and 210 males, with a mean age of 55 years) consecutive patients. Inter-examiner concordance for rTNS© was high (92%); moreover, a highly significant correlation was demonstrated between both the TNS© reduced version and oncological scales. In particular, the correlation was higher for sensory items. The authors concluded that both rTNS© and cTNS© are reliable and effective in reporting and grading CIPN. Given that no advantage was seen for rTNS© versus cTNS©, subsequently a prospective multicenter study addressing the use of cTNS© as an outcome measure was performed (Cavaletti et al. 2007). The primary aim of the latter study was to test responsiveness to CIPN severity changes, comparing the results of TNS© and the cTNS© version with the NCI-CTCAE v.2.0 scale. Two different series of subjects were enrolled. In Study 1, data from 122 consecutive patients were retrospectively analyzed; these patients were enrolled before chemotherapy only if no neuropathy and no risk factors for neuropathy were present and TNS©, cTNS©, and NCI-CTC v2.0 data were available. Study 2 was, instead, a prospective one: 51 consecutive patients were enrolled and evaluated before and during chemotherapy and TNSc© and NCI-CTCAE data at each cycle were recorded. For both studies a preliminary analysis was performed in order to confirm the reliability of recorded data: in both studies TNS© or cTNS© and NCI-CTCAE v2.0 showed a highly significant correlation, as seen in the previous 2003 study conducted by the same group (Cavaletti et al. 2003). In Study 1, the multiple evaluations over time, for each patient, were analyzed: changes in TNS© score were highly significant when subjects with a stable NCI-CTCAE v2.0 were compared with patients who showed a change in NCI-CTCAE v.2.0 score (i.e., change = 1). Moreover, both TNS© versions tested showed more sensitivity than NCI-CTCAE v2.0, without giving “false positives” in detecting mild sensory changes. In Study 2, it was confirmed that changes in cTNS© scores were highly significant when patients with no change in NCI-CTCAE v2.0 score were

compared with those who showed a deterioration (n=1) in NCI-CTCAE v2.0 grade. Again, mild sensory damage was more sensitively detected by TNSc© than by NCI-CTCAE v2.0. In conclusion, the authors suggested to implement TNSc© in CIPN patient evaluation, provided that the examiner has been adequately trained to perform the scoring. In another study performed by several participants in the same working group (Frigeni et al. 2011), a comparison between NCI-CTCAE and TNS© was again performed, aiming at identifying possible discrepancies in CIPN diagnosis via these two different instruments. One-hundred fifty-five consecutive patients with a grade 2 or 3 sensory and/or motor peripheral neuropathy, as assessed by NCI-CTCAE v3.0 by an experienced oncologist, were enrolled. The screening evaluation was performed by a certified neurologist, blind to the NCI-CTCAE score. Examiners underwent a pre-study training session that was performed by the same experienced instructor in each site. To allow a similar data collection in all sites, the devices used were the same, apart from the neurophysiology apparatus; however, to ensure homogeneity in nerve-conduction-study interpretation, a centralized peer-review of all traces was performed by the coordinating center (the same certified neurologist and a senior neurophysiology technician took care of this task). One-hundred fifty-five patients were available for analysis. When comparing single TNS© items to the NCI-CTCAE score, a significant agreement was observed between the sensory NCI-CTCAE subscale and pin sensibility as well as between vibration sensibility and deep tendon reflexes; instead, a significant disagreement was found between the NCI-CTCAE motor subscale and the formal strength assessment. This discrepancy was attributed to TNS's ability to correctly assess true weakness, whereas NCI-CTCAE's "false positive" motor impairment is scored on the basis of patients' points of view. Cancer patients' referral can be biased by many confounding factors (sensory ataxia [Cavaletti et al. 2019], fatigue, depression, reduced muscular mass [Spence, Heesch, and Brown 2010]). The authors also explored the correlation between clinical and instrumental TNS© items. A significant agreement between sensory and motor NCS recordings and clinical findings was found; moreover, a highly significant correlation between the use of the vibrometer and the tuning fork demonstrated that the 2 tools are equally informative. In conclusion, the authors state that TNS© is more accurate than NCI-CTCAE in assessing CIPN and avoiding motor neuropathy misdiagnosis; moreover, given that NCS and the vibrometer were in agreement with clinical items, they suggested that cTNS© is the ideal scale to be used in CIPN patients.

The Italian NETox group joined the international US/EU study group, CI-PeriNomS, wishing to standardize outcome measures in the CIPN setting. After a consensus among experts was formed in 2007 (Pomezia, Italy, June 22, 2007), the CI-PERINOMS protocol was developed (Group 2009); neurologists and oncologists from 21 centers performed a large multicenter cross-sectional study aiming to define the validity and reliability of a selected set of outcome measures. A total of 281 subjects (with a median age of 63.9 years) with a stable CIPN were enrolled (Cavaletti et al. 2013). Two different trained examiners evaluated the same patient twice, two weeks apart, blind to the other examiner's score; both times, patients also filled in questionnaires that aimed to score their quality of life (QoL). The following tools were used: NCI-CTCAE v3.0, cTNS©, mISS (modified Inflammatory Neuropathy Cause and Treatment [Merkies et al. 2000]), light touch with the 10g monofilament, VAS and PI-NRS for pain scoring, and the two questionnaires (EORTC QLQ-C30, and CIPN-20). All the selected physician-based outcome measures had at least an acceptable intra-observer and inter-observer agreement; for TNSc© the agreement was almost perfect ($k>0.81$) both for the inter- and intra-observer versions. Both TNSc© and mISS showed a higher correlation with the NCI-CTC. Thus, both TNSc© and mISS were found to be reliable and their construct validity, as well as good discriminative value, was demonstrated versus the NCI-CTCAE scale.

A secondary analysis on the same population that aimed to compare physician-based and patient-based outcome measures was then performed (Alberti et al. 2014). The authors tested two TNSc© items, pinprick and vibration sensibility, the NCI-CTCAE v3.0 sensory subscale, mISS versus EORTC QLQ-C30, and CIPN-20. None of the scales had a perfect correlation with the questionnaires, with the major discrepancies being present in the intermediate CIPN severity grades. Thus, the authors concluded that the clinical and patient-reported outcome measures (PRO) should be combined to achieve a comprehensive evaluation of CIPN patients. A further analysis was conducted on the same population, subjecting TNSc© to Rasch analysis to determine the fit with the model (Binda et al. 2015). Data from seven domains were tested: sensory symptoms, motor symptoms, autonomic symptoms, pinprick sensibility, vibration sensibility, and deep tendon reflexes. The scale tested did not meet the requirements of the Rasch models. After removing autonomic symptoms and then deep tendon reflexes, a Rasch Transformed cTNS© (RT-cTNSc©) was obtained with the advantage of unidimensionality and a proper parametrical evaluation, since it allows the shift from an ordinal (cTNS©) to a linear scale (RT-cTNS©); despite being an interesting

option, as the authors warn, the RT-cTNS© has not yet been validated and it requires further testing in a longitudinal study to verify its responsiveness.

Other groups explored the clinimetric properties of TNS©: Smith et al. (Smith et al. 2010) published a paper that aimed to test the reliability and validity of a modified TNS©; internal consistency reliability (ICR) and interrater reliability (IRR) as well as structural validity were tested. The modified version of the TNSr©, mTNSr©, was used. The mTNSr© is similar to cTNS© but two items (autonomic and motor symptoms) were excluded in mTNSr©. One hundred seventeen patients (with a mean age of 58.86 years) who received neurotoxic chemotherapy were enrolled. The whole population was tested with a questionnaire on neuropathic pain (NPS-CIN), while 10 patients were evaluated with mTNSr©. All assessments were performed by an oncologist nurse practitioner who had been trained to perform a focused neurological examination; moreover, data were matched with an mTNSr© score provided by a neurologist with expertise in neuropathy. Each examiner was blind to the other's scoring. The ICR was quite low; thus, on the basis of the results of the reliability and structural validity testing, the authors proposed a revised and shortened TNS©, TNSr-SF©: strength, deep tendon reflexes, and pin sensibility were excluded and symptoms grading was modified. The new scale showed an improved ICR. Regarding interrater reliability, no significant disagreement was found between the two examiners; however, single items showed an agreement ranging from fair to substantial. Inconsistency arose mainly when symptoms extended midway toes and ankle, or halfway up to the calf. Then the authors performed a factor analysis, after excluding strength and deep tendon reflexes items, given their low interim correlation. Following the iterative process, 4 items remained as components of the new TNSr-SF© scale.

The same group further tested TNSr-SF© in patients receiving taxanes and platinums (Lavoie Smith et al. 2011). They aimed to determine the validity of this scale as well as for neuropathic pain measurements in a longitudinal study. One hundred seventeen patients (with a mean age of 58.9 years) were enrolled; 107 patients were evaluated during or soon after completion of chemotherapy; 10 patients were evaluated 3 months after treatment. The examiner was a nurse practitioner who had been trained by a neurologist. Regarding the construct validity, the following was confirmed: TNSr© and TNSr-SF© scores were higher in patients who received a higher cumulative dosage; moreover, concerning single items, deep tendon reflexes showed a construct validity for the same reason, whereas strength and pin sensibility did not.

Construct validity was confirmed (TNSr© and TNSr-SF© scores were higher in patients who received a higher cumulative dose); concerning the single items, deep tendon reflexes showed a construct validity, whereas strength and pin sensibility did not. However, all the items and the global score for both scales were higher in patients with comorbid conditions, thus confirming the construct validity on the basis of neuropathy risk. Both TNS© variant scores correlated moderately with the sensory NCI-CTCAE subscale, thus confirming also their construct validity. However, the same convergence was not seen for motor NCI-CTCAE subscale, in accordance with what had previously been reported by Frigeni et al. (Frigeni et al. 2011). In conclusion, the authors suggest that the TNSr-SF© can be used for CIPN detection and grading in patients undergoing platinum and taxanes chemotherapy; the inclusion of deep tendon reflexes was still not evaluated as an appropriate option to avoid a negative impact on the ICR as demonstrated in their previous study.

Wampler et al. (Wampler et al. 2007) performed a prospective study on the postural control of women who received taxane chemotherapy in order to find an outcome measure that correlated with impairments in balance/physical abilities and QoL. They enrolled 20 women (with a median age of 50.35) who had received taxanes and compared data from 20 age-matched controls. Peripheral neuropathy was assessed via TNS©, mTNS©, Michigan Diabetic Neuropathy Score (MDNS), quantitative touch threshold, and quantitative vibration threshold. Moreover, subjects underwent nerve conduction studies, pain and QoL questionnaires, a quantitative balance test, and a physical performance test. Variables were collected 30 days after the last chemotherapy cycle. All measures to detect peripheral neuropathy were able to discriminate between taxane-treated patients and the control group, except for vibration thresholds. The mTNS©, MDNS, and vibration threshold at the wrist correlated with the TNS© score. The mTNS© moderately correlated with the balance and QoL scores while it did not correlate with pain scores.

Lakshman et al. (Lakshman et al. 2017) tested TNSr© and TNS©, as well as NCI-CTC v4.0, in a different setting, that of solid cancers: myeloma multiple patients who were candidated for bortezomib-based induction were enrolled in a prospective study. Twenty-six, treatment-naive, consecutive patients were included in the study and 20 of them were re-evaluated for treatment-emergent neuropathy. They were all evaluated by a certified neurologist. Neuropathy was assessed with the rTNS©, cTNS©, and NCI-CTCAE v4.0 at the baseline, when the patients developed a grade 2 neuropathy or worse at NCI-CTCAE at the termination of therapy or at treatment discontinuation. The authors elected

rTNS© as a reference and evaluated the sensitivity of the other scales: NCI-CTCAE v4.0 had a 77.8% sensitivity, whereas cTNS© had an 88.9% sensitivity; they both had a 63.6% specificity. They also tested correlation among the 3 tools: rTNS© and cTNS© had a similar correlation with NCI-CTCAE v4.0 (Spearman's Rho of 0.6 and 0.53, respectively), whereas the comparison between rTNS© and cTNS© showed a 0.53 correlation coefficient. Moreover, even in patients who had no post-treatment deterioration of the neurological condition according to NCI-CTCAE v4.0, a wide range of change was recorded via rTNS© and cTNS©; interestingly, 40% of patients who had no neuropathy as scored by NCI-CTCAE v4.0, were assessed as burdened by neuropathy at rTNS©. In conclusion, the authors, despite acknowledging the small sample size, state that the data supports that rTNS© and cTNS© are more sensitive than NCI-CTCAE v4.0 and suggest that the oncological toxicity score should be replaced by the composite scale based on a formal neurological evaluation.

In general, all the reported studies clearly describe the scoring procedure, examiners were trained and bias/confounding factors were adequately avoided. However, some observations were mainly based on small cohorts and in cross-sectional studies. Despite these limitations, it clearly emerges that TNS© and its variants are superior to the common toxicity oncological scales in detecting and grading CIPN. Reduced versions that do not comprehend an instrumental evaluation did not show less efficacy in CIPN detection. A large prospective study on a real-life population is needed to finally ascertain the role of TNS© and its variants in CIPN detection and scoring.

Patient-reported outcome measures (PRO)

Valuable information when assessing CIPN patients is generated by the assessment of patients' QoL and functional state. PROs were devised to collect patients' perception of their condition. The most frequently used tools are the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group's (GOG) Neurotoxicity (FACT/GOG-Ntx) Subscale and the European Organisation of Research and Treatment of Cancer's (EORTC) QLQ-CIPN20 (later in this chapter addressed as CIPN20 for brevity).

The FACT/GOG-Ntx was developed by GOG in 1998; the questionnaire comprises 11 items aimed at exploring positive and negative neuropathy symptoms in upper and lower limbs as well as functional impairment (Huang et al. 2007, Calhoun et al. 2003). Each item is scored

on a 4-point scale where 1 corresponds to "not at all" and 4 corresponds to "very much." Calhoun and colleagues (Calhoun et al. 2003) demonstrated its good internal reliability (Cronbach's alpha average = 0.83) as well as construct validity (Spearman rank correlation 0.6–0.8) for sensory neuropathy. In a subsequent study (Huang et al. 2007), Huang and colleagues were able to assess its criterion validity since it was demonstrated to be able to distinguish patients with and without neuropathy. Moreover, the 4-item reduced version ("sensory subscale") was also tested in the same study: it accounted for 80% of change developed during treatment as assessed via the 11-item tool. The usefulness and psychometric properties of FACT/GOG-Ntx were also demonstrated in a population that was not treated with taxanes, but with oxaliplatin, suggesting that its use is likely generalizable regardless of the chemotherapy agent used (Kopec et al. 2006).

The CIPN20 was developed by Postma and colleagues in 2005 (Postma et al. 2005) to accurately collect information on patients' functional limitations and symptoms related to CIPN. A large and international group of oncologists, haematologists, neuro-oncologists, oncology research nurses, and neurologists devised a first version composed of 68 items. They were subsequently tested with the formal methodology used by EORTC, arriving at the current 20-item version. The scale has been translated and validated in several different languages (Cavaletti et al. 2010). The 20 items related to neuropathy are scored on a 4-point scale (where "1" means not at all and "4" means very much). There are 9 sensory, 8 motor, and 3 autonomic items. There are specific indications of who evaluated each patient's status. The score obtained by adding all items together is linearly transformed into a 0–100 scale; the new indicator thus obtained represents the severity of neuropathy (i.e., a higher number means the neurological status is worse). CIPN20 obtained an even more widespread use than FACT/GOG-Ntx and, thus, its psychometric properties have been extensively tested. The previously mentioned study by Postma and colleagues (Postma et al. 2005) showed initial reliability and adequate internal consistency; Cronbach's alpha coefficient was 0.82 for the sensory subscale, 0.73 for the motor subscale, and 0.76 for the autonomic subscale. However, some issues emerged in subsequent studies concerning the use of the subscale per se without considering the whole scale. When factor analysis was performed, a poor fit was demonstrated for the three subscales considered by themselves (Smith, Banerjee, et al. 2019, Lavoie Smith, Barton, et al. 2013, Smith et al. 2018, Cheng and Molassiotis 2019, Kieffer et al. 2017); moreover, items in the 3 different subscales did not cluster together. Thus Kieffer and

colleagues (Kieffer et al. 2017) proposed using the CIP20 as a simple additive checklist in order to reach an acceptable validity, and not to consider the three subscales as separate entities.

The responsiveness of CIPN20 was tested over the years with unconvincing results. Lavoie-Smith and colleagues (Lavoie Smith, Barton, et al. 2013) evaluated data from 173 patients demonstrating good responsiveness for the sensory subscale (effect size 0.82) and moderate responsiveness for the motor subscale (0.48). More recently, the responsiveness of the CIPN20 Chinese version was found to be low to moderate (Cheng and Molassiotis 2019) for the whole scale, the low performance probably being due to the autonomic items and the ceiling effect. The validity and reliability were good. Yeo and colleagues (Yeo et al. 2019) evaluated the minimally clinically important difference for CIPN20, identifying a significant change of 2.5–5.9 for the sensory subscale and 2.6–5.0 for the motor one. Despite their interest, these results need further validation in large prospective studies.

To ameliorate the CIPN20 performance, some suggestions have been proposed. Smith and colleagues (Smith, Zanville, et al. 2019) subjected CIPN20 data from over 1000 patients to Rasch analysis. They observed that the 1–4 scoring range was not adequate to detect small changes and identified psychometric weakness in more than half of the items, with autonomic and hearing being the most troublesome. The authors proposed some strategies to ameliorate the CIPN20 performance, such as eliminating or revising problematic items and converting the scoring system for each item to a 0–10 scale. Smith and colleagues (Smith et al. 2018) developed a 15-item version of the original CIPN20 excluding the items concerning difficulty in using pedals, autonomic symptoms, and hearing loss; moreover, some items were reordered. With these changes, the reliability of the new scale was higher and improvement in other properties was detected: a 0.57 correlation with cTNS© was observed and a higher responsiveness to small changes in severity was also demonstrated. Another shorter (16 item) version of the original was tested (Smith, Banerjee, et al. 2019), omitting items related to autonomic symptoms and hearing loss, thereby improving internal consistency and sensitivity.

Another PRO which is increasingly used is a “PRO” version of the NCI-CTCAE—PRO-CTCAE—which was validated by Dueck and colleagues (Dueck et al. 2015) in 2015. The PRO-CTCAE explores the severity of numbness and tingling in upper and lower limbs; the interference on QoL of these symptoms is also assessed (investigating effects in the seven days before the questionnaire was completed, scored

on 5-point scale ranging from “none” to “very much”). Recently, Tan and colleagues (Tan et al. 2019) tested the PRO-CTCAE, comparing data from the nursing-assessed NCI-CTCAE. A correlation was found between the two tools, but the correlation for individual patients was poor. Thus, the authors suggested that complementary PRO information should be used to better monitor CIPN besides physician-based tools. Nyrop and colleagues (Nyrop et al. 2019) performed a secondary analysis of data from two different prospective studies and observed high patient-clinician agreement (87%) only for grade 0 (i.e., no neuropathy); whereas, for grades 1 and 2, the neuropathy agreement was less than 50%. In summary, the study demonstrated that CIPN severity was underestimated by clinicians and therefore the need to couple a physician-based and patient-based tool was suggested.

A tool specifically devised to accurately evaluate QoL in CIPN patients is the Rasch-built Overall Disability Scale for patients with chemotherapy-induced peripheral neuropathy (CIPN-R-ODS) (Binda et al. 2013); data analysis was performed on the CI-PeriNomS study dataset (Cavaletti et al. 2013). A large set of questions was evaluated and a 28-item questionnaire was obtained, exploring different daily activities potentially altered as a consequence of CIPN. CIPN-R-ODS is a promising tool, but it still requires further validation since it was elaborated in a cohort of stable CIPN patients and its validity and responsiveness are yet to be explored.

Oxaliplatin-related CIPN

Oxaliplatin has a unique toxicity profile combing the classical chronic manifestations described so far and a peculiar acute neurotoxicity syndrome, normally lasting 24–72 hours after oxaliplatin i.v. administration (we will call it “acute oxaliplatin CIPN” [acute OIPN]). Acute OIPN consists of cold-induced, transient, paresthesia/dysesthesia (not only at limb extremities, but also in the face and in the upper digestive tract). Jaw-spasm and cramps/muscle spasms have also been described, even if more rarely (Briani et al. 2013). All these phenomena resemble a cold-induced acute neuromyotonia-like syndrome, characterized by both motor and sensory nerve hyperexcitability, a condition related to voltage-gated ion channel impairment (Newsom-Davis 2007). Therefore, acute OIPN is generally considered a functional, transient channelopathy, as supported by *in vitro* (Adelsberger et al. 2000, Krishnan et al. 2005) and clinical studies, addressing nerve excitability in patients treated with oxaliplatin (Krishnan et al. 2006, Heide et al. 2018). Acute OIPN has been

shown to be a predisposing factor for CIPN (Argyriou et al. 2013, Velasco et al. 2014). Oxaliplatin is more neurotoxic than other platinum-derived drugs, therefore it is hypothesized that acute OIPN is an adjunctive mechanisms of neuronal damage on the top of pathogenetic mechanisms common to all the compounds belonging to this class (Grolleau et al. 2001, Park et al. 2009).

Oxaliplatin-specific tools were devised to better describe the whole phenomenon: these include the Levi scale and the Neurotoxicity Criteria of Debiopharm (DEB-NTC). However, these two instruments do not accurately discriminate between acute and chronic neurotoxicity manifestations. For this reason Argyriou et al. (Lucchetta et al. 2012) proposed a yes/no 11-item questionnaire to record all symptoms related to acute OIPN: the Acute OIPN Questionnaire (OXA-NQ).

The Levi Scale (Lévi et al. 1994) is a 0–4 scoring system: 0 means "nothing," 1 is "paresthesia and/or dysesthesia (induced by cold) with complete regression within 1 week," 2 is "paresthesia and/or dysesthesia with complete regression within 21 days," 3 is "paresthesia and/or dysesthesia with incomplete regression within 21 days," and 4 is "paresthesia and/or dysesthesia with functional consequence." Its responsiveness was found to be higher if compared to NCI-CTCAE v2.0 for detection of symptom progression (Lévi et al. 1994, Kautio et al. 2011). However, it is far from being the ideal tool for discriminating between acute and chronic conditions (Cavaletti et al. 2010).

The DEB-NTC (Inoue et al. 2012) is a 1–3 grade scale rating oxaliplatin neurotoxicity; grade 1 means "paresthesia/dysesthesia of short duration," grade 2 means "paresthesia/dysesthesia persisting between cycles," grade 3 means "paresthesia/dysesthesia causing functional impairment." The DEB-NCT, as the Levi scale, was demonstrated to be more sensitive than NCI-CTC (v3.0) in detecting neurological deterioration; moreover, it was also able to detect earlier amelioration of neurological status (Inoue et al. 2012). But, again, the overlap between acute and chronic conditions was present.

The OXA-NQ (Lucchetta et al. 2012) is a potential alternative tool for the comprehensive detection of all and acute OIPN phenomena. This yes/no 11-item questionnaire explores the presence of frequent (cold-induced perioral paresthesia, cold-induced pharyngolaryngeal paresthesia, muscle cramps, jaw stiffness) and infrequent (shortness of breath, difficulty in swallowing, laryngospasm, visible fasciculations, voice changes, ptosis visual field changes) manifestations related to acute neurotoxicity syndrome. This questionnaire was used in longitudinal studies (Lucchetta et al. 2012, Argyriou et al. 2012, Velasco et al. 2014)

following up oxaliplatin-treated patients and was also used in a clinical trial testing a neuroprotectant agent (Bruna et al. 2018). However, its clinimetric properties have not been tested; at present, it can be used as a check list for acute oxaliplatin-induced neurological manifestations. A more pronounced acute OIPN, as assessed via OXA-NQ during the first cycles, was found to be predictive of a more severe neuropathy at the end of chemotherapy (Argyriou et al. 2012).

Pain issues

Neuropathic pain is one of the possible positive symptoms of neuropathy; however, it is not a prominent feature in the majority of CIPN patients (Alberti et al. 2013, Kerckhove et al. 2017, Gewandter et al. 2017). However "pain"—in general, not necessarily related to a PNS disease—may be present in up to 30% of patients at the time of diagnosis and in up to 70–80% in advanced cancer patients (Caraceni et al. 2012). "Cancer pain" encompasses, in fact, several types of pain: somatic, visceral, or neuropathic. The PNS can be disturbed by the neoplasm itself, directly (cancer infiltration) or indirectly (such as "paraneoplastic neuropathies") or affected as a consequence of treatment (e.g., surgery, radiotherapy, and chemotherapy).

The CI-PeriNomS study explored pain in 281 CIPN patients with two widely used "general" pain scales, the 11-point Pain Intensity Numerical Rating Sale (PI-NRS) and the visual analogue scale (VAS), which are intended to describe pain intensity (Cavaletti et al. 2013). The authors demonstrated a good test–retest reliability for both instruments. Moreover, they observed a 25% incidence of moderate-severe pain. This is relevant information; however, a confounding factor was present, given that only pain intensity was rated and its quality (neuropathic or nociceptive) was not explored.

A further instrument to discriminate between general and neuropathic pain is the Douleur Neuropathique 4 (DN4) scale. This scale is known to have a sensitivity and specificity higher than 90% for neuropathic pain detection (Bouhassira et al. 2005), though it has not been widely evaluated in a CIPN setting so far; however, Pérez and colleagues (Pérez et al. 2015) demonstrated that DN4 was quite sensitive in the assessment of intermittent or severe pain in a 268-person population of patients treated with neurotoxic chemotherapy.

In general, a combination of a scale rating pain intensity with the DN4 can be suggested to collect all relevant information regarding pain in CIPN patients.

Pediatric population

Childhood cancer diagnosis has steadily increased since the 1950s as has the decrease in mortality (overall, a 5-year survival has been observed in 80% of cancer types in children) (Kaatsch 2010). Thus, as well as for adults, there is a large population of long-term survivors (Phillips et al. 2015). The is the same need to monitor CIPN at the present. However, the pediatric population is an even more complex population to be evaluated. When assessing younger children, it is sometimes difficult to obtain the appropriate collaboration for all examinations, and there is an increased difficulty in obtaining a direct answer to questionnaires. In this case, parents and guardians are also a target of interest to collect relevant information, with the adjunctive bias of "referred" or "interpreted" symptoms/functional impairment.

A few tools were specifically devised to test children with CIPN: the Paediatric Modified: Total Neuropathy Scale (ped mTNS) (Gilchrist et al. 2009, Gilchrist and Tanner 2013) and the Total Neuropathy Scale: Paediatric Version (TNS-PV) (Lavoie Smith, Li, et al. 2013).

The ped mTNS is based on the clinical version of the TNS© and was elaborated by Gilchrist and colleagues (Gilchrist and Tanner 2013). They then evaluated ped mTNS in 41 subjects (aged 5–18 years) treated with vincristine or cisplatin and 41 age-matched and 41 gender-matched controls. The ped mTNS score was compared with standardized measures of balance and manual dexterity. The authors found a correlation (i.e., the higher the ped mTNS score, the worse the balance and manual dexterity). They subsequently compared the ped mTNS assessment with NCI-CTCAE v3.0 (Gilchrist, Marais, and Tanner 2014), and no correlation was found between the ped mTNS and the combined motor and sensory score of NCI-CTCAE. Notably, 84% of subjects individuated as having neuropathy with the ped mTNS were scored as normal by NCI-CTCAE. Nor was any correlation seen in the sensory symptoms score of the ped mTNS and the NCI-CTCAE, or in motor symptoms of both tools. A correlation was however present between the strength assessment in ped mTNS and the NCI-CTCAE motor score.

The Total Neuropathy Score: Pediatric Vincristine (TNS-PV) was proposed by Lavoie Smith and colleagues (Lavoie Smith, Li, et al. 2013) in 2013. It is based on the mTNS©, with an adjunctive item for "laryngeal hoarseness" and "thermal sensibility." There is an "A" and "B" version of the scale: the former for upper limbs and the latter for lower limbs. The authors observed no statistical difference in scoring between the "A" and "B" versions. The items most responsive to alterations of the neurological

status were DTR and vibration. However, age class influenced the possibility of items to be measured. For children younger than 3 years, vibration and temperature assessment was not possible in 87% of cases, whereas positive neuropathy symptoms were not measurable in 48%. DTR testing was, instead, obtained in 91% and formal assessment of strength in 78%. In children aged≥ 6 years, all the items were easily assessed. The TNS-PV correlated better than the NCI-CTC v4.0 with the drug cumulative dose, indirectly demonstrating its validity. However, a warning should be made for subjective symptom assessment since, taken alone, they are not able of correctly detecting neuropathy, being present in 44% of the population, despite 78% of children beinr affected with neuropathy.

Conclusion and future perspectives

In the last 20 years many efforts have been made to promote recognition of and a cure for CIPN. There is still a huge gap to be filled in regard to a scale to grade and detect CIPN. Gold-standard outcome measures are still to be developed. The data presented so far suggest that the best compromise might be to couple a physician-based tool and a PRO, as well as a tool to detect and grade neuropathic pain. The best option among physician-based tools seems to be the TNS© and its reduced variants, whereas FACT/GOG-Ntx and EORTC are the most promising PROs. The DN4 questionnaire plus PI-NRS could be a feasible option to describe neuropathic pain features. However, to finally select the best strategy, a solid, large, multicenter epidemiological international study is required. A possible location where such a study could blossom is the Toxic Neuropathy Consortium (TNC). The TNC is a special interest group (SIG), part of the Peripheral Nerve Society since 2018, that is becoming more and more active in making such collaboration possible (for more information, see https://www.pnsociety. com/i4a/pages/index.cfm?pageid= 3389).

Table 1. Scale to detect and grade CIPN. General features, applicability and where to find each tool described in this chapter.

TOOL	TYPE	EQUIPMENT	WHERE TO FIND IT
Eastern Cooperative Oncology Group (ECOG) scale	Oncological toxicity scale	It does not require specific equipment	http://www.ecog.org/general/common_tox.html
World Health Organization (WHO) scale	Oncological toxicity scale	It does not require specific equipment	Paper by Cavaletti et al., 2010[1]
Ajani scale	Oncological toxicity scale	It does not require specific equipment	Paper by Cavaletti et al., 2010[1]
National Cancer Institute—Common Toxicity Criteria Adverse Event (NCI-CTCAE)	Oncological toxicity scale	It does not require specific equipment	https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
Total Neuropathy Score (TNS©) scale	Physician-based scale	It requires: neurological examination, vibrameter, neurophysiology apparatus	Paper by Cornblath et al., 1999[2]
rTNS© scale	Physician-based scale	It requires: neurological examination, neurophysiology apparatus	Paper by Cavaletti et al., 2006[3]
cTNS© scale	Physician-based scale	It requires only neurological examination	Paper by Cavaletti et al., 2006[3]
RT-cTNS©	Physician-based scale	It requires only neurological examination	Paper by Binda et al., 2015[4]

mTNSr©	Physician-based scale	It requires only neurological examination	Paper by Smith et al., 2010[5]
rTNS-SF©	Physician-based scale	It requires only neurological examination	Paper by Lavoie-Smith et al., 2011[6]
Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group (GOG)-neurotoxicity (FACT/GOG-Ntx)	Patient-reported outcome	It does not require specific equipment	Paper by Huang et al. 2007[7]
European Organisation of Research and Treatment of Cancer (EORTC) QLQ-CIPN20	Patient-reported outcome	It does not require specific equipment	https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-CIPN20-English.pdf
PRO-CTCAE	Patient-reported outcome	It does not require specific equipment	Paper by Tan et al., 2019 [8]
Rasch-built Overall Disability Scale for patients with chemotherapy-induced peripheral neuropathy (CIPN-R-ODS)	Patient-reported outcome	It does not require specific equipment	Paper by Binda et al., 2013[9]
Levi scale	Questionnaire for acute Oxaliplatin	It does not require specific equipment	Paper by Levi et al. 1994[10]

	neurotoxicity		
Neurotoxicity Criteria of Debiopharm (DEB-NTC) scale	Questionnaire for acute Oxaliplatin neurotoxicity	It does not require specific equipment.	Paper by Inoue et al., 2012[11]
Acute Oxaliplatin neurotoxicity questionnaire (OXA-NQ)	Questionnaire for acute Oxaliplatin neurotoxicity	It does not require specific equipment	Paper by Lucchetta et. al, 2012[12]
Pain Intensity Numerical Rating Sale (PI-NRS)	Pain scale	It does not require specific equipment	Paper by Cavaletti et al., 2013[13]
Visual analogue scale (VAS)	Pain scale	It does not require specific equipment	Paper by Cavaletti et al., 2013[13]
Douleur Neuropathique 4 (DN4) scale	Pain scale	It does not require specific equipment	Paper by Bouhassira et al., 2005[14]
Pediatric Modified – Total Neuropathy Scale (ped mTNS)	Physician-based scale for children	It requires only neurological examination	Paper by Gilchrist et al., 2013[15]
Total Neuropathy Scale – Pediatric Version (TNS-PV)	Physician-based scale for children	It requires only neurological examination	Paper by Lavoie-Smith et al, 2013[16]

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CHAPTER 2.5

METHODS FOR ASSESSING NEUROMUSCULAR FUNCTION

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Abstract

The neuromuscular system is rarely investigated in follow-ups for cancer patients, although it plays a key role in the progression of the disease and tolerance to treatment. Many techniques can be used to characterize the muscle by considering its different facets: its volume (or mass) by imaging techniques, its excitability by electrophysiological techniques, its strength by dynamometry and the resulting motor skills by various timed tests. In this chapter, an overview of the various approaches is considered along with their advantages and limitations. The fact is that, at the moment, there are still several burdens that render difficult the routine investigation of the muscle.

Keywords: neuromuscular system, muscle strength, muscle volume; muscle mass, outcome measures

Methods for assessing the neuromuscular function

1. The different levels of investigation of the neuromuscular system

In order to fully perform their function, muscles must be organized (in the geometric/architectural sense), excitable (in the electrophysiological sense), and efficient (in the mechanical sense) to produce a force to generate movement and perform the motor tasks of daily life. Loss of this

function of force generation can cause impairments that can lead to disability and loss of autonomy. These disabilities can be exacerbated by a vicious circle, leading an individual to do less physical activity, which accelerates the process of physical deconditioning, often amplified by a loss of muscle mass.

The characterization of muscle tissue is based on both quantitative and qualitative measurements. Muscle strength largely depends on the amount of contractile muscle tissue but also on its composition (presence of fat infiltration, fibrosis, or oedema), its metabolic capacities and its motor control. Muscle tissue is often characterized by measurement of its quantity, either in terms of mass (in kg) or volume (in cm^3). Several proxies exist to measure the quantity of a muscle. This measurement of muscle mass will be the subject of a special section (see paragraph 4.5.8) where the measurement of muscle composition will also be discussed.

Skeletal muscles are subordinate to the motor cortex. Each muscle fiber is innervated by a branch of an alpha motor neuron. The arrival of a nerve impulse (nerve action potential) at the end of the axonic branch causes the release of a quanta of acetylcholine into the synaptic space, which will cause ionic movements and a local depolarization. If this depolarization is above the excitability threshold, it will generate an action potential that will spread along the sarcolemma and trigger the chemical and mechanical phenomena of muscle fiber contraction. The motor unit obeys the law of all or nothing: only an effective stimulation carried by the motor neuron determines an action potential in each of its fibers, which maximally contract. The force developed by the muscle results mainly from the number of motor units recruited (spatial summation) and the firing rate (temporal summation).

The main function of a muscle is to generate a force mediated by the shortening of muscle fibers and the tension of the elastic structures of the muscle and tendons. This tension causes movement of the bone segments to which the muscle is attached, producing controlled movements required to perform the motor tasks of daily life. There are several levels of evaluation of the neuromuscular system, levels which should be considered as complementary and which reveal different facets of this system (Figure 2.5.1). If an individual loses muscle strength, it is necessary to identify whether it is the muscle mass that has decreased, whether it is the motor control of his or her muscles that has degraded, whether there is a fault in force generation, or whether the problem lies outside the muscular system, such as osteoarticular pain or a deficiency of the central nervous system, for example.

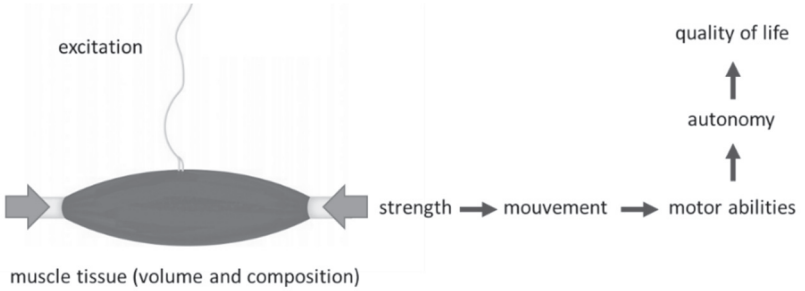

Figure 2.5.1. Complementarity of outcome measures: an excited muscle mass generates strength to create movement, perform the motor tasks of daily life, and ensure autonomy and quality of life.

The aim is to standardize measures as much as possible to ensure the most rigorous follow-up of individuals during the course of a disease, particularly in the context of treatment. This is the aim of outcome measures. However, practical outcome measures are lacking and there is an urgent need for the development of clinical practice guidelines for detecting low muscle mass and impaired performance. As was recently underlined by Baracos et al.,[1] "muscle has always been difficult to evaluate in a clinical setting other than by a purely functional or crude anthropometric approach."

2. What is an optimal outcome measure?

An outcome measure is an assessment tool used to measure the various consequences of a condition or disease. They can directly measure the organ involved in the disease, by-products that are secondarily released in fluids such as blood or urine, functional impairments of the organ itself, or the repercussions of these impairments on the daily life of an individual. For consistent follow-up of an individual, neuromuscular outcome measures should fulfill certain criteria. They should be:

- simple and fast to perform,
- adapted to the population to be assessed,
- cost effective (which is a relative notion),
- reliable (repeatable, reproducible),
- sensitive to change,
- clinically meaningful (which is also a very relative notion, particularly with respect to the clinical status of the individual),

- easily standardisable (which is critical for multicenter trials),
- with no floor or ceiling effects,
- with limited learning effects (minimizing the possibility to adapt motor strategies),
- with minimal constraints for the individual and evaluators (non-invasive, non-painful, minimal risks).

The measurements must be performed by qualified people, specifically trained and certified, using strict standardized operating procedures. This is mandatory during therapeutic trials but also when centers want to compare their data. Quality control of the practice of the evaluators and of the data is fundamental for obtaining reliable data. Companies may spend billions of euros developing a therapy. It is conceivable that some funding is allocated to the assessment of its effects. Also when designing an evaluation protocol, one may consider fatigue, which can occur when accumulating assessment tests.

3. Motor control

Muscle contraction is the result of multiple electrical and chemical phenomena starting in the motor cortex and terminating in the muscle fibers. Muscle tissue is an excitable tissue and its contraction is triggered by the circulation of electrical activity along the muscle fibers that compose it. This activity can be measured using electrophysiological or electroneuromyographic (ENMG) techniques for the exploration of either motor (or sensory) nerves, muscles or neuromuscular junctions. ENMG techniques are numerous and are described in most electrophysiology textbooks, including the exploration techniques specific to neuromuscular junctions.

The measurement of the amount of excitable muscle tissue is performed using motor unit number estimation (MUNE) techniques. There are several, each with its own advantages and limitations. A recent review acknowledges that, “all current methods have individual shortcomings.”[2] However, none of the aforementioned methods have been applied to the field of cancer so far. These methods are mainly applied in neuromuscular or neurological diseases, even though the estimation of the number of excitable motor units could provide a better understanding of the process of muscle mass loss during cancer and associated treatments.

The role of neuromuscular junctions is to transmit excitation information from the motor nerve to the muscle. The genesis of a muscle action potential in response to a nerve stimulus involves many steps. In

addition to some animal toxins, other pathophysiological processes may interfere with neuromuscular transmission. Disorders of the neuromuscular junction can be pre- or post-junctional and have immunological, toxic or genetic origins. The release of acetylcholine quantum into the synaptic space is triggered by a calcium flux entering the presynaptic termination. Some paraneoplastic syndromes can lead to the secretion of antibodies that block neuromuscular transmission, including calcium channel antibodies such as Lambert-Eaton syndrome, a presynaptic myasthenic syndrome found in some cancers.

The exploration of neuromuscular transmission involves electrophysiological techniques based on repetitive electrical stimulation, either at rest or following efforts of varying intensity and duration, with or without cooling. The most common examination is repeated stimulation at supra-maximal intensity. It involves stimulating a motor nerve and collecting the motor response on the muscle it innervates. Stimulation is low frequency (3 Hz) when it is necessary to show overall failure of the neuromuscular junction or high frequency (greater than 10 Hz) when it is necessary to specify the pre- or post-synaptic origin of a defect in neuromuscular transmission. The duration of stimulation is generally 2s. The decrease or increase in amplitude of the motor response will identify a transmission anomaly. Stress and temperature are factors that also make it possible to be more specific in finding the cause of the junction failure. Registration procedures must follow a rigorous, standardized protocol. The examination is very sensitive to technical errors (electrode placement, temperature control, muscle relaxation, etc.). High frequency stimulation is generally quite unpleasant and is often not well received.

4. Muscle strength

The force of a muscle contraction is controlled by the number of activated motor units (spatial recruitment) and their firing rates (temporal recruitment). The maximum force generated by a muscle mainly depends on its size. But other factors (mainly metabolic, architectural, and nervous) can influence the muscle's production of strength.

The main function of a muscle is to produce a force in order to fulfill motor tasks in daily life (including breathing, speaking, communicating, standing against gravity, etc.). However, in most clinical protocols, only maximal voluntary isometric strength is assessed. This is supposed to reflect the best performance a muscle is able to produce in terms of force. Force and strength are generally thought to cover the same concept. However, some authors prefer to consider force as a mechanical concept

and strength as a physiological concept. This is because muscle force should be measured within the muscle itself. Thus, what is measured is the magnitude of the external action of several forces generated within several muscles to produce an action. As an illustration, knee extension strength is mostly the result of the contraction of the quadriceps, which is comprised of four muscles. The muscle force of each individual muscle is unknown and only the external resultant is measured. Also, what should be measured is a torque (or a moment), because the measurement takes place at a certain distance (the lever arm) of a joint that is rotating around its axis. The unit of torque is a Newton Meter (Nm).

Most strength assessment methods measure a joint movement (even in isometric conditions where there are no real movements), also referred to as a muscle function, such as knee extension. There are several methods to estimate maximal muscle strength (or maximal voluntary contraction: MVC), which could be schematically divided into 5 classes (see Figure 2.5.2):

- manual muscle testing
- hand-held dynamometry
- fixed dynamometry
- isokinetic dynamometry
- specific dynamometry

Manual muscle testing (MMT) is the most practical way to measure muscle strength in routine clinical practice. It requires no particular equipment except an examination table. The assessment is performed by a physician or physiotherapist applying his or her hand against the desired movement. Several scales are available, the most commonly used being the modified MRC scale and the Kendall scale (mostly in the USA). MMT measures not only strength but also range of motion. Detecting muscle weakness is not that straightforward because the evaluator must judge what is normal with respect to age, gender, and stature, which is all the more difficult in children. MMT suffers from major drawbacks: mostly as it is an ordinal, non-linear and subjective scale, poorly sensitive to change and presents with ceiling (and to a lesser extent floor) effects. MMT should not be used for a precise quantification of the strength of individual muscle groups. Instead, composite scores can be used keeping in mind the aforementioned limitations of MMT.

Hand-held dynamometry (HHD) is a practical means for helping clinicians to better quantify muscle strength. Dynamometer cost ranges typically between 1 and 5 k€. HHD uses a device that can be seen as an

interface between the hand of the evaluator and the individual to be tested. It measures the compression (may work in traction too) an individual is able to apply to the dynamometer. The measurement is expressed in kilograms (kg) or Newtons (N), rarely in pounds, which is not a recognized international unit. There are two main methods for performing the HHD assessment: the make and the break method. In the make method, the evaluator maintains the dynamometer as static and stationary as possible and the individual to be tested pushes against it. In the break method, the evaluator applies resistance to the body part being tested until the individual's maximal muscular effort is overcome and the joint being tested gives way. The break method generally yields higher strength estimates because the muscles work in eccentric conditions. The main limitations of HHD are when the individual is very strong or very weak. When an individual is very strong, the evaluator may have difficulties maintaining the evaluation position in static conditions. Thus, the measure of maximal strength tends to be underestimated. When an individual is very weak, the influence of the evaluator may be very large, leading to a substantial relative error.

Fixed dynamometry (FXD) is also known under the name QMT (quantified muscle testing) but the name is misleading since all the methods are quantified. The measure of strength is performed using a load cell (or force transducer) attached to a fixed point (a metallic frame generally attached to a wall) on one side with a snap hook and the individual on the other side using an adjustable strap. It resolves the limitation of HHD for strong individuals but definitively not for weaker individuals because the individual needs to lift the load cell and stretch the strap, which can be challenging. FXD systems cost between 4 and 15 k€ and a particular room is required in which to install it. An electronic board and software are necessary to acquire the force signals delivered by the load cell. Some techniques have adapted HHD using straps to help support the person; this means they are also close to FXD.

Isokinetic dynamometry (IKD) are performed using large dynamometers which can be used in many contraction conditions: isometric, isokinetic, isotonic, concentric, or eccentric contractions and in active or passive modes. Isokinetic dynamometers are rather expensive (roughly between 60 to 100 k€) and an appropriate space is necessary for the device to be installed in. They are able to measure the torque around most joints of the body (ankle, knee, hip for lower limbs and wrist, elbow, shoulder for upper limbs). Some of them have accessories for the low back and neck. They are considered the gold standard for knee extension measurement. Owing to their price, they are rarely used in multicenter

clinical trials. They are however, largely used for rehabilitation and strengthening programs.

Specific dynamometry is performed by means of dynamometers that are used for one particular function, such as handgrip or key pinch, or one particular joint, such as ankle flexion/extension or wrist flexion/extension. Aside from grip and pinch, for which several dynamometers are on the market, specific dynamometers are mostly used for research purposes to perform more reliable measures compared with those obtained using versatile techniques. Their price generally ranges between 1 and 5 k€.

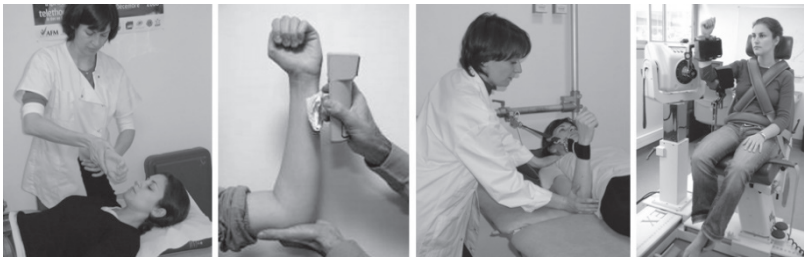

Figure 2.5.2. Elbow extension strength evaluated using MMT, HHD, FXD, and IKD (from left to right).

Grip strength is a particular function that has been extensively studied in many conditions since it is a simple, cost-effective, and standardized examination. As advocated by Bohannon,[3] "grip strength should be considered for routine use as a vital sign." There are many dynamometers on the market for a price ranging from 100 to 3500 €. Maximal grip strength has been shown to be related to functional limitations and to different forms of disability, especially those with a progressive onset, and to be associated with nutritional status, length of stay in hospitalization, postoperative complications, morbidity, mortality, and even life expectancy.

Except isokinetic dynamometers and some specific dynamometers, all of the other methods are sensitive to the lever arm, that is, the location of the application point of the dynamometer with respect to the axis of rotation of the joint. This implies that the device must be placed on the same location using anatomical landmarks. While this can be easily addressed in adults, this may be a critical issue in children who are growing.

An objective measure is not necessarily an exact or precise measure because the system whose property you wish to measure can be difficult to access, can be complex, and can have inherent fluctuations.

This is often the case in the field of *in vivo* physiology. To take the reasoning to the extreme, the "true value" (the measurand) is not accessible most of the time. It is important to be aware that the measurement is affected by many factors other than its value itself. These factors can be technical and technological (instrumentation), methodological (operating procedure), environmental, and human (evaluator skill, subject motivation, evaluator-subject relationship . . .). In most protocols, for a given function, MVC is retained as the maximum value reached by the subject from three maximum trials maintained for a period of 2 to 5 seconds. Under strict experimental conditions, the MVC measurement is highly reproducible. Calibration of the sensors is a necessary condition for the proper functioning of the equipment and conditions the measurement performed. For each function tested, the MVC recording procedures must be specified: the number of trials performed, the duration of the trial and the force plateau, the recovery time between trials, the respect (or not) of a reproducibility coefficient between trials, and the recovery time between each function tested. In some protocols, it is stipulated that the subject be informed that he or she must not use compensation to help achieve the requested movement. Faced with this issue, evaluators may adopt different strategies with regard to stabilization and applying resistance. This is why a common training of all evaluators is essential.

Finally, evaluation of the respiratory muscles in general and of the diaphragm in particular are performed using specific pulmonary function tests through the assessment of forced vital capacity, forced expiratory volume in one second, and maximal inspiratory and expiratory pressures. Sniff and cough tests can also be useful.

5. Motor abilities

Muscles are required to fulfill motor tasks that are performed under controlled conditions when an individual is assessed at the hospital. Motor tasks do not generally require maximal voluntary contractions. There are two main families of motors tasks: timed tests where subjects are asked to perform a motor task within a minimal duration and time-limited tests where subjects are asked to perform a maximal number of actions during a given time. There are plenty of motor ability tests (or physical ability tests) to measure the restriction in ability to perform a function that may result from a neuromuscular impairment.

The most commonly used measures for neuromuscular assessment are the 6-minute walk test (6MWT), the 10-minute walk/run test, the 5-times sit-to-stand test, the 30-second sit-to-stand test, the four-

step climbing test, the nine-hole peg test, the Purdue pegboard test, the Mingazzini test, and the Barré test. All these tests have rarely been considered so far in individuals with cancer. A recent study concluded that the 6MWT could be used as a measure of global health in women with breast cancer and could be useful for their follow-up during an exercise program.[4]

The main issue with timed tests is their inability to quantify the time when the subject is no longer able to perform the test. In such situations, statistical analyses may be limited. For instance, if an individual is not able to perform five sit-to-stands then the time taken to perform the five sit-to-stand test is infinite, a critical limitation for performing proper statistics. This is why time-limited tests should be preferred because they do not present this kind of limitation (even if they may have a floor effect). For instance, a non-ambulant subject will have zero in a 6MWT.

There are also a very large number of scales for assessing disabilities in activities of daily living. They are either evaluator-assessed or self-questionnaires (patient-reported outcomes). These instruments are presented in another chapter.

In order to ensure consistency and reliability, all the tests must follow strict standardized operating procedures. Most of the tests can be performed with no or very little equipment (a stopwatch, a pen, two cones, a chair . . .).

All the aforementioned tests are performed in a controlled environment, generally a hospital. A new era is opening with e-health. Many devices, connected objects, and smartphone applications may help clinicians follow patients at home in their daily lives. Actigraphy (or actimetry) is becoming more and more used for measuring daily physical activities (mostly characterized by their numbers, intensities, and durations), but also sleep quality and circadian cycles, number of falls, and so on. All the data acquired during daily life may also benefit from the development of big-data processing methods and so-called artificial intelligence algorithms.

6. Expression of results

When strength is measured, the results are generally expressed in absolute values, that is, in kg or Nm. Doing so precludes the possibility of comparing individuals and of computing composite scores because both individuals and muscles do not have the same strength capacities. Comparing a small woman measuring 160 cm and weighing 50 kg and a large man measuring 190 cm and weighing 100 kg is meaningless. As is

combining wrist extension strength with knee extension strength. This is where norms are useful. They allow us to express the values in a relative way as a function of age, gender, weight, height, and/or other variables. The unit becomes a percentage of predicted normal values, which is probably more useful for a clinician to appraise an individual strength and quantify his or her actual impairment. The literature proposes several norms for most of the methods, joints, and populations.

It is current practice to compute composite strength scores for MMT for the whole body or for the lower and/or upper limbs. It is generally a sum of all individual scores, which can also be expressed as a percentage of the maximum score. This composite score can give a valuable picture of the global muscle strength of an individual but may be biased because the distance (in strength) between each grade is not the same. When expressed in percentage of predicted values, composite scores can also be computed for dynamometry. This score is considered more robust than individual measures because the variability of each measure is drowned within the average of all the individual measures.

In the different definitions of sarcopenia, different thresholds of strength have been proposed to detect muscle weakness. However, these cut-offs are expressed in absolute values, which does not seem adequate for the aforementioned reasons. Also, different algorithms are employed to diagnose sarcopenia, which yields varying results in terms of prevalence.

7. Impairments, disabilities, handicap, autonomy, and quality of life

For proper definitions of each of the terms "impairments," "disabilities," and "handicaps," the reader is invited to refer to the book published by the World Health Organization[5] and particularly to the chapter "The Consequences of Disease." This is useful in making a clear distinction in the terminology and understanding of how the different levels can be linked. The relationships between outcome measures are not straightforward nor always causal. For instance, the relationships between muscle strength and motor abilities are generally non-linear. When an individual loses their strength, the human brain has the power to build new motor strategies to compensate for this weakness and to maintain function. Thus, strength is more sensitive to change at the beginning of the disease. After this stage both strength and function decrease together up to a certain point where function cannot be fulfilled anymore. But there is still a small amount of strength to be measured. This implies that sensitivity to change

is not the same for different outcomes depending on the clinical status of a subject.

Finding correlations between outcome measures cannot be an objective in itself. For instance, if a researcher finds a significant correlation between a motor scale and muscle strength in a group of patients, thus he or she will tend to conclude that the scale is effective and meaningful. But correlation is not sufficient. Applicability, validity, responsiveness, sensitivity to change, precision, and other metrological properties are also to be considered when characterizing an outcome measure.

8. Sarcopenia and cachexia: definitions and concepts

Cancer and/or related treatments can lead to a loss of muscle mass. However, the terms used to describe this loss of muscle mass on the one hand are not specific to oncology and on the other hand are not clearly defined. Thus, there is considerable confusion in the use of the terms "cachexia" and "sarcopenia," simply because there is not yet a consensus on their definition. The term "myopenia" was proposed in 2011 by Fearon et al. as "a new universal term for muscle wasting" in an attempt to clarify awkward terminology.[6] However, this proposal has not been very successful so far. When used as a keyword search in PubMed, about 30 articles come up (whereas "cachexia" or "sarcopenia" bring up almost 10,000 articles). As mentioned by Pring et al.,[7] "cachexia is a well-recognized phenomenon in clinical practice, however, at this time, myopenia alone is not." Baracos et al. added that "debilitating muscle atrophy is a significant (and under-appreciated) adverse effect of cancer treatment."[1]

Muscle wasting is a process that can occur for different reasons in chronic diseases such as cancers or neuromuscular diseases, but also during aging, immobilization, physical inactivity, or inappropriate nutrition. Whatever the reason, muscle wasting results in a loss of muscle mass. Even the term "muscle mass" can be subject to debate since the muscle may become infiltrated by tissue other than contractile muscle tissue within the aponeurosis or even within the cells themselves. This other tissue is not very useful for muscle contraction since it adds viscosity inside the muscle, decreasing its contraction efficiency. What seems important to evaluate is finally the functional (or effective) muscle mass, the one that is useful for moving, breathing, communicating, and ensuring autonomy in daily life.

As mentioned by Fearon et al. (2011) in a consensus process, "cachexia has been recognized for a long time as an adverse effect of cancer"[8] and, as already suggested,[9] "was defined as a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass)." Cachexia probably results from the inflammatory response due to the presence of the tumor, which in turn alters body composition and metabolism. The precise mechanisms of cachexia still remain incompletely understood. Several interesting reviews on the mechanisms, consequences, measurement methods, and treatments of cachexia have recently been proposed[1,10–12].

Sarcopenia is a relatively recent term since it was first proposed in 1989[13] to refer to the loss of muscle mass associated with aging.[14] In the United States (NIH), as in Europe (European Working Group on Sarcopenia in Older People: EWGSOP), working groups have agreed to include notions of physical performance in the concept of sarcopenia and have proposed evaluation criteria to help quantify functional loss and autonomy in older people. However, changes in muscle mass and muscle strength/function are not equivalent. Using a single word (sarcopenia) to describe their decrease implies a direct mechanistic link between them, which is not the case. Indeed, the loss of muscle mass does not alone explain the loss of muscle strength. As underlined by Narici and Maffuli,[15] "although muscle weakness is indeed an inevitable consequence of sarcopenia, these two terms should not be used interchangeably since this would imply a direct proportionality between the two, which is not the case since skeletal muscle becomes intrinsically weaker in old age." In 2008, the term "dynapenia" was proposed by Clark and Manini[16] to reflect the loss of function associated in part with sarcopenia in its original sense. Many factors other than just loss of muscle mass interact to produce loss of muscle strength. However, an abundant literature suggests that the terms sarcopenia and dynapenia must be clearly identified and dissociated. Also, combining the loss of muscle mass and the decrease in physical performance leads to associate causes and consequences, which adds confusion.

The definition of sarcopenia, its mechanisms and treatments, have been debated in several interesting reviews.[17] Several definitions are found in diverse sources.[18–20] In a recent editorial titled "Sarcopenia: New Definitions, Same Limitations," Mayhew and Raina[21] discussed the challenge of an agreement on the definition of sarcopenia.

The decrease in muscle mass is essentially due to two main phenomena: the decrease in the size of muscle fibers and the decrease in the number of fibers. These two phenomena have multiple causes that interfere with one another: nervous, hormonal, inflammatory, metabolic,

architectural, and mechanical, and even social, cultural, and environmental factors. Losses of up to half of one's muscle mass between the ages of 20 and 80 have been described in the literature. However, it has been shown that not all muscle territories are equally involved. For example, the muscles of the lower limbs are twice as affected as the muscles of the upper limbs, implying greater functional loss in activities involving the lower limbs. With age, skeletal muscles become less voluminous and weaker, with functional loss exceeding structural loss. Although the many mechanisms involved in sarcopenia and dynapenia are still far from being fully understood or known, it is well recognized that appropriate physical activity can slow neuromuscular aging, including training based on resistance-type exercises. Finally, nutritional and pharmacological interventions can also be very effective and remain a very active area of research. These elements reinforce the importance of detecting the occurrence of muscle loss as early as possible.

During aging, not only does the quantity of muscle decrease, but also the quality as the muscle becomes infiltrated by fat and connective tissue (also called myosteatosis). Perkisas et al.[22] recently underlined that "intramuscular tissue mistakenly considered as muscle mass can represent an important bias in the evaluation of the muscle mass component in sarcopenia." It was also emphasized that myosteasis should be addressed in the workup of sarcopenia,[23] that is, measuring both intermuscular fat and intramuscular fat. For details on the physiology of adipose deposits, the reader is referred to the excellent review by Hausman et al.[24] As already pointed out,[15] "the net contractile muscle mass is actually smaller than that measured by a simple cross-sectional area (CSA) and mistakes in the estimation of the contractile muscle mass are likely to be made if the non-contractile mass is not accounted for." What is thus to be measured is the lean muscle mass appreciated here as the effective muscle mass. Yamada clearly explained the concepts of skeletal muscle mass and muscle cell mass and why they should be considered different.[25]

Regardless of the field (aging, cancer, or other conditions), a low lean muscle mass is linked to negative health outcomes: higher risks of death, higher incidence of hospitalization, higher length of hospital stays, lower functional independence, higher risk of comorbidities, lower quality of life. Regardless of the name (cachexia, sarcopenia, myopenia, muscle wasting) or the aetiology or mechanism(s) (which can be cumulative, for instance in aging people with cancer), the result is the same: a loss of muscle mass quantity and/or quality (Figure 2.5.3). However, the concepts of sarcopenia, cachexia, and muscle wasting are still often misleading and confusing.

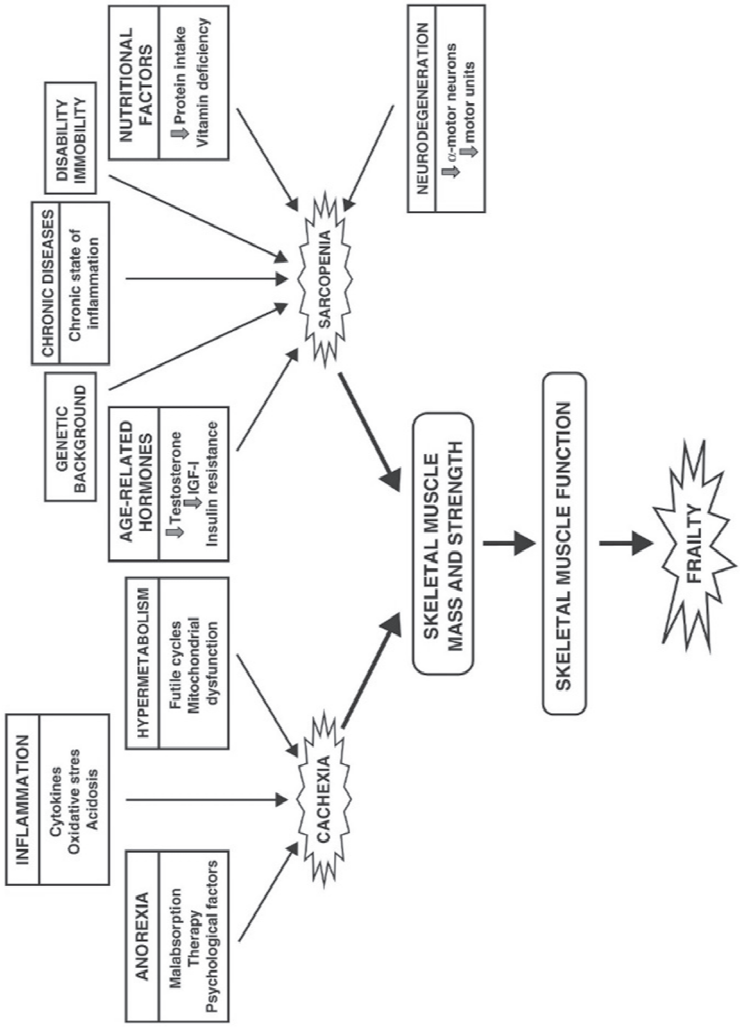

Figure 2.5.3. Differential factors involved in cachexia and sarcopenia. The factors promoting cachexia are different from those behind sarcopenia. Thus, in cachexia, proinflammatory cytokines play a very important role together with the hypermetabolic state and anorexia. In sarcopenia, endocrine changes together with neurodegenerative alterations are very important (reprinted from *Current Opinion in Pharmacology*, vol. 22, Argilés et al., "Cachexia and sarcopenia: mechanisms and potential targets for intervention," pages 100–106, Copyright 2015, with permission from Elsevier).

9. The estimation of skeletal muscle mass

As pointed out by Yamada,[25] "all methods of assessing skeletal muscle mass are indirect methodology since human body composition cannot be measured directly except for [a] cadaver. As they are indirect methods, there are always hypotheses." In these conditions, muscle mass is not measured but rather estimated.

The estimation of skeletal muscle mass is addressed in the bibliography mainly using four techniques that implement distinct technologies (see, for instance the extensive historical overview and state of the art paper by Heymsfield et al.[26] and the recent review on pitfalls in the measurement of muscle mass by Buckinx et al.[27]): computed tomography (CT), magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), and bioelectrical impedance analysis (BIA). Evaluation of creatinine excretion rate, anthropometric measurements, or hydrodensitometry are other methods that we will not consider here either because they are unreliable or because they cannot be used easily. Also, peripheral quantitative computed tomography (pQCT) is rarely available at the moment (see for instance Erlandson et al.[28]). The use of ultrasound imaging and elastography is also advocated by several researchers as a means of quantifying muscle mass, but this technique still faces issues with reproducibility.

MRI is the most accurate technique for estimating muscle mass because it allows the muscles of the human body to be segmented and intramuscular fat infiltration to be taken into account. It can therefore be considered as the gold standard even though a consensus has not yet been reached among the scientific community. However, this technique is very time-consuming and expensive, which most of the time prohibits its routine use. As a result, muscle mass measurement is generally performed using DXA, although it incorporates the contribution of several tissues and fluids whose influences cannot be separated. Baumgartner et al. defined a sarcopenia index as the lean appendicular mass divided by squared height, established for a reference population of individuals aged 18 to 40 years.[29] However, it is important to remember that the DXA measures fat-free mass, which is not exactly equivalent to muscle mass for the reasons already explained above. A critical debate is ongoing within the scientific community concerning which method should be considered as the reference method. The debate focuses on the use of MRI versus DXA. The reader is strongly invited to consider the excellent paper by Tavoian et al.,[30] which clearly poses the right questions and the real issues in this debate.

Apart from imaging techniques, whole-body and segmental BIA methods also provide estimates of muscle mass. They are cheap and accessible methods, but they exhibit major caveats. Specifically, conventional BIA methods have critical limitations. First, they oversimplify body/limb geometry as the fat-free compartment is assumed to be cylindrical with uniform electrical characteristics. Second, differences between individuals in electrical path length are accounted for by body height (for whole-body approaches) or segment length (in segmental approaches). Third, most of the models rely on BIA measurements at 50 kHz, which is considered insufficient to penetrate the intracellular space and this may also produce inconsistency related to high variation in skin-electrode impedance. Multifrequency BIA may be more promising in estimating muscle mass. Fourth, importantly, predictive models for the estimation of muscle mass are statistically derived from BIA and reference methods of measurement (e.g., DXA, CT, MRI). These models are highly population specific, making them poorly generalizable (see for instance Janssen et al.[31] or Buckinx et al.[27]). Most of the time, equations are not made available to the users by companies, thus the BIA devices are black boxes delivering numbers that cannot be scrutinized. New BIA methods are under development, which should refine the estimation of muscle mass as a more affordable, rapid, and inexpensive alternative to other methods.

DXA tends to overestimate muscle mass compared to CT or MRI (despite a strong correlation between methods). Also, BIA tends to overestimate muscle mass compared to the other methods but this depends on the equation used. But in some conditions, that is, when non-muscle tissues are present between or within muscle fibers, as is the case for instance with aging or cachexia, all methods overestimate muscle mass. Some specific MRI sequences (e.g., multi-point Dixon) can estimate the fat fraction present within a muscle, leading to the estimation of lean muscle mass. However, both image acquisition and processing are not compatible with routine practice. MRI can however be used as a reference to validate other methods.

Thus, currently muscle mass loss is frequently either not measured or inaccurately measured. The failure to correctly diagnose muscle mass loss results in significant healthcare as well as socio-economic costs as physicians are unable to alert patients in advance to a condition that may be attenuated. Healthcare costs include increased hospitalization, additional visits to physicians, additional medication (for a recent review, see Norman and Otten[32]). Socio-economic costs include increased involvement of caretakers, decreased participation, emotional well-being, and quality of life.

There are several muscle mass indexes used for either sarcopenia or cachexia detection. There is no consensus yet on which muscle(s) should be selected and which variable(s) should be used (a single CSA or whole volume). For instance, a cachexia index has been proposed by Jafri et al.[33] and combines a radiographically derived skeletal muscle index, serum albumin level, and neutrophil to lymphocyte ratio. The skeletal muscle index was computed as the cross-sectional area of the muscle in the L3 region normalized by height squared. However, owing to the fact that not all the muscles are affected the same way by the disease, there is still a lack of indexes of muscle mass to be used routinely.

10. Relationships between muscle mass and clinical outcomes

The loss of muscle mass is a strong negative prognostic factor both for cancer outcomes and treatment toxicity outcomes. This has been shown in many studies, for instance on progression-free survival in aggressive lymphomas using the cachexia index,[34] on dose-limiting toxicities in metastatic colorectal cancers using the skeletal muscle index,[35] on various outcomes (postoperative complications, overall survival, and dose-limiting toxicities) in gastric cancers (for a review, see Kuwada et al.[36]). Thus, maintaining muscle mass is also essential in the management of individuals with cancer. Both nutrition and physical activity should be tailored in order to optimize the maintenance of muscle mass, which is also mandatory for functional independence. Also, various pharmacological approaches are now considered because our physiological understanding and knowledge are progressing.

From the beginning of the century, it has been shown that muscle can release hundreds of different agents and largely participates in the complex network of metabolic, hormonal, immunological communications. Several studies have shown that muscle acts as an endocrine organ (see the pivotal paper by Pedersen[37]) by secreting cytokines (namely myokines) involved in autocrine, paracrine, and endocrine signaling as immunomodulating agents. Some of the most studied cytokines are interleukins IL-6, IL-8, and IL-15, myostatin, decorin, irisin, myonectin, the brain-derived neurotrophic factor, and the leukaemia inhibitory factor (Figure 2.5.4). Their role in regulating skeletal muscle mass and function is largely recognized (for a review, see Lee and Jun[38]) and paves the way for new treatment strategies.

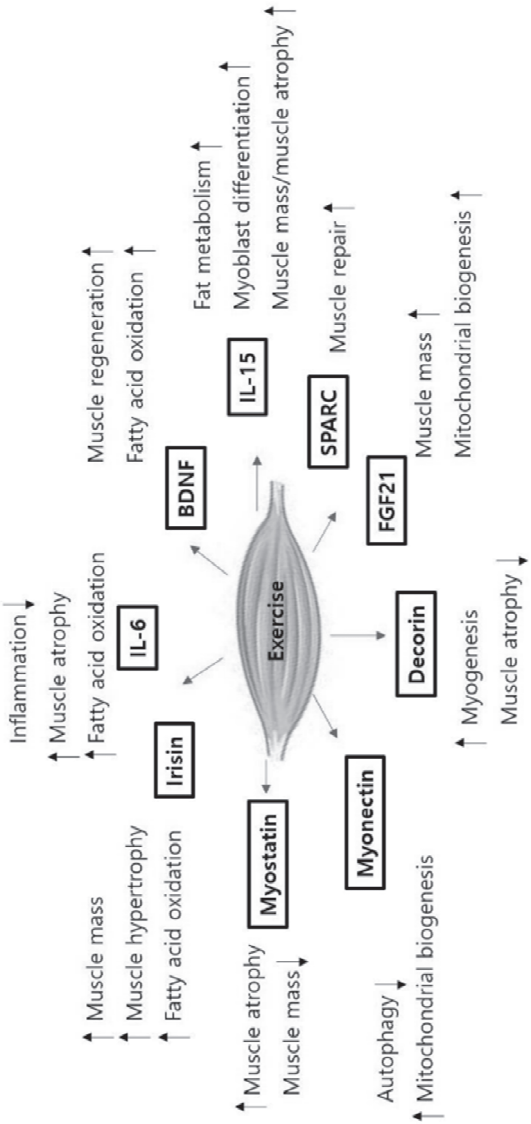

Figure 2.5.4. The function of muscle contraction-induced myokines. BDNF: brain-derived neurotrophic factor; FGF21: fibroblast growth factor 21; SPARC: secreted protein acidic and rich in cysteine; IL: interleukin (reproduced with permission from Lee and Yun, 2019[38]).

Myokines have been identified as possible therapeutic targets in cancer cachexia (see for instance the review by Manole et al.[39]). It is highly realistic that this field will largely progress over the coming years. This will require multidisciplinary collaborations, since most researchers are highly specialized in one particular pathway or one particular molecule. A step back should be made to obtain an integrative and global view of the whole system. The muscle secretome is in close interaction with other tissues and organs including bone, adipose tissue, brain, or liver. Interdisciplinary research is thus necessary.

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CHAPTER 2.6

EVALUATION OF NEUROPATHIC PAIN IN CHEMOTHERAPY-TREATED PATIENTS

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Abstract

Neuropathic pain is an important issue in cancer treatment, producing symptoms of burning, electrical sensations, and allodynia. These symptoms adversely affect patient quality of life, with potentially long-lasting effects on cancer survivors. However, relatively little is known about optimal assessment tools and treatment strategies, in contrast to other neuropathic pain syndromes. Neuropathic pain can be difficult to assess and diagnose, particularly within the context of cancer treatment. A systematic approach to pain assessment is warranted given the potential for multiple causal factors. Interestingly, only a subgroup of patients with chemotherapy-induced peripheral neuropathy develop neuropathic pain and our understanding of underlying risk factors and potential treatment strategies is limited. It is critical to develop tools to monitor neuropathic pain in chemotherapy-treated patients, both in the clinical setting and in order to design better clinical trials to target these patient subgroups. Neuropathic pain may be more amenable to treatment with pharmacological agents than symptoms such as numbness, and accordingly appropriate assessment and monitoring of pain is crucial. This chapter will review the assessment tools available to examine neuropathic pain in the setting of cancer treatment, including clinical examination, quantitative assessment tools, and patient-reported outcomes. It will examine the spectrum of pain symptoms associated with particular chemotherapeutic agents, including the incidence and phenotypic profile

of chemotherapy-related pain with taxanes, platinum-based chemotherapies, vinca alkaloids, and thalidomide and bortezomib. Finally, a discussion of treatment options and limitations of existing treatment trials and outcome measures is included. Further research to standardize clinical assessment of neuropathic pain in cancer and identify the best assessment tools to categorize patients will assist in the development of optimal treatment and management strategies to reduce patient burden and improve quality of life in cancer survivors.

Keywords: neuropathic pain, assessment, chemotherapy, cancer, taxane, platinum

Introduction

In light of tremendous advances in cancer diagnosis and treatment, there is now a growing global population of cancer survivors. Accordingly, it is critical to understand the impact of cancer treatment on long-term quality of life and daily activities. Pain is a common symptom in cancer patients and can arise from multiple aetiologies, including direct tumor invasion, metastatic disease, and cancer treatment. A systematic approach to the assessment of pain in cancer patients is required given the overlapping causes and treatment options.[1] In particular, it is critical to dissociate the cause and type of pain experienced in order to direct appropriate treatment.

In contrast to other types of pain, neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[2] Neuropathic pain is estimated to occur in 19% to 39% of cancer patients,[3] characterised by burning, electrical sensations, and allodynia.[4] Neuropathic pain is a significant issue for cancer patients, leading to troubling symptoms including sleep disturbance, anxiety and depression, and reduced quality of life.[5] However, although neuropathic pain may differentially respond to treatment compared with other types of pain, it can be difficult to accurately assess and categorize.

Further, there is a significant overlap between neuropathic pain syndromes produced by cancer treatments and chemotherapy-induced peripheral neuropathy (CIPN), reviewed in chapter 2.6. As expected, patients treated with potentially neurotoxic agents are more likely to develop neuropathic pain.[6] However, it is important to appropriately assess and monitor pain in addition to other symptoms of neuropathy as neuropathic pain may be more amenable to treatment with pharmacological agents than negative symptoms such as numbness. Further, only a subgroup of patients with CIPN develop neuropathic pain and our

understanding of this subgroup, the causal factors, and potential treatment strategies is limited. It is critical to develop tools to monitor neuropathic pain in chemotherapy-treated patients, both in the clinical setting and in order to design better clinical trials to target patient subgroups reporting pain. This chapter will review the assessment tools available to examine neuropathic pain in the setting of cancer treatment and the spectrum of pain symptoms associated with particular chemotherapeutic agents.

Evaluation and diagnosis of neuropathic pain

The diagnosis of neuropathic pain requires a history of relevant lesion or disease of the nervous system as well as a consistent pain distribution.[4] The association of pain with sensory signs evident on examination suggests neuropathic pain with a greater probability, with definite neuropathic pain confirmed in the presence of abnormal diagnostic testing indicating a lesion to the nervous system.[4] The diagnostic criteria for neuropathic pain highlight possible, probable, and definite neuropathic pain according to these probabilities—with definite diagnosis requiring confirmatory diagnostic tests to indicate damage to the somatosensory nervous system.[7] Confirmatory diagnostic tests that can be utilized to examine nervous system dysfunction include bedside sensory examination, quantitative sensory testing (QST), neurophysiological studies, and skin biopsy,[4] which are outlined below. However, it is important to note that sensory abnormalities evident with these techniques are not solely associated with neuropathic pain and that there is substantial overlap with clinical assessment tools used in the assessment of peripheral neuropathy. Accordingly, such techniques can provide insight into altered sensory function and the type of sensory fibers involved; however, they do not readily dissociate between patients reporting neuropathic pain and those who develop painless peripheral neuropathy following chemotherapy treatment. Further, despite standardised criteria to define the probability of a neuropathic pain diagnosis,[7] there remains a lack of a validated gold standard for identifying neuropathic pain.

Clinical examination of modalities including touch, vibration, pinprick, and thermal sensation can be performed and graded to define profiles of sensory dysfunction that may be associated with neuropathic pain. Bedside examination can assess both loss of function (numbness or reduced sensory perception) and gain of function (hyperalgesia or allodynia).[4] However, modalities of touch, vibration, and pinprick sensation are often disturbed in CIPN, regardless of the presence of neuropathic pain.[8] Similarly, QST examines somatosensory function via

psychophysical testing of patient response to calibrated stimuli (including thermal, mechanical, and painful stimuli), providing a quantification of sensory disturbance. QST has been utilized to examine chemotherapy-specific patterns of sensory dysfunction—broadly revealing prominent large Aβ fiber loss with some evidence of mixed fiber neuropathy.[9–10] However, systematic differences in QST profiles between CIPN patients reporting pain and those without pain have not been identified,[10] again suggesting that other techniques are required to stratify patients.

Skin biopsy allows for direct quantification of intraepidermal nerve fiber density (IENFD) as a marker of small nerve fiber damage and is regarded as a sensitive technique for the diagnosis of small fiber neuropathy. Several studies have demonstrated reduction in IENFD in CIPN, although only a small number of patients have been evaluated and there has been some discrepancy in findings.[9] However, IENFD values do not readily differentiate between chemotherapy-treated patients with and without neuropathic pain. Accordingly, similar to QST, skin biopsy may not be a useful tool to identify neuropathic pain in the context of CIPN.

While neurophysiological techniques such as nerve conduction studies are not sensitive to changes in small nerve fibers, other techniques including laser-evoked potentials (LEPs) have been utilized to identify damage to nociceptive pathways.[9] LEPs activate Aδ and C fibers, providing a means to assess their activity *in situ*.[4] Similarly, corneal confocal microscopy has been developed as a non-invasive technique to quantify small nerve fibers and may demonstrate sensitivity to diagnose small fiber neuropathy.[11] However, these techniques have not yet been broadly utilized to examine painful neuropathy in chemotherapy-treated patients and their ability to stratify patients according to pain status remains unclear.

Accordingly, patient-reported outcome tools or composite tools are often utilized to identify neuropathic pain. However, it should be noted that while neuropathic pain-screening questionnaires are useful for routine use, they typically fail to identify 10–20% of patients with neuropathic pain.[12] Key features that are included in pain-assessment measures include questions relating to pain intensity, timing, and interference with daily activities.[13] Different options to provide patients with a standardized means to capture pain intensity include descriptive words, numerical rating scales, visual analog scales, and drawings. However, a number of pain scales record information about pain in general and are not specific to neuropathic pain,[13] thus limiting their utility in distinguishing between pain types.

To address this, multiple specific neuropathic pain-screening and assessment tools have been developed (described in Table 2.6.1). These tools have been classified into screening tools for facilitated identification of neuropathic pain and assessment tools for phenotypic profiling and measurement of symptom burden.[14] The majority of these tools rely on patient symptom reports, although a number also combine features of clinical assessment, such as touch, brush, or pinprick sensation to provide characterization of neuropathic pain syndromes. However, these tools have not routinely been implemented in studies of cancer-treatment-related pain and most have not been specifically validated in patients with CIPN. Accordingly, there remains a gap in defining the best methods to assess and quantify neuropathic pain in both routine clinical practice and for the design of clinical trials.

In addition to the tools described above, several specific scales have been utilized in cancer patients. The location-based assessment of the sensory symptoms in cancer (L-BASIC) instrument enables the rating of intensity and unpleasantness of pain or sensory symptoms in different body parts, specifically for cancer patients.[15] However, the scale is not limited to neuropathic pain, with no correlation evident between L-BASIC scores and other pain questionnaires. The revised Neuropathic Pain Scale for Chemotherapy-Induced Neuropathy (NPS-CIN) consists of six neuropathic pain severity items (rated from 0, not at all, to 4, excruciating) addressing pain intensity, unpleasantness, sharpness, deepness, numbness, and tingling in a 24-hour period.[16] The scale demonstrated convergent validity with sensory peripheral neuropathy (as measured by the National Cancer Institute Common Toxicity Criteria) assessed in 177 patients, but only 30% of the cohort reported neuropathic pain, limiting the ability to comprehensively validate the data. General pain scales have also been utilized in chemotherapy-treated populations, with patients asked to rate pain perceived as related to chemotherapy toxicity on an 11-point pain intensity numerical rating scale and a visual analogue scale in an international study.[8] Of the cohort of 281 CIPN patients, 64% reported pain of any severity with 25% reporting moderate to severe pain. While the tools demonstrated good test-retest reliability over two weeks, further validation is required to demonstrate responsiveness. In addition, some CIPN patient-reported outcome tools also include one or two questions regarding pain, although they do not provide comprehensive assessment (e.g., EORTC CIPN20).[17]

Incidence of chemotherapy related neuropathic pain

Neuropathic pain is common in cancer patients; however, there is a wide range of prevalence across studies. Similarly, neuropathic pain is common in cancer patients undergoing treatment with neurotoxic chemotherapies. However, due to a lack of consistency in the use of neuropathic pain measures, as well as variations in time since completion, the cumulative dose, and the use of pain medication, estimates of neuropathic pain remain broad. Although the proportions vary across different chemotherapy types, typically 20–40% of patients with CIPN produced by various neurotoxic chemotherapies report painful symptoms (Table 2.6.2). However, typically patients report numbness and tingling more commonly than pain following treatment with neurotoxic chemotherapies.[18] In addition, neuropathic pain typically occurs as part of the spectrum of CIPN rather than as an independent syndrome. There is also some evidence that numbness and tingling precede the development of pain in patients with CIPN.[19] While pain arising directly from cancer is more likely to be nociceptive, cancer treatment pain is more likely to be neuropathic.[20]

A systematic review of neuropathic screening tools in cancer patients suggested that LANSS and DN4 were generally able to distinguish neuropathic and non-neuropathic pain.[1] Items relating to pins and needles/tingling, mechanical allodynia, and altered pinprick threshold were independent predictors of neuropathic pain in multivariate analyses across screening tools.[1] Similarly, neuropathic pain screening tools were utilized in a study of 268 patients treated with neurotoxic chemotherapy—of whom 22% had a clinical diagnosis of neuropathic pain.[20] The DN4 questionnaire was the most sensitive and specific to identifying neuropathic pain, while the LANSS was better suited to the assessment of intermittent or severe pain. Pain DETECT was less sensitive to detecting neuropathic pain.[20] In a separate study of 240 breast cancer patients, ID-Pain demonstrated good discriminative validity to diagnose neuropathic pain.[21] However, neuropathic pain was of varied etiology, produced by chemotherapy, surgery, radiotherapy, or cancer.

In a sample of 146 chemotherapy-treated patients with neuropathy, 58% reported painless neuropathy and 42% reported neuropathic pain.[10] Objective parameters were unable to dissociate painful CIPN from painless CIPN, including nerve conduction, quantitative sensory testing, clinical examination or clinical severity. However, patients with painful CIPN had higher anxiety and depression scores, suggesting that they may have a modulating effect of psychological factors on pain perception.[10] There was also some evidence of musculoskeletal

pain in addition to neuropathic pain in the cohort, which may be amenable to different treatment options. While these studies have examined neuropathic pain in mixed cohorts of cancer patients treated with different chemotherapies, there are important chemotherapy-specific differences in the incidence, presentation, and clinical features of neuropathic pain syndromes, which are outlined below.

Profiles of neuropathic pain following chemotherapy treatment

Taxanes including paclitaxel, docetaxel, and abraxane are utilized in the treatment of a wide variety of malignancies. Taxanes are associated with a sensory-predominant peripheral neuropathy that develops with cumulative dosing, with paclitaxel considered to have the most neurotoxic potential.[22] Paclitaxel-acute pain syndrome (P-APS) has been described with a phasic pattern of symptom exacerbation surrounding each infusion, lasting 5–7 days and peaking on day three.[23–24] Despite patients describing a predominately dull/aching pain mostly in the legs and feet, further investigation revealed reports of shooting and burning pain, leading to the suggestion that P-APS may result from nociceptive neuron pathology as opposed to relating to arthralgias or myalgia.[23] The majority of patients experience pain following paclitaxel infusion, with 36% reporting severe pain on a numerical scale.[19] Patients with more severe P-APS may be at risk of greater chronic peripheral neuropathy, suggesting that the pathological mechanisms are linked.[19] A similar syndrome has been reported for docetaxel-treated patients, although the mechanism was not clearly attributed to neuropathic pain.[25] Accordingly, it remains unclear if the pathological basis for acute taxane-induced pain is neuropathic, with further analysis required to determine specific mechanisms.

With increased cumulative exposure, chronic taxane-induced neuropathy develops with neuropathic pain reported in the hands and feet in a proportion of patients. Typically pain is less severe and less commonly reported than tingling or numbness.[24] In patients with established taxane-induced peripheral neuropathy, 50–80% report pain in hands and feet.[26–29] Peripheral neuropathy and pain are associated with impairments in Aβ and Aδ-fibre function, whereas modalities conveyed by unmyelinated C-fibres, such as the detection of cooling, warmth, and heat pain were preserved.[30] There is some discrepancy in the reported prevalence, distribution, and timecourse of pain: it is likely dependent on the patient population and assessment methods used. The most commonly used descriptors for pain include pricking, aching, numbness, tingling, and

burning.[28–29] Some reports indicate pain in both hands and feet[29] while others indicate lower limb predominance.[28] Interestingly, pain scores were not correlated with composite neuropathy scores or neuropathy severity, suggesting that they may represent a separate phenomenon and require parallel assessment techniques.[29] However, patients with taxane-induced peripheral neuropathy were more than three times more likely to subsequently develop neuropathic pain.[31] In addition, patients with neuropathic pain were more likely to require medication and medical appointments compared with those without neuropathic pain,[31] highlighting the additional burden on healthcare systems and individual patients.

Platinum-based chemotherapies including oxaliplatin and cisplatin are associated with prominent chronic sensory neuropathy. Oxaliplatin is a third generation platinum-based compound with proven efficacy in both early and advanced stage colorectal cancer. Oxaliplatin produces neurotoxicity in both acute and chronic profiles.[32] Acute neurotoxicity occurs immediately following infusion and leads to sensory symptoms such as cold allodynia in more than 90% of patients, which is generally resolved within a week.[24] Acute oxaliplatin-induced neurotoxicity produces sensations of paresthesia, dysesthesia, and pain.[33] Typically described phenomena include sensitivity to cold, throat and jaw discomfort, muscle cramps, reaching a symptomatic peak on day 3 following infusion.[24] Acute neurotoxicity is accompanied by electrophysiological evidence of peripheral nerve hyperexcitability.[32] Over the course of treatment, 56–74% of patients experiencing symptomatic acute neurotoxicity described cold-evoked symptoms as painful.[33] Patients experiencing acute neurotoxicity as painful described sensations such as tingling, cold, and freezing and demonstrated a QST profile of cold, heat, and mechanical hyperalgesia.[34]

With cumulative dosing (typically >750mg/m^2), oxaliplatin produces a chronic sensory neuropathy. Typical characteristics include distal paresthesia and numbness, with large fiber neuropathy evident on nerve conduction studies.[22] Neuropathic pain is reported by a subset of patients—with prevalence ranging from 5–44% in post oxaliplatin-treated patients (Table 2.6.3).[27–28,35–38] However, numbness and tingling were rated as more severe than pain both during and after treatment.[24] In a large sample of 346 oxaliplatin-treated patients, tingling was perceived as the most severe symptom, followed by numbness and then pain.[39] Interestingly, while pain was less severe than tingling or numbness, it was also less likely to improve post-treatment in affected patients.[39]

Using the neuropathic pain symptom inventory,[38] it was found that 44% of oxaliplatin-treated patients experienced neuropathic pain at

treatment completion. However, the neuropathic pain symptom inventory also includes sensations of "pins and needles" and "tingling" as well as "burning" or "stabbing pain," which may lead to increased reports of neuropathic pain from patients who experience prominent painless neuropathy. Using the PainDETECT questionnaire, distal pain, predominately in the feet, has been reported to persist in 25% of patients with oxaliplatin-induced peripheral neuropathy up to 20 months post-treatment, suggestive of long-term neuropathic pain.[28] Oxaliplatin-treated patients reporting pain were more likely to have severe CIPN and were older.[36] Patients with painful neuropathy (62% oxaliplatin-treated) had higher serum nerve growth factor levels than those without painful neuropathy, suggesting that nerve growth factor may provide a marker of pain in this cohort.

Cisplatin is a platinum-based chemotherapy utilized for multiple cancer types including testicular, bladder, ovarian, and small-cell lung cancer. At doses exceeding 400 mg/m^2, a sensory neuropathy develops, similar to chronic oxaliplatin-induced neuropathy.[40] However, reports of pain are extremely rare and are limited to a few cases.[40]

Bortezomib is a proteasome inhibitor commonly used in the treatment of multiple myeloma. Painful sensory neuropathy can present in up to 50% of patients.[41] Use of analgesics for neuropathic pain is common, with 35% of patients reporting severe symptoms at a cumulative dose of 18mg.[42] Often characterized by sharp or burning pain in the toes and feet, these symptoms can present in the absence of abnormal nerve conduction studies.[41] Rates of bortezomib-induced peripheral neuropathy and neuropathic pain vary (Table 2.6.4) and are dependent on the screening tool utilized. However, despite this variability, neuropathic pain is clearly very prominent in bortezomib-treated patients. In a small study of 22 bortezomib-treated patients evaluating neuropathic pain with a number of screening tools (brief pain inventory, DN4, LANSS), all patients with symptoms of CIPN reported pain in the feet and pain, which had a significant impact on the activities of daily living.[43] Importantly, neuropathic pain detrimentally affected daily activities even when classified as mild.[43] A detailed examination of 16 bortezomib-treated patients revealed severe pain in fingers and toes bordered by a larger region of numbness.[44] However, rates of neuropathic pain may be greater in previously treated patients, with 80% of previously treated patients (vincristine, cisplatin, or thalidomide) developing neuropathic pain following bortezomib treatment compared with 50% of previously untreated patients.[45] While there was no difference in the development of neuropathy, pre-treated patients had a longer median time to neuropathic

pain recovery as well as a greater risk of dose reductions.[45] Examination of bortezomib-treated patients revealed 77% with significant pain intensity (>4/10) with overall moderate neuropathic pain, typically requiring analgesia.[46] The majority of patients also had large fibre neuropathy and potential evidence of pathological sprouting of parasympathetic fibers in skin biopsies.

Thalidomide is an immunomodulatory drug often used to treat patients with multiple myeloma. Peripheral neuropathy is a common adverse effect of thalidomide treatment occurring more commonly in those who are treated long-term. Thalidomide-induced neuropathy produces symptoms that can include distal paraesthesia and sensory loss usually occurring in the lower limbs.[47] Neuropathic pain or dysesthesias, mainly in the lower limbs, have been reported to affect 30–50% of patients treated with a cumulative dose of 20g.[48] While there are reports of painful paraesthesia,[49] neuropathic pain has seldom been quantified in thalidomide-treated patients. In a study of thalidomide and bendamustine, severe peripheral neuropathy developed in 4.3% myeloma patients while severe pain developed in 13%.[50] A population-based cohort study suggested that lenalidomide, an analog of thalidomide, was associated with less risk of peripheral neuropathy but that both drugs were equivalent in producing neuropathic pain requiring prescription medication, which was required in 28–31% of patients.[51] However, in myeloma patients treated with long-term lenalidomide, 50% developed sensory axonal neuropathy but no patients reported neuropathic pain.[52]

The vinca alkaloid *vincristine* is often used in the treatment of hematological malignancies, but has also shown efficacy in the treatment of solid tumors. Neurotoxic effects commonly manifest with vincristine treatment, including sensorimotor neuropathy, which is common at cumulative doses over 40 mg (Table 2.6.5). At low dose intensity (0.67mg/week), numbness and paraesthesia occurred in a high proportion of patients (34–43%) with pain reported in 14%.[53] However at high dose intensity (1.33mg/week), 70% reported numbness and 62% reported pain, with severe pain in 16%.[53] At follow-up 34 months post-treatment, neuropathy persisted in 32.5% of vincristine-treated patients, with pain reported by 46% of the cohort with neuropathy.[54] Somatosensory profiles have been examined in vincristine-treated patients reporting pain, demonstrating elevated touch, sharpness, and heat detection thresholds suggesting dysfunction in Aβ, Aδ-, and C-fibers.[55] The pain was characterized as numb, tingling, throbbing, burning, and sharp.[55] A case report of extreme burning pain due to vincristine treatment has been reported in association with genetic polymorphisms in the gene coding

cytochrome P450, leading to reduced activity of cytochrome P450 CYP3A4/5.[56]

Pain management and treatment

There are a number of pharmacological treatments recommended for neuropathic pain, including tricyclic antidepressants, gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors.[57] However, efficacy may be variable between individual patients and it is not yet possible to individualize treatments on the basis of clinical phenotypes. Further, the identification of successful treatment and management strategies for chemotherapy-induced neuropathic pain has been hampered by the lack of a gold-standard assessment measure. Given the variable and often low prevalence of neuropathic pain compared with other manifestations of peripheral neuropathy, it has often been difficult to examine treatment efficacy in patient subgroups reporting pain compared with those with painless neuropathy.

The serotonin-norepinephrine reuptake inhibitor duloxetine is the only agent moderately recommended by the American Society for Clinical Oncology clinical practice guidelines for the treatment of painful chemotherapy-induced peripheral neuropathy.[58] Duloxetine was trialed in paclitaxel- or oxaliplatin-treated patients who reported pain (>4/10 on a numerical rating scale), with 59% of patients reporting a reduction in pain compared with 38% treated with a placebo.[59] Duloxetine treatment was not successful in all patients and was more efficacious in oxaliplatin-treated patients.[59] Treatment was also more successful in those with better emotional status at trial entry, demonstrating that psychological features such as anxiety may modulate responsiveness to treatment.[60]

There have been many clinical trials of other pharmacological interventions for neuropathic pain in CIPN, which have been limited due to significant methodological design issues.[61] A number of non-pharmacological options for pain management have also been trialed, but there remains insufficient evidence to recommend their clinical use. A critical feature has been the lack of appropriate outcome measures that evaluate neuropathic pain without contribution from other neuropathy symptoms such as tingling or numbness. It was recommended that future trials utilize validated pain measures and defined patient populations.[61] A recent small clinical trial examined whether baseline QST variables could be utilized to stratify treatment response to pregabalin in patients with painful CIPN.[62] While the trial was underpowered and unable to detect any

impact of patient stratification, the concept of personalized treatment based on phenotypic stratification of patients is promising.

Another important feature of chronic pain syndromes following chemotherapy treatment is central sensitization, which reflects altered excitability in the central nervous system produced following nerve damage.[17] Central sensitization leads to allodynia, hyperalgesia, and pain and may convert to a chronic presentation, leading to long-term pain. It is important to recognize that chronic neuropathic pain following chemotherapy treatment may reflect a combination of neuropathic pain directly caused by toxic peripheral nerve damage as well as the effects of central sensitization and further psychological effects that modulate patient perception. Greater understanding of these features will facilitate the development of effective treatment strategies.

Conclusions

Neuropathic pain is a significant concern both during cancer treatment and in cancer survivorship. However, in contrast with other neuropathic pain syndromes, relatively little is known about optimal assessment tools and treatment strategies. A key feature of pain assessment is to distinguish between nociceptive and neuropathic pain, particularly given the multiple potential causes of pain in cancer patients. Much further work is needed to standardize clinical assessment of neuropathic pain in cancer and identify the best assessment tools to categorize patients. Further understanding of the factors leading to the development of neuropathic pain in some patients following chemotherapy but not in others will also assist in the development of optimal treatment and management strategies to reduce patient burden and improve quality of life in cancer survivors.

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Table 2.6.1. Screening and assessment tools for neuropathic pain.

Neuropathic pain tool	Description	Reference
Douleur Neuropathique en 4 (DN4) questionnaire	Combination of sensory description and signs obtained from sensory examination (touch, pinprick hypoesthesia and brush allodynia)	Bouhassira 2005[63]
Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)	Contains both symptom report and evaluation of signs (touch allodynia and pinprick sensation)	Bennett 2001[64]
Self Report-Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)	Self-report version that aims to identify neuropathic pain without clinician examination	Bennett 2005[65]
PainDETECT	Patient symptom report involving descriptors, location, and timing characteristics	Freynhagen 2006[66]
ID-Pain	Patient-based screening tool with 6 items designed for clinical use	Portenoy 2006[67]
Neuropathic Pain Symptom Inventor*	Numerical-based rating system with 4 subscales and 12 items	Bouhassira 2004[68]
Neuropathic Pain Questionnaire	Patient symptom report involving symptom description, induction and consequences	Krause and Backonja 2003[69]
Neuropathic Pain Scale*	Numerical based rating system with 10 descriptors and a time-based item	Galer and Jensen 1997[70]
Pain Quality Assessment Scale*	Neuropathic Pain Scale plus 10 nociceptive pain descriptors	Jensen 2006[71]

*classified as assessment scale by Attal 2018.[14]

Table 2.6.2. Incidence of neuropathic pain in chemotherapy-treated patients.

Patient cohort	**Neuropathic pain**	**Reference**
268 patients treated with neurotoxic chemotherapies	21.6% neuropathic pain	Perez 2015[20]
281 patients with established CIPN	20–25% reporting a score >50% of the most severe pain possible	Cavaletti 2013[8]
199 patients with established CIPN	"Quite a bit" or "very much" burning pain in hands (18%) or in feet (33%)	Wolf 2012[18]
60 treated with neurotoxic chemotherapies	21.7% neuropathic pain	Velasco 2017[37]
117 taxane and/or platinum treated patients	30% neuropathic pain	Lavoie Smith 2011[16]

Table 2.6.4. Peripheral neuropathy and neuropathic pain in Bortezomib-treated patients.

Chemotherapy (Cancer type)	N	Neuropathic pain assessment tool	Neuropathic Pain	Peripheral Neuropathy	Reference
Oxaliplatin (CRC)	74	PainDETECT	28.1% at 1 year post-treatment	63.6% at 1 year post-treatment	Ventzel 2016[28]
Docetaxel (Breast)	100	PainDETECT	36.4% at 1 year post-treatment	44.8% at 1 year post-treatment	Ventzel 2016[28]
Oxaliplatin (CRC)	39	EORTC CIPN20	20.5% at 1 month post-treatment	N/A	Velasco 2017[37]
Oxaliplatin (CRC)	100	MD Anderson Symptom Inventory	5% moderate to severe pain at week 26	48% moderate to severe numbness/tingling at week 26	Wang 2016[36]
Oxaliplatin (CRC)	78	Questionnaires and body map	20% at 6 months post-treatment	75% at 6 months post-treatment	de Carvalho Barbosa 2014[35]
Oxaliplatin (CRC)	35	Neuropathic pain symptom inventory; NCI CTCAE	44% painful neuropathy at end of treatment; 26% at 6 months post-treatment	91% at end of treatment	Delmotte 2018[38]
Oxaliplatin (CRC)	207	EORTC CIPN20	13% burning or shooting pain in feet at 4 years post diagnosis	30% tingling toes or feet at 4 years post diagnosis	Beijers 2015[72]
Oxaliplatin (CRC)	20	Neurological symptom score	30% at 9 months post-treatment	Entire sample	Krøigård 2014[27]
Oxaliplatin (CRC)	20	PainDETECT	25% at 20 months post-treatment	Entire sample	Ventzel 2018[28]

Abbreviations: CRC colorectal cancer EORTC CIPN20 European Organization for Research and Treatment of Cancer Chemotherapy-induced Peripheral Neuropathy 20 Questionnaire

Table 2.6.4. Peripheral neuropathy and neuropathic pain in Bortezomib-treated patients.

Chemotherapy (Cancer type)	N	Neuropathic pain assessment tool	Neuropathic Pain	Peripheral Neuropathy	Reference
Bortezomib (MM)	22	WHO-PN (Grade ≥2 includes painful symptoms)	41%	50%, all of which developed symptoms after second cycle	Exposito Vizcaino 2018[43]
Bortezomib (MM)	20	NCI-CTCAE-neuralgia	40%	45% developed symptoms on NCI-CTCAE, 40% on TNSc and 55% on TNSr	Lakshman 2017[73]
Bortezomib (MM)	125	NCI-CTCAE-neuralgia	27% in previously untreated; 81% in previously treated	55% in previously untreated; 52% in previously treated	Corso 2010[45]
Bortezomib (MM)	636	NCI-CTCAE-neuralgia	15%	37% within 30 days of end of treatment	Orlowski 2007[74]
Bortezomib (MM)	456	NCI-CTCAE-	14% grade 1–2 neuralgia, 2% grade 3; 1% grade 1–2 pain in extremities, <1% grade 3	21% grade 1–2; 5% grade 3; <1% grade 4	Dimopoulos 2016[75]
Bortezomib (MM)	147-SC 74-IV	NCI-CTCAE-neuralgia	SC- 24%, 3% grade ≥3 IV- 23%, 9% grade ≥3	SC- 35%, 5% grade ≥3 IV- 49%, 15% grade ≥3	Moreau 2011[76]
Bortezomib (MM)	340	NCI-CTCAE-neuralgia	36%, 9% grade ≥3	44%, 13% grade ≥3	San Miguel 2008[77]
Bortezomib (MM)	66	NCI-CTCAE-neuropathic pain	32%, 3% grade 3	80%, 2% grade 3	Richardson 2010[78]
Bortezomib (MM)	100	NCI-CTCAE-neuralgia	32%, 12% grade ≥3	32%, 12% grade ≥3	White 2013[79]

Abbreviations: MM Multiple Myeloma WHO-PN World Health Organization Common Toxicity Criteria for Peripheral Neuropathy NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events SC Subcutaneous IV Intravenous

Table 2.6.5. Peripheral neuropathy and neuropathic pain in vincristine-treated patients.

Chemotherapy (Cancer type)	N	Neuropathic pain assessment tool	Neuropathic Pain	Peripheral Neuropathy	Reference
Vincristine (Pediatric ALL)	498	Diagnosed on the basis of subjective descriptors (pain localized in the jaw, back, lower extremities, or abdomen; generalized body pain; or indicators of functional impairment)	34.9%, with 16% experiencing at least one recurrence after initial episode	Not reported	Anghelescu 2011[80]
Vincristine (Mixed cancer types)	27	Interview questions	7%	44% presented with paraesthesia 108 days from first treatment	Kavcic 2017[81]
Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) (Lymphoma)	42	NCI-CTCAE- neuralgia	Neuralgia 0%; pain in extremities 2%	24%; 2% grade ≥3	Drach 2018[82]
Vincristine (Lymphoma)	40	Questionnaire	15%	32.5% at long term follow up 34 months post-treatment	Postma 1993[54]
Vincristine (low or high dose intensity groups) (Lymphoma)	114	Cumulative symptom score questionnaire	Low dose intensity: 14% High dose intensity: 62%	Low dose intensity: 43%; High dose intensity: 70%	Verstappen 2005[53]

Abbreviations: ALL Acute Lymphoblastic Leukemia NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events

PART 3

CHAPTER 3.1

PATIENTS IN THE DEVELOPMENT OF STUDY CONCEPTS AND DESIGN

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Abstract

The role of the patient in healthcare settings is changing and patients are increasingly incorporated into research as key stakeholders. This movement towards more patient-centered research design has the potential to improve research methods, implementation (including recruitment and retention), and outcomes. It also ensures that researchers and resources are focused on what is most important to patients and patient communities.

This chapter will explore the foundational principles and diversity of approaches to engaging patients in the biomedical and clinical research space, including real-world examples of methods and the impact of engaging patients. Patient level of involvement in biomedical research falls along a continuum, and methods to engage patients are dependent on the intensity of their involvement as well as the phase(s) in which they are engaged in the research process. Challenges to patient engagement in research are also examined. These include time, resources, and team culture.

Keywords: patient engagement, patient-centered outcomes research, clinical research

Introduction

The role of patients is changing. They are increasingly being engaged in both healthcare delivery and biomedical research with the goal of improving health outcomes. Moving patients from the role of research participant to research partner brings opportunities and challenges. The

lived experience and personal expertise patients bring to projects has the potential to improve research by shifting the focus to questions more relevant to the patient community, employing patient-centric methodology thereby increasing recruitment and retention, and expediting the translation of results to clinical practices that affect care and improve outcomes.

As the research paradigm shifts to a patient-engaged model, scientists and clinician researchers will need to adapt. This will involve identifying where the patient perspective will add value and learning new research methodology to successfully engage the patient throughout the life of the project. Researchers will also need to hone the skills required to effectively integrate non-traditional stakeholders into the research process and develop strategies to overcome the challenges this approach brings.

This chapter will provide the background and foundational principles required to understand the importance of, and approaches to, involving patients in the development of study concepts and design. It will also provide the key considerations that researchers need when designing patient-centered research and developing a plan for engaging patients. Finally, case examples are provided to illustrate how this work is being successfully executed in real-world settings.

Background

Patient engagement has been an area of growing focus and attention in medicine. This trend is due in part to the growing consensus that engaging patients in their own healthcare and treatment plans has been shown to lead to shared decision-making, lower costs, and improved patient outcomes.[1] More recently, there has been a trend in engaging patients in biomedical research, as they can bring valuable lived experience to research projects, providing significant benefits that include challenging the assumptions of professional researchers, increasing transparency and trust in research, and ensuring that research aligns with the needs of patients. Ideally, this will ultimately lead to research that has a greater impact on the care and outcomes of patients.[2] Engaging non-researchers in research projects is not a new concept. Within public health and the social

[1] James, "Patient Engagement"; Ocloo and Matthews, "From Tokenism to Empowerment"; Barello, Graffigna, and Vegni, "Patient Engagement as an Emerging Challenge for Healthcare Services"; Carman et al., "Patient and Family Engagement."

[2] Duffett, "Patient Engagement"; Domecq et al., "Patient Engagement in Research"; Sacristán et al., "Patient Involvement in Clinical Research."

sciences, engaging stakeholders external to the research field is a common strategy designed to bridge the gap between researchers and the people, communities, or topics of study.

Engaging patients in biomedical research is commonly referred to in the United States as patient-centered outcomes research (PCOR).[3] It draws on principles established by the practice of patient-centered care and integrates these into the approaches practiced by community engaged researchers from other fields. Despite the resources allocated to biomedical research, the time it takes to get from research results to advancements in treatment are frustratingly slow. Incorporating engagement into biomedical research development is a promising strategy to help close this gap between knowledge generation and practice change. This approach to bringing patient engagement into the realm of biomedical research has been a recognized practice in the UK since the mid-nineties (commonly referred to as patient and public involvement, or PPI), and was more formally recognized in the United States in 2010 with the establishment of the Patient Centered Outcomes Research Institute (PCORI).

This chapter will focus solely on patients' involvement in biomedical research projects. In this context, patient engagement is defined as the practice of including patients as part of the research team and letting them share in the work of framing questions, collecting data, interpreting results, and disseminating conclusions.

The case for patient engagement in research

Engaging patients in biomedical research has many documented benefits, with even more that have been hypothesized and are currently being studied. It has been demonstrated that engagement can improve research quality, heighten impact, enhance the public perception of research, and improve the applicability of research for addressing real-world problems. Patient engagement in research also changes how the team approaches the topic and defines the problem. Involving patients on the research team early in the research process encourages scientists to value topics important to patients, define research questions that resonate with the patient community, and design research protocols that are responsive to the patient experience. Continued engagement with patient partners

[3] Frank, Basch, and Selby, "The PCORI Perspective on Patient-Centered Outcomes Research"; Gabriel and Normand, "Getting the Methods Right—The Foundation of Patient-Centered Outcomes Research."

throughout a project ensures that the research findings are interpreted and communicated in ways that resonate with broad and diverse audiences.

Improved methods and outcomes

Involving patients in research influences what research is done, how it is designed, and what is being measured.[4] Patient engagement in the methodology of biomedical research most commonly influences the research topics or specific research questions being asked, how the intervention is designed, how comparators are defined, which outcomes should be used, and how these outcomes will be measured. While patients do not always directly address these aspects of the project, they share their lived experiences with the research team and feedback on how the project might best address the preferences, concerns, challenges, and cultural issues that they face in their life and care.

Enhanced recruitment and retention

Patient engagement in research has the power to change the patients' experience as participants in the research project. Therefore, engaging patients in the design, execution, and monitoring of research recruitment is an identified strategy to improve recruitment rates and help ensure retention. Evidence exists that patient-engaged research projects are more likely to be focused on what patients feel is important to them and framed in a way that is more inviting to the patient community.[5] Additionally, patient-informed recruitment processes and materials are more likely to resonate with potential participants. When patients feel that research is designed with them in mind, they will be more likely to participate and complete the research journey.

Improved translation to practice

If biomedical research has been focused on the questions and topics that are of most importance to patients and designed in a way that incorporates considerations commonly faced by patients in everyday life and care, it follows that the results are more likely to be applicable to practice

[4] Forsythe et al., "Methods and Impact of Engagement in Research, from Theory to Practice and Back Again."
[5] Bower et al., "Improving Recruitment to Health Research in Primary Care."

change.[6] Patients not only support dissemination efforts in a traditional way (e.g., peer-reviewed journals, conference presentations, etc.), they also inform the translation and dissemination of results via less traditional methods. These patient-informed approaches are more likely to reach the desired "end-users" (patients and clinicians) and are less targeted to an academic audience. Patients are also instrumental in the development of "lay reports" that make the results more accessible to the general public and help the patient community understand the research and advocate for practice change.

How to involve patients in research

Foundational principles

The Patient-Centered Outcomes Research Institute (PCORI), has taken the ideas and principles of patient engagement in care and developed a framework for research-driven practices that can help bring about more useful evidence for researchers, clinicians, and patients alike.[7] Entering into a climate that is already fraught with the use of terms such as "engagement," PCORI specifically lays out its understanding of the term "patient engagement" as it relates to research: "by 'engagement in research,' we refer to the meaningful involvement of patients, caregivers, clinicians, and other healthcare stakeholders throughout the research process—from topic selection through design and conduct of research to dissemination of results."[8]

In seeking to fund, support, and connect researchers and organizations that are developing more patient-centered solutions to the issues facing medical research today, PCORI has set out four principles of engagement that can be used to guide efforts to involve patients in research initiatives:[9]

> 1. Reciprocal relationships: all research partners, including patient and stakeholder partners, have a defined role and decision-making authority.

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[6] Esmail, Moore, and Rein, "Evaluating Patient and Stakeholder Engagement in Research."
[7] Frank, Basch, and Selby, "The PCORI Perspective on Patient-Centered Outcomes Research."
[8] "The Value of Engagement."
[9] Sheridan et al., "The PCORI Engagement Rubric."

2. Co-learning: patients and stakeholder partners understand the research process and researchers will understand patient-centeredness and patient and stakeholder engagement in order to collaborate.
3. Partnership: the time and contribution of patient partners are valued, which is demonstrated in fair financial compensation, as well as reasonable and thoughtful requests for time commitment by patient and other stakeholder partners. When projects include priority populations, the research team is committed to diversity across all project activities and demonstrates cultural competency when appropriate.
4. Transparency, honesty, and trust: major decisions are made inclusively, and information is shared readily with all research partners. Patients, other stakeholders, and researchers are committed to open and honest communication with one another.

In patient engaged research designs, patient-centered research processes are highly emphasized. These projects are based on the logic that if researchers, clinicians, and patients are able to come together to work in innovative and equitable ways, new and better forms of research will come about.

Approaches and methods to engage patients

Patient involvement in biomedical research falls along a continuum that spans from patients being a passive subject from which data is collected, all the way to patients actively serving as lead investigators of research projects (figure 3.1.1). Patient engagement starts when patients move out of the research "subject" role and begin having a role on the research team. Once this shift happens, projects are considered to be patient-centered regardless of the level of patient involvement. While there is a push to engage patients in more meaningful and dynamic ways to ensure their perspective influences the decision making of the research team, not all projects (or even phases of the project) will engage patients at the same intensity or using the same methods. The decision on how to engage patients is dependent on many factors that include the resources available, team capacity, and stage in the research process. This continuum can be broken down into stages, based on the intensity of engagement and the role the patient plays on the research team.

Fig. 3.1.1. The continuum of engagement.

At the far-left end of the continuum lies the lowest intensity of patient engagement, using patient-reported data. This strategy includes collecting patient perspectives to inform a specific aspect of the research project. Collecting patient voices can be done via digital or in-person mechanisms (e.g., surveys, focus groups, etc.). This approach resembles, and is often confused with, a qualitative component to the project. The difference is how the information collected is used. A qualitative component of the research project will collect data to answer the research question. In contrast, as a strategy to conduct patient-centered research you will use this patient-generated data to make a decision about some aspect of the research project itself. While this may be done numerous times over the course of the project with the same (or a different) patient population, what distinguishes this category from the more intense stages of engagement in the continuum is the lack of integration of patients into the research team and the lack of decision-making authority given to this group of stakeholders. This strategy is most commonly used in the early phases of research (topic selection or prioritization, generating a research question of refinement, study design, or recruitment strategies).

At the *patient-informed* stage of the continuum, researchers will inform a patient or group of patients about aspects of the research initiative, but this communication is often unidirectional. This is effectively the opposite of the previous stage but is considered to be of higher engagement because the patients involved often gain information about aspects of research that they wouldn't have received if not for the project being patient-centered. This approach is often used in the later phases of the research process, specifically dissemination and translation. Combined with the previous stage, this can create a very low level of engagement that appears to be bi-directional and iterative (patients giving data and researchers sharing back information) but does not incorporate strategies that are designed so that the patient voice directly influences the research team.

In the next stages, *patient consultants* and *patient collaborators*, the structure of the research team changes to incorporate patient stakeholders. In these stages, individual patients are recruited to contribute to the research team and activities. In the *patient consultant* phase, a

patient or a group of patients provides ongoing review of the project and/or provides insight and advice about specific aspects of the project. This could be done by hiring a patient as an individual consultant, but it more often includes building an advisory group[10] consisting of patients or including patients as members. Strategies from this stage can be used throughout the project, but usually happen during the implementation phase, after a project has been designed and funded. Issues of recruitment and retention are topics frequently tackled by this type of engagement strategy.

The *patient collaborator* stage takes this model a step further by embedding a patient (or patients) into the research team to work collaboratively with the group across many aspects of the project. A collaborating patient, or "patient partner," will be well informed about the project, attend meetings, contribute as an equal team member, and be recognized for their patient expertise that comes from their lived-experience. These patient collaborators also frequently serve as a liaison and/or gatekeeper to their wider patient community and can facilitate other patient-engagement efforts or recruitment activities.

Depending on how the team structure was designed, these individuals and/or groups may or may not have decision-making authority. There is much variation within these middle stages. What distinguishes these stages of engagement is the bi-directional nature of the relationships. They function as a part of the research team and influence the day to day operations and decisions of the research team.

The most intense stage of the engagement continuum is *patient directed*. In this stage, patients are the researchers, or partner with researchers as co-investigators to drive a research agenda. Patients in this role will have influence and responsibilities, equal to those of a scientific researcher, to lead a team and ensure the success of the research project.

Patient engagement across the lifespan of a project

Patients can play a role in all phases of the research journey—from identification of a clinical problem and drafting a protocol for funding, to interpreting results and initiating policy or practice changes. The activities used to engage patients are often dependent on the intensity of the engagement and where it falls on the engagement continuum detailed earlier in this chapter. Before identifying the appropriate approach to engagement, one must define the role that the patient perspective will play

[10] This may also be called a "steering committee."

in each particular stage of the process. The goal is not to train patients to act and think like researchers, but to instead work collaboratively to share the complementary expertise of each group.[11]

For example, early in the research process the patient voice often plays a critical role in identifying the clinical problem and refining or prioritizing the research question(s). This can be done in a number of ways. In a highly engaged model, researchers may actively seek out patients to work with them to identify topics of interest or co-develop research questions. Researchers who adopt an approach with less intense engagement may review previously collected patient reported data to identify emerging themes and develop research questions, then ask patients for feedback or to prioritize this researcher generated list. In both of these examples the patient role was to help identify and prioritize research topics and questions, but each took a different approach based on where their engagement approach fell on the continuum.

Patients are experts in their lived experience. This expertise can help shape the entire project from design to dissemination, and the roles that a patient can play in the research process are endless. It is the responsibility of the research team to think creatively, outside their scientific/clinical box, to identify the value that the patient perspective will bring to each part of the project. Below is just a small sample of the roles that patients can play in a research project.

Developmental phase

- identifying or prioritizing the research topic
- refining the research question
- selecting the outcomes and outcome measures
- anticipating and trouble shooting challenges related to recruitment, inclusion or exclusion criteria, or project design

Recruitment and data collection phase

- drafting or editing recruitment materials (flyers, emails, ads, etc.)
- ensuring the consent documents and process are patient-centered
- designing the user interface and beta testing the data collection platform(s)
- informing recruitment and retention strategies

Analysis and results phase

- reviewing preliminary analysis to help explain unexpected data/results

[11] Moss et al., “Involving Pregnant Women, Mothers and Members of the Public to Improve the Quality of Women’s Health Research.”

- ensuring adherence to patient-identified research questions and topics
- identifying interesting themes or questions that emerge from the data
- collaborating on results interpretation

Dissemination phase

- identifying effective dissemination strategies specific to the patient community
- producing "lay" abstracts and reports
- co-author conference presentations and manuscripts

Challenges of patient involvement in research

While patient inclusion in research does provide a project with a variety of benefits, there are also associated challenges that need to be understood and addressed before researchers commit to undertaking a patient-centered research project.[12]

Time

The dimension of time affects patient engaged research in a number of ways. Researchers must be sensitive to, and transparent about, the amount of time they are asking patients to commit to the project and how that time will be valued and compensated. For most researchers, this work is part of their full-time job. For most patients, this work is done outside their other professional and personal responsibilities. Considerations should be made regarding the amount of time as well as the scheduling: Are these meetings all taking place during the workday? Is a patient able to take time away from their other responsibilities to fully participate in the project? What negotiations can be made to make participation easier (i.e., virtual meetings or asynchronous participation)? How will their time and contributions be equitably compensated?

Researchers also need to understand the amount of time patient engagement will take from the project and team's perspective. Engaging patients requires time and effort to find patients, train them on the project and critical aspects of patient-centered research, and support them as they participate in project-related activities (i.e., help with interpretation of clinical jargon, answer their questions, navigate team dynamics). This will affect the amount of time individuals working on the project will spend, as

[12] "PCORnet Engagement Assessment Project."

well as potentially extend the timeline of the project itself. This can become particularly salient if scheduling becomes challenging, there is a significant mismatch between the perspectives of the patients and researchers that takes time to negotiate, or the project is highly technical and requires an extensive amount of work to support patient understanding and inclusion.

Resources

Closely related to time is the consideration of resources. Involving patients will likely include increased costs related to meetings, meals, travel, and salary or honorariums. These financial costs are the more obvious resources required for engagement. Researchers should also consider and budget for the costs associated with team members' time required for successful engagement, which may include funding a staff member dedicated to engagement efforts. If engaging patients will extend the timeline of the project, this should also be accounted for when budgeting and managing the resources of the project.

Team culture

Engaging patients in biomedical research is fairly new and many researchers are not experienced or trained to engage with patients in this way. For many clinical researchers, their experience with patients has been in a patient–provider or subject–researcher relationship. Recognizing patients as experts and including them as equitable members of a research team can be challenging. It is imperative that researchers engaging in patient-centered research be trained in the foundational principles and practices of patient engagement.

To overcome this challenge, project leadership needs to create a team culture that is conducive to patient engagement. They can do this by creating a dedicated space for the patient voice, modeling behavior that treats the patient as an equitable member of the team, clearly defines the role of the patient and sets the expectation that the patient perspective is valuable and will be included in all key activities and decisions.

Evidence in action

Case study 1: the CHICAGO study

A group of Chicago area Emergency Departments (EDs) engaged patients/caregivers and providers in a comparative effectiveness trial. The project developed and evaluated an asthma discharge tool for African-American and Latino children presenting in the ED with uncontrolled asthma.[13]

Engagement methods

The study team engaged a variety of stakeholders, including a total of 20 patients and caregivers, in the development and evaluation of the discharge tool. In the developmental phase, the patient perspective was gathered by researchers conducting one-on-one interviews in the patient's home or office that included direct observation of the patient engaging in relevant tasks. The data collected provided information on patients' baseline asthma knowledge, self-management, and experience in the ED.

Caregivers were again engaged in the refinement of the tool. Researchers shared three drafts of potential discharge tools, developed from the information collected in the initial phase. They then engaged in collaborative review and editing to ensure the final tool resonated with users, was clear, and was easy to use.

Once the tool was developed, patients and caregivers were involved in the evaluation of the tool. The team used surveys and "card sorting" to capture the attitudes and behaviors the new tool elicited.

Impact of engagement

As a result of patient and caregiver engagement, this project developed a discharge tool that was user-friendly, culturally appropriate, and effective at producing the desired change in knowledge and behavior. Involving stakeholders allowed the team to look at the problem in a unique way and develop a tool that supported collaborative communication. Without the involvement of patients and caregivers, the end product would likely have been an updated version of a standard tool designed to deliver information.

[13] Erwin et al., "Engaging Stakeholders to Design a Comparative Effectiveness Trial in Children with Uncontrolled Asthma."

Case study 2: the TrACER study

The National Cancer Institute's cancer cooperative clinical trials network engaged stakeholders to help design a pragmatic trial to evaluate the effectiveness of primary prophylactic-colony-stimulating factors (PP-CSFs) in reducing febrile neutropenia (FN) among patients with solid tumors receiving modern chemotherapy. The project also looks at the impact of PP-CSFs on patient-centered outcomes.[14]

Engagement methods

The project created an external stakeholder advisory group (ESAG) that included patient representatives (along with a number of other representatives from key stakeholder groups). The ESG was chaired by two members of the study team and was convened throughout the project to provide input and guidance.

The ESAG was convened via webinars, in-person meetings, and email. Early in the grant-proposal writing phase it helped refine the research questions and patient population, reviewed the intervention and study design, and provided feedback on the study end points, relevance to patients, feasibility, and potential impact.

Impact of engagement

The ESAG's early involvement was vital to ensuring that the project focused on questions and outcomes that were relevant to patients and other stakeholders. The group sharing its experiences of PP-CSF alerted researchers to issues around prescribing, risks of treatment, cost, and adherence. The ESAG informed the identification and selection of Patient-Reported Outcomes (PROs) to collect as secondary outcomes to better explore issues. Engaging patients and other stakeholders strengthened the study design and maximized the potential impact of results.

[14] Bansal et al., "A Stakeholder-Informed Randomized, Controlled Comparative Effectiveness Study of an Order Prescribing Intervention to Improve Colony Stimulating Factor Use for Cancer Patients Receiving Myelosuppressive Chemotherapy."

Case study 3: the PROP UP study

This multi-center prospective observational study investigates and documents the long-term harm and benefits of direct-acting antiviral (DAA) therapies used to treat chronic hepatitis C viral (HCV) infection.[15]

Engagement methods

People directly affected by HCV were involved from inception through design and implementation. Patient interviews were conducted throughout the year preceding the proposal submission. In these interviews, patients shared what type of information they felt was important for them in making an informed treatment decision. This data was coded into 17 subcategories, where 9 of these categories were informational and covered treatment-related harms or benefits that lacked robust empirical literature.

During the nine months leading up to the proposal submission, the research team established an HCV Patient-Engagement Group (HCV-PEG). This seven-person group included patients in active treatment, patients previously treated and cured, and patients contemplating treatment. The HCV-PEG met five times for 2.5 hours in the months leading up to the proposal submission. This group reviewed the data collected in interviews and prioritized the nine informational categories, helped researchers translate these categories into patient-centered outcomes, and was involved in the measurement/instrument selection. The HCV-PEG also provided expertise on the more logistical elements of the study design including the data-collection schedule and approach (when and how will the data be collected), participant reimbursement, and retention.

Impact of engagement

The detailed data collection from patients and the HCV-PEG's deep involvement in the early project design was instrumental in creating a project that filled the gaps that patients identified as most critical for decision-making and was designed in a way that was meaningful to participants to ensure successful execution. Because of patient involvement, the project was designed to maximize recruitment and retention. The research team incorporated patient-centered approaches to introductions and consent, patients were appropriately compensated for their

[15] Evon et al., "Patient Engagement and Study Design of PROP UP."

participation, the measures and topics resonated with the participants, and data was collected in a way that worked for the target patient population. Once the project is complete, the HCV-PEG will also be involved in not only supporting dissemination of this information to their respective networks but also informing creative ways that the research team can extend the reach of their findings.

Conclusion

Engaging patients in biomedical research topic selection, design, and execution is a promising practice that is gaining traction. There are many reasons to incorporate the patient voice into biomedical research projects. Researchers have found that patient involvement improves everything from project feasibility to a wider reach and more "real-world" applications of results.[16] The first step is identifying the goal of engaging patients. Next, one matches one's goals with one's capacity to determine the intensity of that engagement, or where it will fall on the "continuum of engagement." Time and resources should also be considered when determining the approach and methods for engagement.

While numerous articles in the literature look at *how* research projects integrate patients, researchers still largely base their strategy on personal knowledge, team capacity, availability of resources, and the goals of the project. These decisions may be "evidence-informed," but there is currently limited research looking at the methodology of engagement to examine which methods and approaches are most effective. There is also limited evidence on the impact patient engagement has on health outcomes. As the science of "patient engagement" matures, these are areas that will be explored. It is the responsibility of all biomedical researchers who use patient-centered approaches to document and disseminate how effective their methods are and the impact engagement has had on the project's process and outcomes.

Patient engagement has the potential to bridge the divide between patients and researchers, create more trust and transparency in biomedical research, and shift us towards a more patient-centric culture. When patients are working alongside clinicians and researchers, they are not only contributing their expertise in the lived experience, but also infusing their humanity into every decision that is being made. When patients are in the room, it changes the conversation and reminds biomedical researchers of the ultimate goal of their work—to improve health outcomes.

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[16] Forsythe et al., "Patient Engagement in Research."

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CHAPTER 3.2

QUALITY OF LIFE IN PEOPLE LIVING WITH A BRAIN TUMOR

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THE BRAIN CANCER PEOPLE

Abstract

When diagnosed with a brain tumor, people cycle through the emotions of fear, anxiety, sadness, and anger. The reaction is unguarded and visceral. Inevitably the values and beliefs that have made them the person they are come into question—their sense of identity and purpose, and their relationship to those around them. This chapter explores the complexity of challenges that come into play when someone is diagnosed with a brain tumor and his or her quality of life is threatened. It describes what is important to the patient and their caregivers, where this concords with clinical perspectives, and where it divides. It draws upon years of interaction with the brain tumor community and highlights two fundamental threats to quality of life: behavior and personality change and fatigue. The effects of these on daily life are profound and do not occur in isolation, destroying the warp and weft of lives so carefully fabricated over so many years. A patient's physical, social, concentrative, and emotional capabilities, and their spiritual beliefs, will be tested to the extreme, such that there must be a reinterpretation of what they have learned about their purposes and attachments—and the principles that underlie the regularity of experience—radical enough to trace the thread out again. To do this, the loss of quality of life that they have had must first be accepted as something they have to understand—not just as an event that has happened but also as a series of events that they must now expect to happen, and a retrospect of earlier events whose familiar meaning has now been shadowed by changed circumstances. The conservative impulse will make

them seek to deny the loss. But when this fails, it will also lead them to repair the thread, tying the past, present, and future together again with rewoven strands of meaning. The final section of the chapter explores some approaches to dealing with the skews that a brain tumor diagnosis brings, so that no matter what a person's relationship with the cancer is, they are able to optimize quality of life. Resilience, resourcefulness, purpose: these are things that should be foregrounded so that no matter where a patient is on the pathway, they can have their best possible day.

Keywords: quality of life, shared decision making, brain tumor, patients, caregivers, fatigue, behavior personality change

Introduction

> It would be good to see a more holistic approach. After my treatment for a brain tumor had finished, I was left to my own devices. It would be helpful to have a road map for the patient for how to get back to as much normality—if there is such thing—as possible. Many things required are of a fairly practical nature: moving from independent to assisted living, travel support, dietary support, exercise planning and tracking, hairdressing. (Patient)

Let's start with what this chapter is not. It is not an academically rigorous paper on the current state of play about quality-of-life research in the neuro-oncology world. It is not representative of everyone's views. It is not a polemic establishing the truth of one position, or falsifying another. It is more about setting our collaborative sights on tackling an area that is lacking in focus, that is fragmented and could offer so much more—to patients diagnosed with a brain tumor, their caregivers, and the healthcare professionals who look after people living with a brain tumor, a very vulnerable group of people. It is about humanizing a focus that comes with a brain tumor diagnosis.

We know that living with a brain tumor is challenging—on so many fronts. We know, too, that dealing with the challenges that come with a brain tumor diagnosis makes life distressing—for everyone involved. We know this from our daily interactions with our community. Patients feel remorse and guilt. Caregivers feel isolated and lost. Some professionals feel ill-equipped and uncertain. These challenges resonate:

- threat to way of life
- the certain knowledge of neurocognitive decline
- lack of control with behavior

- impact on relationships
- systemic problems leading to isolation
- access to support.

So how is quality of life defined? The World Health Organization (WHO) definition of *quality of life* is:

> An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships, and their relationship to salient features of their environment. (World Health Organization, 1)

Maintaining quality of life is one of the biggest challenges facing anyone who is living with a brain tumor—our community says that it is. Not only that, but researchers also tell us it is. Quality of life encompasses so many domains: culture, values, beliefs, goals, physical, and psychological states, and social dynamics. This is hardly surprising: when illness strikes, a number of structural and emotional skews will follow. Belief systems are challenged, roles are upended, and identities shift. The onset of a brain tumor diagnosis forcefully challenges the emotional and physical boundaries that we have spent a lifetime building. The tumor is an uninvited guest that we must somehow build into our lives while at the same time living with the undercurrent of threatened loss. A brain tumor diagnosis is different too: it brings with it the threat of progressive neurological decline and loss of identity.

We know, from our daily interactions with the brain tumor community, that a brain tumor diagnosis is confusing, isolating, and overwhelming. We know these problems are exacerbated by not being able to access care and information quickly and easily. And we also know that access to proactive support and good information can improve knowledge and understanding, reduce anxiety, increase preparedness for events, instill control, and improve satisfaction with treatment in brain tumor patients. Even if individuals spend as many as six hours a year in a clinic or health professional's office, that leaves them 8,754 hours when they are "on their own" to manage their diet, physical activity, medications, stress, and other factors.

This chapter will explore the impact that living with a brain tumor has on quality of life, from both the patient and caregiver perspective.

Context

Brain cancer is different from other cancers: not only do patients and their caregivers have to come to terms with the diagnosis of brain cancer, but they also do so in the knowledge that this diagnosis will certainly mean progressive neurological and cognitive deficit. Depending upon the location of the tumor and the treatment side effects, patients can experience various neurological and cognitive symptoms that may affect their ability to function independently. Irrespective of the level of functioning or disability, the consequences of a brain tumor can hinder patients in participating fully in vocational and social activities, affecting quality of life for both patients and their family members to a great extent. As the disease progresses, patients rely more heavily on their loved ones for physical and emotional support. They develop workarounds that sometimes hide a change in their circumstances. Consequently, spouses, family members, or close friends assume the role of family caregiver, a role for which they have had no training and have not applied for.

Themes that have emerged from our daily interactions with brain tumor patients, their caregivers, and healthcare professionals include the sense of isolation, a lack of voice, and the daily challenges that they face. Patients are concerned about vitality, their identity and role, limitations, mental health, emotional well-being—all of these are important decision factors for patients.

These considerations resonate:

- varying survivorship
- variable trajectory, even for nonmalignant brain tumor diagnoses
- high frequency of disabling complications
- high severity of disabling complications
- knowledge of increasing cognitive dysfunction
- life context—where there is resilience or a lack of ability to cope.

There is little support available through the usual channels of clinicians—only 47% of UK neuro-oncology multidisciplinary teams have access to neuropsychiatry services.

Mukand (2001) identified the following neurological complications in brain tumor inpatients:

- cognitive deficits, 80%
- weakness, 78%
- visual–perceptual deficit, 53%
- sensory loss, 38%
- bowel/bladder, 37%
- cranial nerve palsy, 29%
- dysarthria, 27%
- dysphagia, 26%
- aphasia, 24%
- ataxia, 20%
- diplopia, 10%

Among inpatients, 75% will have three or more of these neurological complications; 39% will have five or more. Surgery, adjuvant therapies, and supportive treatments (e.g., anti-epilepsy medication, corticosteroids) can negatively affect the person living with a brain tumor while at the same time improving patient functioning and extending survival. Furthermore, a patient's appreciation of what constitutes worthwhile quality of life evolves over the course of the illness, so even in the face of mounting physical, neurological, and cognitive deficits, patients may feel that their quality of life is good enough to continue with treatment. They can still have their "best possible day" at end-of-life care.

Catt et al. (2012) have identified that:

- supportive care pathways for patients and their families differ between hospitals;
- guidelines either omit important aspects of care and follow-up or are based on assumptions with little empirical support;
- as patient treatments is often palliative, more efforts are needed to ensure good continuity of care;
- current follow-up is failing to meet the psychological needs of patients and their caregivers;
- there is a need to develop innovative and integrated interventions that effectively support caregivers, such as proactive counseling or problem-solving services.

In the UK, there are several barriers to the routine identification of neurocognitive impairment and referral for neurocognitive rehabilitation:

- There are shorter neurosurgical admission periods with a focus on efficient throughput and waiting times.
- Neurocognitive difficulties are not appreciated by staff, or staff have too little time to assess them.
- There is a lack of routine neurocognitive screening at surgical admission.
- Mood-related difficulties (anxiety and depression) are considered a normal reaction, and referrals are not made for support.
- There is uncertainty as to whether patients would be accepted by neurorehabilitation specialist services, or what the referral criteria are.
- The wait for rehabilitation referral may delay surgical discharge.
- There is a lack of awareness of availability of community neurocognitive rehabilitation services.
- There is a lack of resource for the delivery of outpatient neurocognitive or psychological support, resulting in delayed opportunities.
- There is the perception that patients may be too tired during radiotherapy and/or chemotherapy to cope with or benefit from early rehabilitation.
- It is not the patient's priority early in their recovery.

Concordance research has also reflected a disconnect between what patients want to discuss with their clinical team and what the clinicians want to talk about. Measuring health-related quality of life with the standardized QLQ-C30 and BN20 enabled detection of more presenting symptoms than by clinician review alone, with concordance highest for gross neurological deficits. Patients are concerned with future uncertainty and fatigue; clinicians want to discuss visual disorder and motor dysfunction (closest concordance), and headaches—focuses that are more easily explained and treatable.

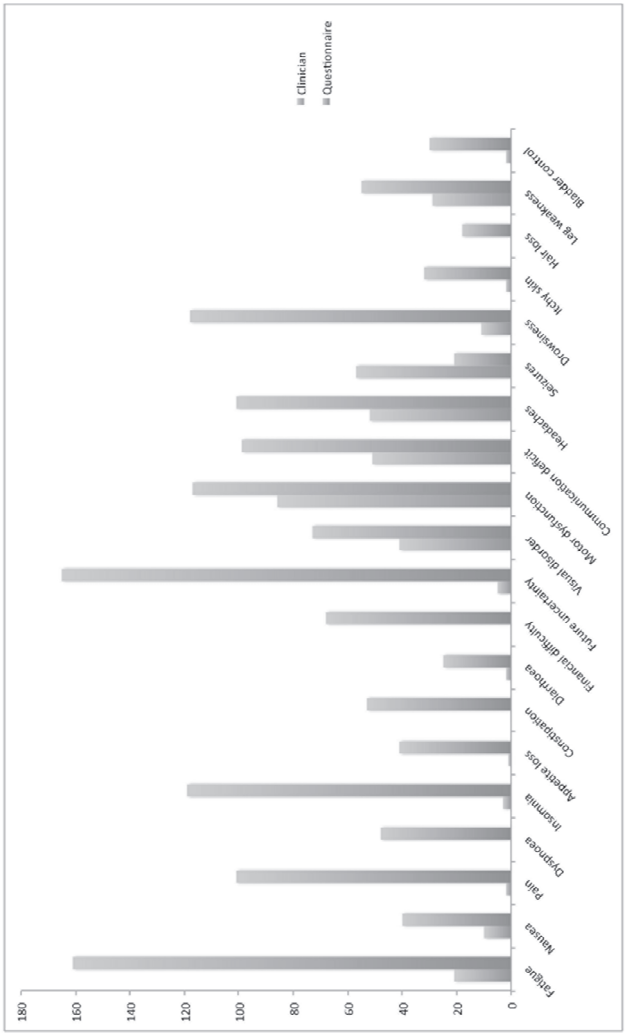

Figure 3.2.1. Concordance: Patients presenting for initial assessment in a neurosurgical oncology clinic were asked to complete the QLQ-C30 and BN20 brain cancer module questionnaires prior to their appointment. Clinician-reported symptoms were determined retrospectively from outpatient clinic letters. Statistical significance was determined using paired t-test and Fisher's exact test. A total of 181 patients were included in the analysis (96 male, 86 female; median age 61).

It is much easier to write a script for headache or refer to neurology for seizure control than to provide treatment for how to live with future uncertainty.

Methodology

We want to make things better. But to do this, we need to understand the issues in more depth, and so over the last thirteen years, we have created an ongoing conversation with our community. Simply by joining the conversation, our community has helped us understand more about the impact that living with a brain tumor has on quality of life, so we can make things better for people who are living with a brain tumor.

Online and offline, people step in and step out of the conversation, sharing their concerns, their needs and wants, creating a self-supporting and regulating community. Gathering the views and ideas of patients, caregivers, and healthcare professionals over a period of time and in this way allows for an accessible and open discussion. This method has allowed us to gather the real-world experiences and opinions of healthcare consumers. Online participant channels include social media, including Twitter and Facebook. Offline channels include:

- face-to-face conversations at health and well-being events, patient and caregiver events, and clinical conferences;
- daily interactions with our community.

This conversation has shared ideas that improve the quality of life and care for people living with a brain tumor. It has given us stories, insights, and ideas that we can take to doctors and other decision-makers to help shape their thinking—they know that there is a gap here too, and they know that collaboratively we can fill it. Our community is a conduit for people to solve collectively and collaboratively the issues that need addressing. We know that social support provides an important contributor to general well-being and it acts as a buffer. This conversation, in all its forms, gives support *to* patients and caregivers *from* patients and caregivers, all of whom have experience of living with brain cancer, and all of whom are willing to share. They will listen and talk with rather than talk and listen to. The essence of the conversation offers experiential empathy and understanding, which is beyond the scope of healthcare professionals. Such sharing of experiences and sense of belonging, developed through peer support and shared narrative, significantly and positively affects well-being, so that patients and caregivers have

improved satisfaction with healthcare, improved mood, positive psychological states, and healthier behavior.

These points are echoed in the findings of a crowdsourcing project. Brain tumor patients and caregivers highlighted four main themes that would improve the quality of life for brain tumor patients post-surgery:

- a desire to know what to expect—thus being better able to live with uncertainty;
- better mentorship, home care, and personal support around the key areas of fatigue and managing behavior and personality change;
- the importance of understanding and accessing long-term care;
- increased uniformity in standard of hospital care from place to place.

> I now realize that stuff like memory loss, not being able to articulate what's in your head, and the bone-aching tiredness that comes on without warning are not just my symptoms. Knowledge is coping, for me. (Patient)

These findings are reinforced by a UK-based survey, which has identified three key potential areas of improvement in neuro-oncology services:

- information provision;
- access to support services;
- inclusion in research.

And when taken with the ongoing conversation, people living with a brain tumor want:

- to be able to get hold of a nurse specialist;
- clear signposting of care in the community;
- access to rehabilitation;
- quicker scan results;
- the right information at the right time;
- equality of care across hospitals;
- public understanding;
- the tools to deal with fatigue;
- clear expectations;
- a more equal relationship with their doctor;

- early diagnosis;
- to be able to get around;
- more honest discussions sooner;
- to know how to get what they want out of a discussion;
- to not be alone;
- to feel in control;
- to know how to deal with death and dying.

Family caregivers often provide the majority of support for patients with a brain tumor. They, too, have high levels of unmet support needs, as caring for someone at home places a huge amount of stress on caregivers. If caregivers are unsupported, that stress can frequently become too much, leading to a breakdown in caregiver health.

Systematic reviews of research with caregivers reveal a consistent and urgent need for clear information and communication with healthcare professionals around symptoms, treatment, and available resources; health services and care coordination; and psychological and social supportive care options.

The two areas that both caregivers and patients tell us most affect quality of life are fatigue and managing behavior and personality change. Both are pervasive and impact in a variety of ways: physical, social, concentrative, emotional, spiritual—all the things that enable us to be who we are. What does this look like?

People stop going out. Their worlds become smaller as they become more isolated. Relationships suffer. Confidence is eroded until one day they realize that they are grieving for the person who has been lost, whether they are a patient or a caregiver.

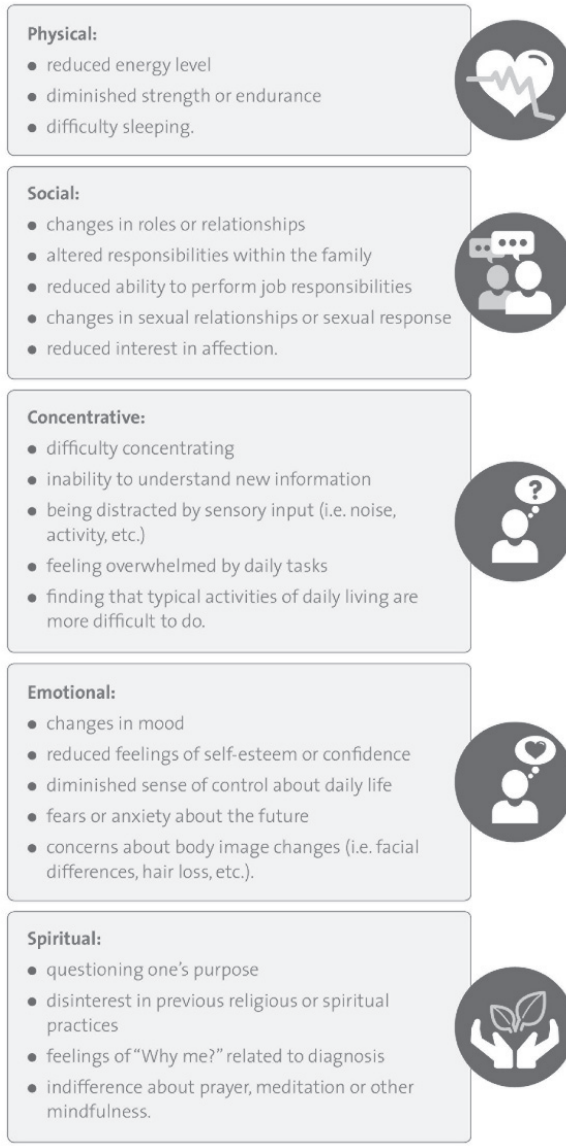

Figure 3.2.2. Examples of physical, social, attentional, spiritual, or emotional changes that may accompany brain tumors and their treatments. Design: Brainstrust.

Fatigue

> I thought I knew what it meant to be tired. I now know I had no idea. This isn't just being tired. This saps at your identity, your confidence, your way of being. I don't go out anymore. I avoid leaving the house. I don't shop. Friends have stopped asking me out. (Patient)

We know that fatigue is one of the biggest challenges facing patients and caregivers who are living with a brain tumor—they have told us it is. Not only that, but research also tells us it is. It is one of the key themes that has emerged from our daily interactions with everyone in our brain tumor community, whether they are a patient, a caregiver, a clinician, a nurse, or an allied health professional. And we know, too, that fatigue caused by a brain tumor and treatment can be very different from fatigue caused by other cancers.

Fatigue is a physical, emotional, and/or mental tiredness that does not go away completely. It is often experienced as overwhelming. It is very different from everyday tiredness, because it lasts longer and can come on without warning. It has a big influence on everyday activities and can make even small chores or routine tasks seem impossible to accomplish.

> I would have a shower and then have to go back to bed. I just couldn't do anything more. (Patient)

Fatigue can last for a very long time (months to years), even after completing treatment for a brain tumor. Fatigue is known to be one of the most difficult side effects of brain injury *and* cancer treatment. It is not known exactly how many people living with a brain tumor suffer from fatigue, but it is estimated that between 40% and 80% of people with a brain tumor experience severe fatigue.

Causes of fatigue

We don't know the precise causes of fatigue. Because of the physical, emotional, and mental aspects of fatigue, the cause is likely to be multifactorial. Chemotherapy and radiation therapy can cause fatigue, but there is not much evidence to suggest that a brain tumor or location can cause fatigue. It may just be that there is a problem in the brain that is causing fatigue. Fatigue can be associated with any brain injury, whatever the cause (e.g., stroke, trauma, inflammation, or tumor) and wherever the location within the brain. On top of that, pain and certain medications,

such as anti-epilepsy medication, can cause fatigue. Emotional side effects of any cancer treatment, such as worrying, feeling anxious and depressed, and having trouble sleeping, can make fatigue even worse. If a patient thinks they have fatigue, they should have a thorough medical evaluation to identify possible reasons for this. Sometimes addressing other issues can reduce or even eliminate fatigue.

What is different about fatigue for people living with a brain tumor?

Because fatigue is common after cancer *and* after brain injury, people living with a brain tumor may be especially vulnerable to fatigue. They are much more likely to be treated with medications that have fatigue as a side effect, such as anti-epilepsy medication. In addition, people who have lived through brain injury often have more trouble processing a lot of information at the same time, for example, when being in a room where several people are talking. Social events can become exhausting.

People living with a brain tumor can also feel drowsy or abnormally sleepy. Although this is related to fatigue, it should be seen as a separate symptom. Drowsiness can be caused by the tumor leading to increased pressure within the skull, but it may also be a side effect of certain medications.

Treatment-related causes can include:

- Surgery and anesthetics. Fatigue occurs for up to one to two years after most major surgeries, not just brain surgery.
- Radiotherapy. This can cause fatigue at any time during and after treatment, including a delayed response. For example, radiotherapy can cause an underactive pituitary gland as a late effect, leading to low thyroid-stimulating hormone or low cortisol production. The combination of fatigue and the impact on cognition is sometimes called “beamo brain,” but it is hard to tease out the symptoms.

> People warned me that four to six weeks after the treatment had finished, I would feel really tired. This lasted about a month. Having a shower was a supreme effort, and I had to lie down afterward. A course of radiotherapy is the equivalent to having another round of major surgery. Listen to your body. (Patient)

> Just how long does the radiation fatigue last? I appreciate everyone is different, but Dean is nearly fifteen months post-treatment and is bone-

> tired most days. He is tapering his steroids, which we know can be tiring, but he is totally fed up now and so wants to feel more like his old self. (Caregiver)

- Chemotherapy. "Chemo brain" is a known phenomenon. This is a loss of mental sharpness associated with fatigue. It can manifest itself in an inability to concentrate or multitask.
- Withdrawal of steroids. Fatigue can be one side effect of stopping steroid treatment, which is why these should never be stopped abruptly but tapered.

Other factors include:

- Attentional fatigue. This describes the tiredness that comes from having to focus on behaviors that used to be second nature, such as needing to focus on information or tasks. They *were* easy; now they require greater effort and concentration, and sometimes need to be relearned. This causes slowed thinking and mental exhaustion. Learning is hard! Sometimes people lose the ability to focus on several things at once; being in a noisy or busy place can cause stress, which in turn causes fatigue.
- Epilepsy, which can come with a brain tumor, causes fatigue. This is due to a range of reasons. For example, sometimes seizures disturb sleep patterns. The side effects of some anti-epilepsy medication can also cause fatigue.
- A sense of urgency to get things done, trying to live at one hundred miles per hour: these are tiring factors. This sense is heightened with a serious illness, when you believe you might not have the time ahead that you thought you had.

> I get tired because when I am having a good day, I try to pack everything in and live every second because it counts. But I can't do this anymore, and when I do, I pay for it. (Patient)

Other factors can include depression, anxiety, physical impairment or disability, pain, low hormone levels, poor nutrition, dehydration, and infection. Many of these are potentially treatable causes, and addressing them can relieve fatigue.

How do we measure fatigue?

This is tricky to answer. How do we know whether someone is fatigued and not simply tired? These are the key signs:

- feeling anything from mild tiredness to total exhaustion;
- feeling drained;
- resting does not make it go away completely;
- having no energy or strength;
- feeling dizzy or light-headed;
- finding it hard to do routine tasks;
- lacking motivation;
- finding it hard to concentrate;
- finding it hard to think or speak;
- low sex drive;
- finding it hard to cope with life;
- difficulty in managing your feelings.

There are other measurement tools that are used by hospitals for clinical and research purposes. These include the Brief Fatigue Inventory and the Fatigue Self-Management Scale.

For patients and their caregivers, a fatigue diary can help see patterns in fatigue. For example, perhaps fatigue is worse after large meals or in the afternoon but better after an hour's rest. Do certain activities create more fatigue than others?

There is no magic wand, no silver bullet that will spirit away fatigue. It's so easy to overestimate the importance of one defining moment and underestimate the value of making better decisions on a daily basis. Almost every habit, good or bad, is the result of many small decisions. Using the principles of marginal gains, or the aggregation of marginal gains promulgated by Brailsford, if you improve every area related to sleep by just 1%, then the small gains will add up to a remarkable improvement. Start by optimizing the obvious things: environment, adjusting the pace of living, habits before going to bed. Then search for 1% improvements in tiny areas that are less obvious and harder to define.

Patients may be fatigued in one or two of the areas outlined in the infographic, or in all of them to different degrees. Once they understand how fatigue is affecting their well-being, they can begin to take steps to address it. These might be small changes to their daily life, such as looking

at sleep hygiene, changing eating habits, creating a sanctuary, unpacking the day, changing bed linen, pacing and prioritizing, decluttering.

> I'm four months post-op and want to know if this fatigue is part of the recovery? I ask because I spend way more time asleep than I do awake, and my clumsiness is off the scale at the moment. I can't help but feel that something is not quite right with me. (Patient)

Looking after someone who has fatigue

> I love it when my husband is tired. He goes to lie down, and so I get a break. And this makes me feel so guilty. We should be making the most of our time together, not enjoying space apart. (Caregiver)

Fatigue can be unpredictable. Caregivers may have planned an event only to find that they can't do it with their loved one, as the person is just too fatigued. So a key part in being a caregiver who is living with someone who has a brain tumor is to be agile and tolerant, accepting of uncertainty, and to manage expectations—their own and those of their loved one. This is quite a tall order when, as a caregiver, they are already digging deep. They may find themselves having to dig even deeper, but they have a right to rest too. Being a caregiver is not a role they applied for, nor is it one for which they have had any training. Caregivers need to know where their sanctuary is, know how and whom to ask for help, and be comfortable in gifting themselves the time to be the person they were before they became a caregiver.

Behavior and personality change (BPC)

> Mood swings take careful controlling. I have to disappear to keep control. (Patient)

> From the perspective of a neuro nurse, I would like to know how to manage personality change and help partners/caregivers/family to adapt to these changes. This is a huge need in my clinical setting, and I would like to implement strategies to improve things and include this in the service I provide. (Clinical neuro-oncology nurse specialist)

Dealing with behavior and personality changes makes life distressing—for everyone involved. We know this from our daily interactions with our community. Patients feel ashamed at their outbursts and loss of control. Caregivers feel isolated, fearful, and lost. Professionals feel ill-equipped and uncertain. Managing BPC is one of the biggest challenges facing

anyone who is living with a brain tumor. Mood disorders are a considerable burden for patients and families living with a brain tumor, with between 16% and 60% experiencing personality or behavioral change.

What do we mean by BPC?

It may be easier to say what BPC isn't. It isn't related to movement and physical sensations, such as balance, coordination, and numbness. These are affected by the parts of the brain that control motor functions. It isn't depression and it isn't anxiety. Yes, these are changes, and they can also affect the way someone living with a brain tumor behaves. But these may be part of a bigger jigsaw puzzle.

Behavior is the way a person responds to certain situations or conditions. It is how they act.

Personality describes the combination of unique qualities that form a person's character.

Cognition is also a key part of behavior and personality change. Cognition includes how we think, what we remember, and how we reason, or make decisions. A brain tumor diagnosis inevitably comes with a loss of cognitive ability, for example, a loss in the ability to make a reasoned judgment, or not being able to do more than one thing at a time.

Causes of BPC

Brain tumors can cause a variety of symptoms. These can be neurological symptoms (headaches, dizziness, loss of speech or movement) or behavioral changes (changes in the way people think or act). These changes can be due to the brain tumor or the treatment for the brain tumor. Changes in behavior, personality, and cognition could be related to the type of tumor, its location, size, and rate of growth or grade. For example, if a brain tumor is in the frontal lobe of the brain, then this could cause a person to be disinhibited—to behave in ways that are completely out of character and at times inappropriate:

- Frontal lobe: movement, intelligence, reasoning, behavior, memory, personality, planning, decision-making, judgment, initiative, inhibition, mood.
- Temporal lobe: speech, behavior, memory, hearing, vision, emotions.
- Pituitary gland: hormones, growth, fertility.

- Parietal lobe: intelligence, reasoning, telling right from left, language, sensation, reading.
- Occipital lobe: vision.
- Cerebellum: balance, coordination, fine muscle control.
- Brain stem: breathing, blood pressure, heartbeat, swallowing.

A malignant tumor is more likely to cause BPC changes. A large tumor can cause more changes, but a small tumor in a sensitive location can also cause big changes. So it's very complex.

Treatments can also cause BPC. Radiation therapy, surgery, medication, chemotherapy: all these can have an impact. "Chemo brain," for example, is a recognized side effect. After treatment, a spaced-out feeling lingers—impaired memory and an inability to concentrate or multitask hinders some patients. It is suggested that the cause lies deep within the brain, in regions where progenitor cells are proliferating. These self-renewing cells, part of the complex structures needed for memory and other normal functions, are particularly vulnerable to toxic chemotherapy medication. On the other hand, the very stress of a brain tumor diagnosis or depression may also contribute to memory loss, so it is hard to say whether chemo brain exists or is exaggerated, and if it is, whether it is prolonged and progressive.

What is different about BPC in a person living with a brain tumor?

Unfortunately, with the progression of a brain tumor, or effects of treatment (including late effects), BPC can worsen and become more difficult to manage. Some patients will have insight into what is happening to them, while others will not. In some cases, BPC can be very subtle, and the patient is more aware of the difficulties, creating a "workaround" to hide the change so that caregivers don't notice it. BPC can mean that the caregiver doesn't recognize the person they know and love—that they have already "lost" the person.

> I've known this man for forty-six years and now feel as if I know nothing about him. (Caregiver)

Some symptoms can be managed with therapy, but seizures, infections, and other medical problems can precipitate symptoms. It is important to take advantage of the times when everything is working well, as we cannot predict the future. Being comfortable with uncertainty and accepting what is happening is key.

How does BPC manifest?

> We are all adjusting to the new us. Looks like quite a few of us have something in common (besides the obvious): frustration, anger, guilt for relying on others. (Patient)

Some people living with a brain tumor will not experience changes in behavior and personality, but given the range of things that can cause BPC, it is not uncommon for patients and their caregivers to experience some changes in behavior and personality. Over 80% of patients who have radiotherapy describe neurocognitive impairments, such as mental slowing and short-term memory loss, and see changes in the following.

Emotions and personality: depression, anxiety, obsessive–compulsive behavior, changes in emotional control, irritability, mood swings, withdrawal, inappropriate behavior.

> My wife says that everything makes me angry now, and she hates it. I don't want to be angry, and I'm not an angry person at heart, but so many things just seem to stress me out and irritate me, and that comes out as me being grumpy or angry. It's horrible. (Patient)

> My father broke a plate on our dog's head because Rufus was after his food; he wasn't aware that what he had done was wrong. I don't know who was more shocked, me or the dog. (Caregiver)

> At first diagnosis, Dave went through a period of intense anger, mostly directed at me. At one point, severe enough that I walked out of the house and told him afterward that I had seriously been looking in estate agents' windows for a place to live on my own, as I wasn't sure our marriage could survive this. I had never done this before or since. (Caregiver)

Attention and concentration: confusion, being distracted, and difficulty multitasking, planning, and thinking strategically.

> My daughter was always the reliable child. If you wanted a letter posting, then Sophie was the one to ask. Then one day she presented her bedding to me and asked me where she should put it. The next day, she asked me where the kitchen was. It was unnerving, as I really felt she was vulnerable. (Caregiver)

Learning and memory: difficulty processing, storing, and retrieving information, short-term memory loss.

> Memory issues control my life, and my waking hours involve a list attached to my forehead with a tick list. (Patient)

> Memory loss—I find it really upsetting. Makes me question myself. Did I or didn't I say that? Did I or didn't I do that? I often ask myself these questions. Yes, my confidence is at an all-time low, but I think I have lots of reasons for this, not just the memory loss. (Patient)

Executive functioning: decreased reasoning and organizational ability, impaired judgment.

> I can't rely on my husband now to do some of the things he has always done, like paying bills on time. I love my husband so much but feel I'm letting him down by saying, 'You can't do that,' and then thinking he's not a child, but I just can't help it. (Caregiver)

Language and communication: difficulty finding the right words, using words in the right order, reading, and writing.

> The loss of words that I need to use as well! I did business studies, was a PA, so needed to be organized. Now I can't organize a fight in a paper bag! (Patient)

> My son forgets nouns. So he makes up phrases to describe things. Yesterday he couldn't remember the word escalator, so he described it as a moving staircase. It's sad, but also it can be quite amusing—and then I feel guilty for laughing. (Caregiver)

> Since my brain surgery, I can't see the left-hand side of the page, so reading right to left has needed a rethink. I just have to turn my head further to the left so I can see the left-hand side. It looks a little odd, but I am just happy I can still read. (Patient)

> I have stopped going out now. I can't remember the most basic words, and it's embarrassing. I used to go to my bowls club and do the shopping, but I don't do either of these anymore. (Patient)

Treatment options

Let's deal with what might seem the obvious way to manage BPC but is actually probably the least straightforward: drug treatments. It is complex, with many things at play. Firstly, neurorehabilitation is in its infancy. It is only in the last few years that this area of quality of life has been considered to be important and so in the past has largely been ignored.

There is little research evidence available to suggest what treatments do and don't work. We need more controlled trials so that the clinical management of BPC is informed.

Second, no drug treatment has been compared to a placebo for the treatment of BPC (which includes depression and anxiety), so there is very little evidence that medication will improve BPC in people living with a brain tumor. An added complication is that drug treatments could cause adverse drug interactions. For example, although antidepressants generally do not trigger epilepsy in healthy individuals, the risk of causing seizures in patients with a brain tumor is unknown. So both doctors and patients may be reluctant to initiate new drug treatments.

At the moment:

- No drug treatment has been compared to a placebo in this group of patients.
- There is limited evidence for the use of certain drugs.
- There is some, but limited, evidence for specific complex psychosocial interventions, but these would be difficult to implement widely so that everyone living with a brain tumor has access to them.

What is recommended is that people living with a brain tumor who have changes in behavior and personality should be assessed whenever possible by neuropsychiatry or neuropsychology services. This is the optimum standard of care outlined by NICE in 2018.

Self-help strategies

Self-help is exactly that: you have a toolkit at your fingertips from which you can "help yourself" to deal with the situation as it arises. There are many benefits to self-help for people who are living with a long-term condition, illness, or disability, as well as their caregivers. People can suffer less pain, anxiety, depression, and fatigue, have a better quality of life, be more active and independent, and live longer.

Developing self-help strategies enables people to be human and to:

- build knowledge, skills, confidence, and resilience to manage the impact that fatigue and BPC are having;
- know where to access the support needed within and beyond their health service so that they can better manage their situation;

- be active partners in working out what is important to them.

Self-help strategies include looking at using breathing, relaxation, diet, exercise, rest, doing pleasurable things, and finding a sanctuary. Acceptance, too, is key. Acceptance helps us accept the difficulties that come with life and what is out of our control, while at the same time committing to action that will improve our quality of life. Life brings joy and pain, and learning the skill of acceptance—to accept things as they are without evaluation or attempts to change them—can bring freedom and help us become "unstuck." It is about living with painful and negative thoughts and feelings, understanding that they are part of the unhappiness of the life challenges we are facing, and not being overwhelmed by them to the extent that we become trapped and unable to move forward in our lives.

Accepting fatigue or BPC can allow people to move forward, whereas obsessively and unhappily playing things over and over keeps us stuck. For example, being frustrated and angry because we can no longer do the things we used to do may mean that our frustration and anger become the focus, and this is using energy that could be used more positively. Accepting the reality of the situation and working with what we have now, living in the present rather than constantly asking "Why?" about the past, reduces helplessness and despair. It can open our eyes to new opportunities, new ways of doing things, new hobbies, and new forms of exercise. Acceptance means allowing the painful feelings and sensations to come and go as part of the natural process of loss while dropping the struggle with them. By giving the feelings permission to exist in the present moment, but not getting caught up in them and being dragged back to the past, it becomes easier for feelings to come and go without getting stuck within them. And so, over time, they lose their influence on our everyday psychological and emotional well-being, improving quality of life.

Dealing with emotion

> My wife says that everything makes me angry now, and she hates it. I don't want to be angry, and I'm not an angry person at heart, but so many things just seem to stress me out and irritate me, and that comes out as me being grumpy or angry. It's horrible. (Patient)

Emotional maturity and emotional intelligence are key skills we use daily in maintaining healthy relationships. But these skills can be affected by a brain tumor and its treatments. This can lead to a breakdown in

communication and, ultimately, complications in or even the break-up of relationships. There is no way to navigate relationship politics without these skills.

An interaction may appear to be happening between two people in the here and now, but the reactions, the language, and the emotions being expressed are all deeply rooted in two very separate histories and two unique experiences.

In the white heat of the moment, it is important to remember two words: "react" or "respond." Choose "respond." When we find ourselves in a disagreement with another person, it is natural to feel some sort of emotional response, particularly a negative one. Acknowledge the emotion (anger, fear, frustration) and respond. Don't react.

Discussion

First we are people.

People with a brain tumor and their caregivers fall into a chasm between improving clinical care, and the quest for a cure. Much can, and needs, to be done for people with a brain tumor to help them establish their "new normal" in society, and rediscover the magic of the ordinary, so that they can have their "best possible day."

Modern medicine prolongs lives and saves lives; it is one of humanity's greatest achievements. The clarity, simplicity, and success of the model are both remarkable and beguiling. One author has noted that "when faced with complexity or uncertainty . . . most healthcare professionals retreat to the safety of the biomedical model" (Blakeman et al., 417).

It was not always so. In the early years of modern medicine, science had fewer tools to offer the physician, and the role of human interaction in medical practice was more palpable. As Sir William Osler noted, "The good physician treats the disease; the great physician treats the patient who has the disease" (Rethinking Medicine, 3).

We need to see a world where people with a brain tumor get the best possible care, no matter who or where they are. But it is vital that they are also involved, resourced, supported, connected, and confident. Only then will they be living the life they want. They have been and always will be people first and patients second.

Why is this important?

- Before we are patients we are people

- As people, we are inherently resourceful. We turn to help outside the clinical setting when we are people rather than patients.
- Emotions and values drive great decisions, not clinicians alone.
- As people, we look for possibilities; as a patient, the focus is on the problems.

This is the zeitgeist. It drives involvement in care, improves quality of life, creates better outcomes, and saves money. To deliver this, we need:

- prepared patients;
- trained teams;
- supportive systems.

These can achieved through the following.

- Shared decision-making (SDM): Provision of tailored information and support for shared decision-making is essential in adjustment for people living with a brain tumor. Drivers to establish SDM include unwarranted variation in clinical practice, a culturally based medical decision ethos that has evolved from a paternalistic model—"When we want your opinion, we'll give it to you"—and ethical and legal consent:

> The value of autonomy . . . derives from the capacity it protects: the capacity to express one's own character—values, commitments, convictions, and critical as well as experiential interests—in the life one leads. Recognizing an individual right of autonomy makes self-creation possible. It allows each of us to be responsible for shaping our lives according to our own coherent or incoherent—but, in any case, distinctive—personality. It allows us to lead our lives rather than be led along them, so that each of us can be, to the extent a scheme of rights can make this possible, what we have made of ourselves. (Dworkin, 226)

- Navigation support available for those patients and caregivers who want it. This involves planning, summarizing, and recording. Before oncology consultations, navigators help patients create a key information and question list to use in consultations. Navigated patients:
  - attribute knowledge and understanding of diagnosis and treatment to feeling better able to cope
  - are less distressed due to being better informed

- feel prepared and use question lists, which result in broader yet more focused consultations
- establish quality of life multidisciplinary team meetings—in every neuroscience center.

This holistic approach ensures that the needs of patients and caregivers are addressed through a focus on the transition points on the clinical pathway, an emphasis on quality of life, a personalized care team, and self-management practices. This includes a full range of support that people need to manage the physical, emotional, and social impact of living with a brain tumor at different stages of the care pathway. Some of this is being done already on a small scale (evidence and practice is there), but it needs traction, a responsive network, shared motivation, and buy-in to achieve scale.

Patients and caregivers have the capacity to take control of their situation to secure the best possible outcomes. By empowering our community through coaching, it has autonomy, a better quality of life, more patient satisfaction, and with these comes a strong health economic argument—it saves money. Empowerment models such as choice and entitlements have focused on responding to a person's needs rather than developing their capabilities. This is common where services have been established with a "deficit" mindset: hospitals exist to provide patients with medical treatment at times of acute need, and doctors exist to diagnose illnesses and provide medications. Coaching takes a different starting point: it rejects the view of the patient as principally a "service user" with needs that must be met. This approach tends to infantilize and disempower people, creating dependency cultures in which people's best hope for improving their lot is to wait for a paid professional to step in. Instead, by seeing capabilities in everyone and in seeking to mobilize these, by discussing a person's needs and aspirations, and then finding the resources available to help meet these needs, people living with a brain tumor can feel anchored, focused, and strong in their approach to managing their brain cancer and the interventions offered.

Navigation to support decision-making and improve understanding and information has been shown to be associated with better knowledge and understanding of diagnosis and treatment, better ability to cope, and improved distress levels. Coached patients felt that by preparing thoroughly for consultations, a discussion of personalized key issues, broader than the prime focus of the consultation, resulted. Patients felt more informed and utilized coaching materials to aid memory, information gathering, and understanding. Clinical feedback revealed that coaching led

to more effective consultations and facilitated communication within consultations by giving insight into information gaps. People who are living with a brain tumor are able to face their challenges, so that they learn how to develop resilience and utilize resources to their full potential.

Following diagnosis and treatment for a brain tumor, patients will have differing trajectories, which may be predicted, ranging from recovery, stability, or progression. Neurorehabilitation and neuropsychosocial support improves quality of life and outcomes for patients diagnosed with a brain tumor. For improved survivorship, close collaboration is required between clinicians involved with neurorehabilitation, supportive care, quality of life, and psychological and palliative care to plan transition points in care. This requires coordination of different specialties and expertise from symptom management to end-of-life care. We know that our patients and caregivers who are coached are better able to manage the complexity of their journey and have more resilience and a better quality of life. It is therefore imperative that improvement in prognosis is associated with improvement in the quality of survivorship—in living with and beyond a brain tumor.

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CHAPTER 3.3

MEASURING WHAT MATTERS TO THE BRAIN CANCER COMMUNITY

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THE BRAIN CANCER PEOPLE

Abstract

Effective measurement and evaluation of health-related quality of life (HRQOL) provides insights into the human condition. Used effectively, these insights can shift the metrics from preserving life to enhancing life, develop and drive service delivery, improve relationships, save money, and build resilience and resources in the community, on the basis of local need. This chapter provides an overview of the complexity of gathering and using data in the brain tumor community, examining how measuring activities of daily living and using real-world evidence can be used to measure and report on HRQOL at scale, so that quality of life is deemed to be as important as survival.

Keywords: narrative, real-world evidence, data, impact, measurement, evaluation, HRQOL, activities of daily living

Introduction

> You need one version of the truth. Remember the power of the narrative when it comes to patient stories and building the case for transformation. There is a human nature element to this—you have to bring people along with you. The commissioner–provider relationship can become too transactional and organization-specific; instead, incentivize and join people up around outcomes. (Primary Care Commissioning)

Andrew is 42. He is recently divorced and has three teenage children. Their care is divided between his ex-wife and himself. He has been diagnosed with a glioblastoma, the most aggressive form of brain cancer. He has lost his driving license, and so has lost his job. He cannot afford to pay child maintenance, is living in rented accommodation, and is geographically removed from his parents and brother and sister. He is angry, fearful, and sad. He feels he should talk to someone but is a proud man and thinks he should be sorting out his problems for himself. He won't ask anyone for help, and his anxiety levels are high. He is losing sleep, his functioning is reduced, and he is becoming isolated. He only has ten minutes with his GP and is unable to articulate what his real concerns are. He believes it is not his GP's role to help him with his stress.

Andrew's challenges are overwhelming. There is the disease trajectory, symptom burden, mental incapacity that comes with the progressive brain cancer, emotion, lack of support, pressure of teleological time, and a focus on treatment. The challenge we face is, How can we make sure that what matters to Andrew is taken into account in the many consultations that he will be having over the remaining months of his life? What matters to Andrew takes us to the very heart of person-centered care, and if we begin to measure what matters to him, we can begin to construct care that places him at the center.

The thrust of integrated care systems is toward system-wide outcomes measurement, but there is a case to be made in that this loses sight of what is key to this: the person living with the disease and what matters to them. There is no story to be told without the patient—the patient is the only form of data—and the value the patient brings to the agenda exceeds that of the purely clinical. A genotype does not explain how a person perceives their health state, what motivates or stands in the way of behavior changes, or what other life events and stressors are competing with the ability to maintain health and well-being. Currently we have numerous ways of measuring the quality of health and social services, but very few of these measures come from the perspective of the person living with the disease. With a focus on the person, we can set about reframing the problem of measuring quality of life so that we are measuring the presence of health, not the absence of health.

Patient involvement is vital here, as quality of life climbs the agenda: patients can misimagine their future state, and this has a significant bearing on decision-making. They have the experienced utility of their current symptoms and imagine the future utility (or disutility) as they live with the disease. People living with the illness can anticipate alternative futures by hearing the experiences of those who have preceded

them. You take what is least valued (death) and what is most valued (symptom relief) and then take into account the different wants and needs, the social context, the core values, and the person's attitude to risk—they are the expert on them—they value things differently. What is possible is the clinician's role. What is preferable and valued is the patient's role. Where do they sit on the distribution of the impact on quality of life? Shared decision-making is fundamental here, a shift from sharing a decision to sharing options.

Having patients as copilots reframes problems, generates insights, shifts dynamics, changes practice; however, all too often with the measurement tools we currently have, we see the target hit, but the point that is meaningful to the patient is missed. We know from our daily interactions with the brain tumor community that they want four things:

- not to feel despondent;
- an understanding that brain cancer is unique;
- to have access to resources;
- a move from "What's the matter?" to "What matters to you?"

If we ignore the patient voice when measuring outcomes, we have a disconnect between the epidemiology of disease (clinicians) and the epidemiology of healthcare (patients). Our experience is that researchers and clinicians focus on overall survival and progression-free survival; patients focus on quality of life, function, and symptom relief. Using shared decision-making allows everyone to become copilots in their care, so that we see a new model of maintenance of wellness as well as treatment of illness.

Context

Significant changes are happening, and have been happening for many years, in the healthcare sector. There is first a clinical need to translate laboratory-based research if survival rates for brain cancer patients are to improve. Then we have the empowerment model—"No decision about me, without me"—which is fundamental to the current political healthcare agenda. The white paper *Equity and Excellence: Liberating the NHS* set out the government's vision of an NHS that puts patients and the public first, where "No decision about me, without me" is the norm. It included proposals to give everyone more say over their care and treatment, with more opportunity to make informed choices, as a means of securing better care and better outcomes.

Influencing the cancer sector includes:

- Integrated cancer care: the agreed model of care sets out the expectation that providers work together in integrated systems to deliver seamless cancer care.
- Political push: the delivery of high-quality cancer care has been an area of focus in the UK for the last fifteen years.
- Stratified medicine: We are now treating the biology of cancer rather than cancer. We have a greater understanding of the biology, so we can identify new genes, predict a likely outcome through biomarkers, and target treatment where the biology is likely to respond. But to do this, large numbers of samples are needed, which is difficult for the less common and rarer cancers. A particular challenge for the coming decade will be the increasing stratification of treatments and their tailoring to much smaller subsets of patients.
- Data is a valuable commodity: an ongoing modernization of cancer registries, combined with new datasets now either mandated for collection or in the process of being mandated, is making a step change in the data available.
- Advances in technology are making it possible to measure personal outcomes, such as improvements in confidence and well-being.

All these are measurable and provide an opportunity for driving change in any healthcare setting. But the "what to measure" and the "how to measure" when the human condition comes into play mean that what was perhaps clean, tidy, and focused in a clinical setting now becomes chaotic, messy, and broad.

New research paradigms are changing the way we collect, measure, evaluate, and act on the data we have; but this is in its infancy. Many of the existing outcome measurements have not been designed for the sort of population-level outcomes we need, nor do they reflect local-level, subset, or key groups of patients—or even what matters to them. Much of the data we need to be using lies in care data systems, as well as those that exist in acute and primary care.

We now have a combination of individual biomarkers and population-wide comparison datasets being mandated, all of which should be transforming research and clinical care into a new paradigm. In this new world, we become responsible for monitoring our bodies, noticing deviations from trends, and making appropriate changes. Using this paradigm allows us to become copilots in our care, so that a new model of

maintenance of wellness, as well as treatment of illness, becomes the norm. We see this in the number of health apps that have flourished; digital health has developed into a sound business, attracting players from various industries outside healthcare. While 60% of stakeholders in digital healthcare are from the health industry, 40% are not from the health industry. These stakeholders are mostly IT and tech companies, and consulting companies or agencies. In 2017 there were 325,000 health apps, with 78,000 new health apps added to major app stores in that year alone. The supply side of the market for mobile health apps shows robust growth of 25% year-on-year. And so the world is growing flatter, blending health and healthcare that is unbounded by place or time. We have lots of data, oceans of data, but only puddles of meaning. The challenges are aggregating smaller data into big data (and back into personalized small data), analyzing big data in appropriate clinical, social, and environmental contexts, and drawing scientific conclusions that show validity.

Using this multidimensional approach means that data can be gathered at:

- Individual level (progress tracker, Patient Activation Measure [PAM], Patient-Reported Outcome Measures [PROMs], and quality-of-life questionnaires): these take into account individuals' experiences and desired outcomes, sense of well-being, quality of life, disability/ability, emotion, sense of social support, and confidence to self-manage.
- Service and organizational level (Person Centered Care Assessment tool, Health Literacy Questionnaire, Consultation and Relational Empathy [CARE] Measure): this focuses on the people who are using the services and access to timely and appropriate services and outcomes for workforces, and should also align with individual-level data.
- Commissioning and planning level (population-wide and local-level data): Outcomes for local people, impact of local services, and associated health economic effectiveness can help commissioners support current services and develop new ones to promote self-management support. Informed, meaningful involvement of people living with a brain tumor, measurement, and evaluation create insight to drive the changes needed.

What to measure

The WHO defines quality of life as:

> An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships, and their relationship to salient features of their environment. (World Health Organization, 1)

Health-Related Quality of Life (HRQOL) is multidimensional and about global well-being. It is a broad term that involves all the things that make us who we are, e.g., physical, social, cognitive, emotional, and spiritual:

Figure 3.3.1. Examples of physical, social, attentional, spiritual, or emotional changes that may accompany brain tumors and their treatments. Design: Brainstrust.

It therefore follows that the measurement of health and the effects of healthcare must include not only an indication of changes in the frequency and severity of diseases but also an estimation of well-being. This can be assessed by measuring the improvement in the quality of life related to healthcare. Although there are generally satisfactory ways of measuring the frequency and severity of diseases, this is not the case in so far as the measurement of well-being and quality of life is concerned.

There is a widening gap between the "traditional" approach to the epidemiology of cancer and questions that the clinical and patient communities have, and so there is a need to broaden the discourse around the epidemiology of care so that some of the wider questions that patients, caregivers, and clinicians have around HRQOL can be addressed. There has been a need, and the scope, for an evolving registration service to develop the conversation about cancer beyond such traditional indicators as:

- one-, three-, and five-year survival;
- mortality and morbidity;
- prevalence;
- incidence;
- gender;
- age.

In brain cancer this has provided an opportunity to look at national registry data in new ways to address important questions for the brain tumor community and to establish a process that can be used by other cancer sites. This project led to recommendations being made to make, shape, and drive change so that both the quality of life and service delivery for people who are living with a nonmalignant brain tumor (NMBT) are more relevant, meaningful, and supportive. The data has been analyzed, so we now know that:

- NMBTs are a diverse group of tumors.
- About 9,000 primary brain tumors are diagnosed every year; 50% are nonmalignant.
- More than one in ten people with a NMBT will not survive the first year (over 550 people annually).
- When crude and net survival data is considered, there is hardly any difference in the > 69 age cohorts.
- People with a NMBT are unlikely to be diagnosed through A&E.

Analyzing and then interpreting the data using the drivers that have come from the brain tumor community has led to the following four key recommendations for everyone living with an NMBT:

1. There must be an increase in public understanding, resources, and information.
    - Support for people living with an NMBT should be stratified more effectively according to a clear set of determinants.
    - Relevant and timely models of support should be developed, including high-quality information and involvement of palliative support.
    - There must be parity of voice between nonmalignant and malignant brain tumor communities.

Because primary brain tumor patients have an incurable disease, HRQOL is becoming an important outcome measure in clinical trials and in the management of disease throughout the illness trajectory. In addition to generic HRQOL instruments, disease-specific questionnaires have been developed, including for brain tumor patients. It has been demonstrated that by assessing symptom burden at diagnosis, HRQOL can be measured using self-reported, validated questionnaires, addressing physical, psychological, emotional, and social issues. This can be predictive of outcome, including progression-free survival and overall survival.

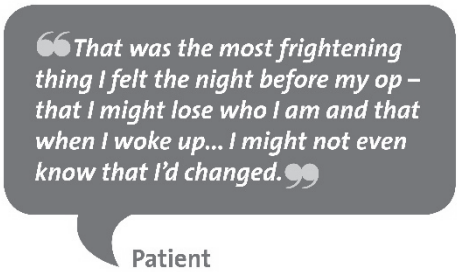
The considerations of measuring HRQOL in people living with a brain tumor are varied. Gathering data around HRQOL is in its infancy, but we have seen sustained interest over the last twenty years. The approach, however, remains fragmented, with no real strategic overview; this is only going to become worse as more people are diagnosed with metastatic brain cancer as they live longer with the primary cancer. More treatments are being trialed, which bring potential morbidities. The doubling and tripling of therapies mean that HRQOL will need a paradigm shift. Across all cancers, we have clinical uncertainty around data quality, and a lack of public understanding and trust about how data is collected, used, and stored. There is a heavy focus on outcomes and a lack of clarity about what it is that we want to know. Path dependency is also an issue: with personalized medicine, people do not follow the same pathway for their disease. It is no longer one size fits all. Brain cancer brings its own challenges. Brain tumors constitute a less common cancer group, with complex effects on both patients and their caregivers. High rates of physical and cognitive morbidity differ in nature to other cancers and may require alternative supportive and palliative interventions to address both

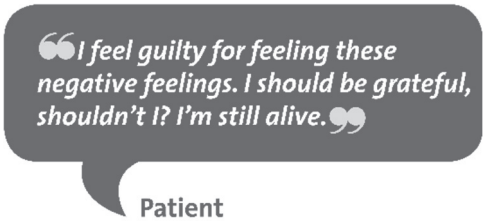
the impact of the tumor and its treatment. It comes with a high attrition rate. The symptoms cover a broad spectrum: at one end of the spectrum, people can exhibit apathy and indifference, and at the other, egocentrism, disinhibition, and aggression. We know through research what the problems are, but we are still novices when it comes to understanding what the impact is. We find it hard to disaggregate what is tumor effect and what is treatment effect, and there is also the uncertain trajectory. Decline can be insidious, over time, or happen very quickly, within a few weeks. Yes, we have validated measurement tools, but none of them do everything, which means that multiple assessments have to be done in a variety of forms. And so for the analysis and interpretation of HRQOL measurements, low compliance and missing data are methodological challenges. It's a big ask for someone who is living with a life-limiting prognosis, whose mental capacity may well be compromised, and who is facing progressive cognitive decline.

In our daily interactions with the brain cancer community, the sentiments expressed more than anything others are:

- the threat to way of life;
- lack of behavior controls;
- the impact on relationships;
- systemic problems that lead to isolation;
- access to support.

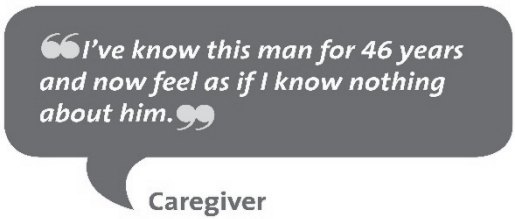
The task, as identified by the EANO guidelines for palliative care for adults with glioma, is to address these gaps so that the community feels as though it has resources and so that there is a better understanding of the uniqueness of the challenges that living with brain cancer brings. Day-to-day interactions tell us we are not there yet. The experience is a loss of relational closeness, and social inactivity, and people are distressed by changes and the potential future disutility, and feel guilty from the distortion of family life that they have caused.





Caregivers have a different discourse. Their quality of life is compromised when they have to:

- be an enabler for others;
- be secure with uncertainty;
- be open with not knowing;
- take risks when their appetite for risk is diminished;
- ensure that their inner dialogue is constructive;
- be strong for others when they themselves are falling apart.



People living with a primary brain tumor face serious and life-changing challenges, which have been well catalogued in the previous chapter. Despite these well-identified problems, there are few well-tested

interventions to improve HRQOL, and guidelines about how to manage symptoms remain impoverished. There is, however, much that can be done to exert commentary and develop strategies to ensure that HRQOL is front of mind. Through building on national and local guidelines, responding to the needs of cohorts of people, and shifting to an asset-based model of healthcare, we can focus on achieving well-being rather than treating well-being as an afterthought.

How to measure

Information is power—but only when it is the right information. Healthcare's love affair with data is rooted in the centuries-old tradition of rigorous medical testing and research, plus the need to keep detailed patient records. Selecting the right data, in the right form, that is meaningful and useful, has become a critical task, and selection has to meet complex needs. It is essential to understand the viewpoint of recipients of the healthcare system and equally important to integrate it into decision-making that leads to rational budget allocation, deployment of healthcare resources, and access to these services. It sets a high bar when deciding how to measure HRQOL.

The recent brain tumor James Lind Alliance Priority Setting Partnership (PSP) gives context to the priority of research in this area in neuro-oncology. Traditional gold-standard metrics for outcomes in cancer treatment trials include time to disease progression and overall survival. However, there is increasing public and healthcare recognition of the need for anticancer treatments—in addition to supportive and palliative interventions—to also demonstrate improvements in patient-focused outcomes, such as function and quality of life.

This is particularly so in conditions with poor prognosis, such as high-grade glioma, where maintenance of cognitive function, physical function, and quality of life throughout the disease trajectory becomes a key additional consideration alongside very modest survival benefits. To measure quality of life, the concept of HRQOL was developed, but at present, no single gold-standard also exists. Generic and disease-specific tools need development and validation.

Patient-Reported Outcomes (PROs)

One method that has gained traction is the use of Patient-Reported Outcomes (PROs). These are measures that are directly reported by patients and that reflect their personal experience of their disease and its

treatment. PROs allow patients to provide their perspective about their health and the health services that they receive. Often, PROs seek to garner data that only patients themselves can provide, such as a condition's impact on quality of life, or pain. PROs are without interpretation or amendment of the patient's response by the healthcare team, partner, or anyone else. Gathering data about PROs can help stakeholders in the health system improve policies and services to meet the needs of patients.

The questionnaires, or instruments, that measure PROs are called Patient-Reported Outcome Measures (PROMs). These can be either generic, which measure an individual's well-being across many dimensions, or condition-specific, which ask questions that are specific to a disease or intervention. Validated PRO measures that are commonly used in clinical research are well documented, and it is generally accepted that, for clinical research, PRO measures need to be used together with other clinical outcome measures. The measures commonly used have arisen through a need to address a clinical trial research objective:

- Efficacy: does the drug provide superior improvement in disease-related symptoms or functional deficits?
- Safety/tolerability: describe the patient's experience while receiving the anticancer therapy.
- Validity (does it measure what it is intended to measure?), responsiveness/sensitivity (sensitive to change or to differences between groups), and reliability (the ability of a measure to create reproducible results) also need to be considered, and in trials evaluating treatment for people with incurable cancer, survival and its quality are the most important endpoints.

A PRO should always be a co-primary endpoint (it is rare to see this), and moving to more use of PRO measures in survivorship care has the potential to improve patient–caregiver–healthcare team communication, symptom management, and quality of care.

PROs constitute one component of a group of patient-focused measures collectively termed Clinical Outcome Assessments (COAs). Clinician Reported Outcome (ClinRO) measures, Observer Reported Outcome (ObsRO) measures, and Performance Outcome (PerfO) measures are others (see figure 2).

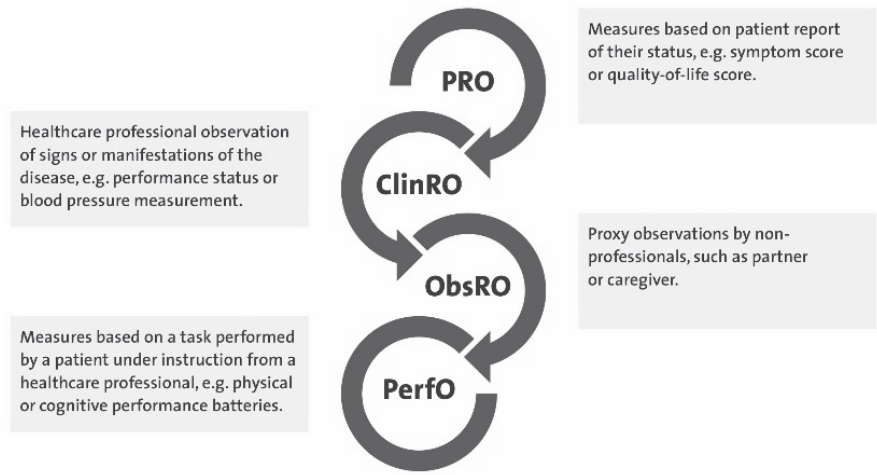


Figure 3.3.2. Examples of Clinical Outcome Assessments. COAs are based on patient, professional, or caregiver assessment and interpretation. Design: Brainstrust 2019.

In healthcare settings with an increased focus on patient-centeredness, PRO measures in clinical practice are becoming critical to the comprehensive evaluation of the benefits and side effects of treatment, and in informing healthcare policy, guidelines, and treatment.

However, this is only possible when there is consistency of approach in the types of measure used, accuracy in matching those measures to the outcomes expected of an intervention, and diligence in data capture, analysis, and reporting.

A lack of due attention to these principles for wider clinical trial outcomes in healthcare is well documented. Inconsistencies in use and bias in reporting are widespread. For example, a systematic review identified that in oncology trials, over 25,000 outcomes were only used and reported once or twice. Reporting of outcomes is often selective, and information on how missing data has been handled is often absent.

PROs face similar challenges. In oncology trials using PROs, often either analyses are not reported or the clinical relevance of PRO results are ignored. A systematic review of glioma randomized trials that used PROs has found that only 14% of these trials met the criteria for high-quality reporting. Remarkably, PRO results were not interpreted in 79% of the trials, and clinical relevance was not discussed in 86% of

studies reviewed. There is also a lack of consensus on which PROs to use in brain tumor trial settings.

Specific challenges for brain tumor patients and their families include the clear definition of outcomes that are person-focused and measurable, and the conducting of fast and efficient trials in an often-deteriorating patient population. The complexity of the causes of symptoms and the distress in people living with a brain tumor make it difficult to evaluate supportive and treatment effects. Despite large variation in the type and location of a brain tumor, treatments, and prognosis, all patients with brain tumors may suffer from impaired functioning. The Response Assessment in Neuro-Oncology Patient-Reported Outcome Group (RANO-PRO) policy review provides guidance on the use of PRO measures in clinical studies and in clinical practice for adults with brain tumors. In conjunction with its guidelines on the collection, analysis, interpretation, and reporting of PRO data, the RANO-PRO guidance might help to improve the PRO evidence derived from neuro-oncological studies, which in turn may inform the research community, policy makers, clinicians, and the people who are living with a brain tumor and who need to be involved in the treatment decision-making process.

The role of new technological solutions that can enable PROs to be structured to measure, document, and communicate to improve the patient's health outcome and survivorship care has been acknowledged. Greater flexibility in the use of PRO measures would encourage patients to report when it is better for them, in real time and when they are able to respond. Using activities of daily living and real-world evidence are gaining ground as a means of sharing or visualizing shifts in HRQOL in a way that everyone can understand.

Activities of daily living (ADLs)

An established method of measuring patients' functioning and collecting patient-reported outcomes is the use of activities of daily living (ADLs). ADLs are used as a measurement of a person's functional status, a concept first proposed in 1950 by Sidney Katz, who developed the first evaluation tool, called the Katz ADL scale. ADLs consist of Basic ADLs (BADLs) and Instrumental ADLs (IADLs). BADLs are more essential for survival than IADLs, which are not necessary for fundamental functioning; but IADLs let an individual live independently in a community. IADLs also seem to be sensitive to the early effects of cognitive decline, and since

cognitive decline is characteristic of brain tumor patients, measuring IADLs is especially relevant.

Activities of daily living (ADLs) are basic tasks that must be accomplished every day for an individual to thrive. Generally, ADLs can be broken down into the following categories:

Personal hygiene
Bathing, grooming, oral, nail, and hair care.
Continence management
A person's mental and physical ability to properly use the bathroom.
Dressing
A person's ability to select and wear the proper clothes for different occasions.
Feeding
Whether a person can feed themselves or needs assistance.
Ambulating
The extent of a person's ability to change from one position to the other and to walk independently.

Understanding how each category affects a person's ability to care for themselves can mean the difference between graceful and independent living and needing daily assistance.

Instrumental activities of daily living (IADLs)

Instrumental activities of daily living (IADLs) are somewhat more complex but nevertheless reflect a person's ability to live independently and thrive. IADLs thus include securing assistance for:

Companionship and mental support
This is a fundamental and much-needed IADL for daily living. It reflects the help that may be needed to keep a person in a positive frame of mind.
Transportation and shopping
How much a person can go around or procure their grocery and pharmacy needs without help.
Preparing meals
Planning and preparing the various aspects of meals, including shopping and storing groceries.
Managing a person's household

Cleaning, tidying up, removing trash and clutter, and doing laundry and folding clothes.

Managing medications

How much help may be needed in getting prescriptions filled, keeping medications up to date, and taking meds on time and in the right dosages.

Communicating with others

Managing the household's phones and mail, and generally making the home hospitable and welcoming for visitors.

Managing finances

How much assistance a person may need in managing bank balances and checkbooks, and paying bills on time.

Asking about a patient's ability to complete their ADLs and/or IADLs, however, may be a simpler way of assessing HRQOL, as it takes into consideration an individual's physical and cognitive abilities. While ADLs are defined as everyday routines generally involving functional mobility and personal care, such as bathing, dressing, toileting, and meal preparation, IADLs are the daily tasks of using the telephone, managing money, preparing meals, doing light housework, shopping, and doing heavy housework, which require higher, intact cognitive abilities that enable a patient to live independently in the community.

When aligned with Maslow's hierarchy of needs, there is a clear correlation to ADLs:

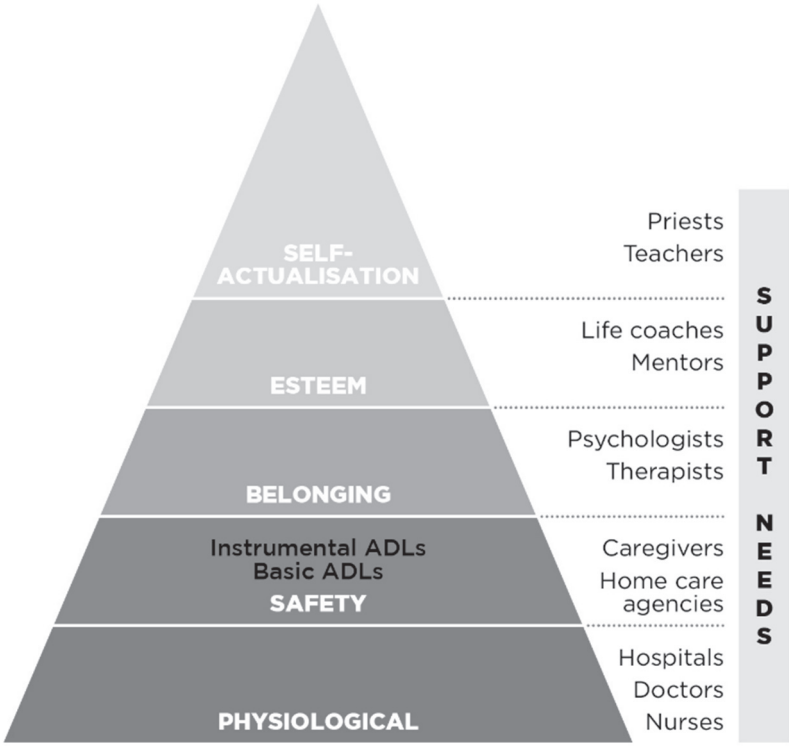


Figure 3.3.3. Maslow's theory aligned with IADLs and BADLS. Design: Brainstrust.

Maslow's theory is that we spend our lives satisfying needs at each step and then moving on to the next. However, when we encounter injury, illness, or the death of a loved one, we metaphorically move down the hierarchy. In the case of being diagnosed with brain cancer, one may fall all the way down to the first level. At that point, the needs could be for breathing, food, water, sleep, and excretion. Maslow called these needs physiological, but they could equally be considered ADLS. As we move up the hierarchy of needs, we experience a sense of accomplishment, with our ultimate goal being self-actualization. However, when something happens, we move down one or more of these levels as we experience fear and a sense of loss. With the onset of disability, needs become reprioritized. A person with new onset disabilities will respond to lost function by looking for a new equilibrium of mind and body within the

physical and sociocultural environments surrounding them. The equilibrium achieved depends on which lower-level goals are achieved within that environment. We all want to regain our functionality and climb back up as high as possible. Failing that, we want to remain at the level we are at for as long as possible.

ADLs and IADLs, therefore, have the potential to not only measure functional ability but also enable the patient to focus on rehabilitation that is meaningful to them. The degree to which the achievement of lower-level goals feeds into higher-level goals determines the relative meaning of those goals to life. By establishing meaningful higher-order goals, the patient can be encouraged to achieve them through more concrete lower-level goals, highlighted by ADLs and IADLs.

The currently developed EORTC IADL-BN32 questionnaire is proving to be a valuable asset in assessing IADL functioning in brain tumor patients and goes some way to addressing the identified gaps; however, it is acknowledged that further validation in phase four is required and is planned.

Real-world data (RWD) and real-world evidence (RWE)

It is increasingly clear that real-world data (RWD) and real-world evidence (RWE) will become key elements of healthcare decision-making. As diseases are becoming more stratified—and treatment more personalized—RWE has the potential to support clinicians and patients in targeting the right treatment to the right patient at the right time. RWE can provide a range of information about a treatment, including efficacy, safety, and effectiveness, and data can be gathered at all stages of the patient pathway. This data is collected outside the highly controlled environment of a traditional randomized controlled trial (RCT) and can include data generated during clinical practice as well as from outside the clinic, such as through a range of sources, including wearable biosensors, social media, and patient-powered research networks, and more accepted sources, such as healthcare databases, electronic health records, and patient registries.

There are one million patient interactions with the NHS every day, each generating multiple pieces of data. When this is coupled with the information generated by the explosion of wearable devices and consumer biosensors, society now has more data than ever before to inform healthcare decisions. By giving patients more control over their own health, and extensive knowledge about their disease and symptoms, these devices are reducing the amount of time and money spent on expensive

medical procedures and doctor's visits. Plus, doctors and medical experts have access to real-time information about their patients, which helps them be more efficient.

Real-world evidence (RWE) can provide a range of information about a treatment or clinical pathway, such as efficacy and safety through to understanding clinical practice and disease stratification, generated using real-world data (RWD). There is, however, some confusion about the definition of RWD and its subtypes. The United States Food and Drug Agency uses the following definitions:

> ***Real-World Data (RWD)*:** RWD are the data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources. RWD can come from several sources, including electronic health records (EHRs), disease registries, and patient-generated data.
> ***Real-World Evidence (RWE)*:** RWE is the clinical evidence regarding the usage and potential benefits, or risks, of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including, but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).

While there are undoubtedly benefits to the whole healthcare system from the use of RWE, it is ultimately people living with the disease that stand to benefit the most. Improving understanding of a disease and the burden of illness, accelerating, or facilitating, clinical trial recruitment, and reducing costs and risks to the development of new therapies will reduce the time and cost to bring new treatments to patients. Equally, the improvement of the patient experience of existing treatments, and the procurement of treatments linked to effectiveness, all serve to improve patient outcomes, including HRQOL. Currently much RWE is fragmented between datasets, including electronic medical records, patient registries, and other datasets. By linking and curating this data, and then applying artificial intelligence algorithms and machine learning, it is possible to analyze large datasets and potentially predict treatment response. This will allow for the development of clinical decision aids and enable clinicians to target the right treatment to the right patient at the right time, as well as enabling presymptomatic patients to be found more rapidly, and also predict positive therapy outcomes. This is particularly relevant in the less common and rarer cancers, where it has been hard to make progress in treatments due to the smaller cohorts of patients. In addition, there is also the weight

of decision-making. With a malignant brain tumor, the capacity to make decisions decreases with disease progression, and the weight of decisions increases with progression.

So, what is needed to ensure that RWE becomes a standard measurement of the patient experience? If the potential is to be exploited, there is further work that needs to be completed. The challenges, though, are many and varied:

- Education has a key role to play. We need to build a learning healthcare system that understands the importance and benefit of RWE and how it can ultimately improve patient experience and outcomes, where RWE generation is embedded as part of clinical practice, fostering a research culture within the healthcare system that closely engages clinicians and patients.
- There is a need for regulators and health technology assessment (HTA) bodies to provide further clarity on the acceptability of RWE and provide guidance on where different types of RWE might be applied to assess safety and effectiveness.
- Leadership and guiding principles are needed on the acceptability of different types of RWE in different contexts—what RWE is used, and how—to be developed by regulators and buying from stakeholders wherever possible. This will provide direction and ensure consistency in approaches to using RWE.
- We need a shift in the perceptions of key stakeholders around the utility of RWE and how different types of RWE might fit into evidence for different uses, developing a richer repository of case studies demonstrating the robustness of RWE for different purposes or its limitations, and for better understanding the practicalities of collecting and interpreting RWD and RWE, and where further research is needed.
- A consensus in terminology is needed surrounding different evidence types to ensure that they are clearly defined and used consistently. While progress has been made and there is a coalescence around the meaning of broad terms in this field (as happened in precision medicines), there are still variations in the terminology around RWD and RWE. There is a role for academia, industry, charities, and the healthcare profession to come together and agree the standardization of these terms and their definitions, perhaps under the auspices of a respected third-party organization. Standardization will not only save time and help frame the public debate but will also reduce the

familiarization time required when different institutions and organizations begin working together on a new project. This also encompasses the identification of technologies and bringing together guidance for data standards and interoperability to ensure the baseline collection of high-quality RWD.

- The need for a fit-for-purpose data infrastructure to support linked, multisource datasets. This includes technology: the right interface (or coordinated interfaces) is needed so that data can be used efficiently and safely. With more and more health and care data being created in healthcare settings, the importance of interoperability between different sensors and systems becomes vital if datasets are to be connected and useable at scale. This requirement is exacerbated further when consumer wearable and other app data is included that can help build a broad picture of a patient or cohort. To make this a reality, it may require investment at all levels of the health system to ensure that systems have the capability and connectivity required to "read" the data without compromising patient confidence and confidentiality.
- Privacy and consent issues around data access through public and patient engagement need to be addressed. While there is undoubtedly positive work being carried out by enthusiastic and digital-native early adopters, patients and the broader public will look to trusted healthcare professionals for reassurance about the use of their data. Currently there is trust in the misuse of data—we believe it will be misused.
- Improved capability and capacity in data extraction and analysis.

Discussion: person-centered outcomes, not patient-reported outcomes

> I'm a doctor, and now I'm a patient. My quest for knowledge is different from what I thought it would be before I was diagnosed. (Cancer patient, 2018)

The transcendental nature of the importance of quality-of-life data, from the decisions that people make about their personal health, to organizations striving to meet these needs, and ultimately the governmental role in assuring a nation's health, means that it is essential that our approach is one of collaborative working. This ensures that the public and patient perspective is central to the narrative. This perspective

is vital to help us navigate the dualities of competing and complementary demands, risk, and benefits to safety, which are often overplayed or underplayed, our appetite for privacy (or not), the complicated nature of reputational risks and returns, and of course, the views of a community of people who have a varied understanding of health-related quality of life, and diverse expectations about what quality-of-life data can help them achieve, in the face of exceptionally challenging life stressors.

Our daily interactions with the brain cancer community tell us, however, that the gathering of such collective intelligence is elusive, and this approach remains challenging for the following reasons. There is a mind-set with some clinicians that once a patient is through a particular phase of their care pathway, they become "somebody else's problem," even if the treatments and disease have left the person with complex (or even simple) rehabilitation needs. It has been noted in the UK that there is "a disproportionate focus on surgical and oncological outcomes" in brain cancer (National Cancer Action Team). Integrated cancer care—the agreed model of care—sets out the expectation that providers work together in integrated systems to deliver seamless cancer care. Having HRQOL indicators validated and accepted will help everyone achieve better outcomes for all—patients, their caregivers, service providers. For improved survivorship, close collaboration is required between providers and clinicians involved in rehabilitation, supportive care, quality of life, and psychological and palliative care to plan for transition in points of care. This requires coordination of different specialties and expertise from symptom management to end of life.

As stated earlier, we have numerous ways of measuring HRQOL, but few of these measures come from the perspective of patients. We tend to measure what we *can* measure, rather than what we *should* measure; it's all too easy to park things in the "too difficult" box. And then, of course, this leads to organizations and individuals orienting themselves in order to deliver on what is measured. So if we collect objective system data, we will organize our delivery system accordingly and, in doing so, run the risk of losing track of what matters to people like Andrew, described at the beginning of this chapter.

If we want to put people first, we need to put person-centered measures first. The right measure in the right place can be transformative, and equally, the wrong measure in the wrong place can be transformative. Humanizing measurement is never going to be easy, as it is never going to be one size fits all, and so we need to get the right measures in the right place by thinking about context and coherence.

Eliciting from Andrew what matters to him, what his core values are, his context, and his appetite for risk would be a transformative conversation, not just for him but for all of the people who are helping him. This places Andrew as a copilot in his care, so that he is regarded as an asset, with his own sense of resourcefulness, with his own unique range of capabilities. Yet discussing PROMs with him would not elicit this information: they are predefined outcome measures that probably won't take into account what matters to Andrew.

There is little evidence that PROMs are used as a measure to improve person-centered processes, and there is often little logical connection between some person-centered processes and PROMs. So we need to embrace the new world order of data and use this to combine person-centered process and outcome measurement. We now have a raft of new patient data that could only have been imagined twenty years ago. These advances, coupled with improvements in computer processing power, social change relating to the use of technology, and the introduction of artificial intelligence and machine learning in order to process that raw data and turn it into insight, mean that we are on the cusp of a transformative period in healthcare. The routine and effective use of big data in healthcare will be as dramatic a change for the modern health sector as the introduction of penicillin was during the 1940s. Used with careful consideration, this change should shift the metrics from preserving life to enhancing quality of life. It should take the discourse around data beyond the traditional indicators of age, morbidity, mortality, gender, and incidence. It should improve relationships, so that better discussions are held with clinical teams, strengthening clinical relationships. It also must help people manage their expectations: they will be able to see how what they are experiencing compares with others in a similar situation ("patients like me"), and their input will improve living with and beyond cancer as more data becomes available about the longer-term impact of treatments. Such data will add color to other datasets, such as early diagnosis; and then there is the health economic argument: in bringing the right resources to the right people at the right time, cost savings will follow. And finally, it must enable the development of services that will help people and their caregivers develop their own inner resources and resilience, on the basis of local need, so that they are copilots in their care. This in turn will improve patient experience of their treatment and care, an important indicator of quality.

We just need to ensure that Andrew is at the heart of this.

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CHAPTER 3.4

LATE EFFECTS

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Abstract

Patients with primary brain tumors face a disease with a fatal outcome, and have to endure symptoms related to the tumor and treatment side effects. Glioma patients with a longer course of disease may encounter late effects of tumor treatment, such as neurological impairment, seizures, fatigue, and cognitive disturbances, affecting quality of life and the ability to accomplish activities of daily living. To support the patient and the caregiver through active involvement and to analyze needs during the disease process, multidisciplinary care is mandated. With a case study of a neuro-oncology patient, the impact of the late effects of glioma treatment during the course of the disease is illustrated. Within multidisciplinary care, the neurology-oncology specialist nurse may act as a patient's care navigator.

Keywords: neurological impairment, neurocognitive disturbances, fatigue, seizures

Introduction

Gliomas are the most common primary malignant brain tumors in adults, and although rare (with a yearly incidence of 6 cases per 100.000 persons[1]) these tumors—low grade as well as high grade—have a fatal outcome. Glioma patients suffer from both cancer with a dismal outcome and from a progressive neurological disease, although prognosis varies from 15 months (for the most frequently occurring type of glioblastoma) to 10–15 years (low grade oligodendroglioma). Apart from headaches,

seizures, and focal and/or cognitive deficits, these patients may also present with, or develop, changes in personality and behavior,[2] which is unique to the brain tumor population compared with patients with systemic malignancies without central nervous system involvement. Glioma treatment is assessed to relieve symptoms and influence the outcome. However, treatment is not curative: eventually the tumor will recur.

The various therapeutic and symptomatic treatment interventions in glioma patients may damage the central nervous system (CNS). The most well-known late side effects of glioma treatment are fatigue, focal deficits, seizures, and, frequently, cognitive disturbances, which alter cognitive, emotional and/or physical performance. Consequently, the majority of primary brain tumor patients—regardless of the grade of the tumor—have multiple impairments often resulting in great suffering and low health-related quality of life (HRQoL). These impairments negatively influence activities of daily living and greatly affect the brain tumor survivor's ability to fully participate in expected roles at home, school, and work.[3] Specialist nurses can play a key role in these matters by guiding patients and their family caregivers from diagnosis until death. They pay attention to side effects of treatment and symptom management, trying to improve quality of life with the use of evidence-based guidelines and supportive care.[4–5] With therapies that significantly prolong survival it is important to understand the impact of treatment—and its late effects—on cognitive function and quality of life,[6] and gain insight into treatment recommendations and the optimalization of supportive care.

This chapter will focus on the different late effects of treatment in brain tumor patients, related to therapeutic interventions such as neurosurgery, radiotherapy, chemotherapy, and symptomatic treatment with medication (e.g., AEDs and dexamethasone). Furthermore, the role of the nurse specialist (NS) in providing supportive care for brain tumor patients is elucidated.

Background

Antitumor treatments and supportive therapies in brain tumor patients, aiming at improved survival and HRQoL, also produce side effects. While patients with benign brain tumors who undergo curative therapy, are frequently left without sequelae, most patients with malignant tumors face a condition that predisposes them to neurological impairment, seizures, and cognitive disorders. Impairment of neurological and neurocognitive functions, remaining or developing during the course of the disease, are very common in brain tumors patients, both as a result of the direct effects

of the tumor and its surrounding edema and the sequelae of therapy. As treatments for brain tumors improve in relation to survival, it is likely that these complications will increase, similar to the situation encountered with childhood survivors of brain tumors, as we learned from Ness et al.,[3] who studied physical limitations and neurocognitive function in 78 childhood brain tumor survivors. Most of the participants had astrocytomas and were 14.7 years after diagnosis, with a median age of 22. Of the participants, 77% underwent a resection, 67% received radiation, and 31% received chemotherapy. The results showed that physical performance and neurocognitive deficits were evident among long-term brain tumor survivors when compared with the general population, limiting the ability to participate fully in life roles. Late effects of radiotherapy treatment have been investigated by Klein,[7] in which the aim was to differentiate between the effects of the tumor (e.g., disease duration, lateralization) and treatment effects (neurosurgery, radiotherapy, antiepileptic drugs) on cognitive function and on the relative risk of cognitive disability. The main conclusion of the study was that many factors contribute to cognitive deterioration, but when comparing healthy controls, patients with haematological malignancies, and irradiated low-grade glioma patients, the last group showed worse cognitive functioning. In a study by Douw[8] of a cohort of long-term survivors of LGG (with a mean of 12 years after first diagnosis), patients who did not have radiotherapy had a stable cognitive status, while patients who underwent radiotherapy showed a progressive decline in attentional functioning. Cognitive impairment has been described after radiotherapy, but the mechanisms leading to this adverse event remain mostly unknown.

In recent clinical research, patient-reported outcome measures, such as cognition, fatigue, and HRQoL, become more important in order to recognize late effects of treatment and initiate supportive and palliative (nursing) care interventions and develop guidelines to improve the HRQoL of patients and caregivers. In neuro-oncology practice, the NS is often a key contact for the glioma patient and for the healthcare professionals within the multidisciplinary team; the NS is responsible for the coordination and continuation of care; assessing the needs of the patient and acting as an information and educational resource; and providing patient-centered care and communicating through a multidisciplinary team.[9] In the following case study, several aspects of late effects are addressed.

Case study

A male patient presented with focal deficits in March 2005, he suffered from a left hemiparesis as well as inertia, on the basis of a tumor in the right frontal lobe. He underwent a resection, and pathology (pathology specimen of tissue pathology) showed a glioblastoma. The patient underwent chemoradiation treatment and six adjuvant temozolomide cycles. Nine months after the diagnosis he was working for 75% and was able to play the saxophone as he used to do. When asked about side effects, he admitted that he had some difficulty with his memory. Although the MRI showed the disease was stable after three years with an unchanged clinical condition, his spouse mentioned that his level of energy was slowly decreasing. There were no abnormalities found in his thyroid function or glucose. In 2008—three years after diagnosis, at the age of 58, the patient was no longer able to work. In May 2010, the patient had temporary focal deficits in the left half of his body as a result of focal epilepsy, for which he was started on valproic acid. In December 2011, he had another episode of temporary focal deficits in the left side of the body without radiological signs of tumor progression. Previously on a low level of valproic acid, the dose was increased. Revision of the tumor sample in 2012—seven years after the initial diagnosis—showed a glioblastoma; however, there were some characteristics of a possible earlier existing low grade glioma, a so-called pleiomorf xantho-astrocytoma, which could be responsible for the favorable course of the disease.

After having a heart attack in December 2012, the patient was referred to rehabilitation, to improve his condition and self-esteem. He experienced a slow deterioration before this event, regarding strength in his left arm and his left leg. He complained of being less able to speak, as well as having less strength in the musculature of his mouth and jaws, which was worsening since the attack. There were also mild mood disturbances.

In retrospect, the deterioration of his condition and initiative had already started by the beginning of 2012. His spouse stimulated her husband to perform activities, but anxiety, uncertainty, and less initiative slowed him down. The patient started physiotherapy and occupational therapy, and underwent neuropsychological tests to improve daily structure with attention on executive functioning.

In 2014, the patient started visiting a psychologist because of fatigue and lack of energy. In 2015—ten years after his initial diagnosis—there were still no signs of tumor recurrence, despite the fact that it was more difficult for him to rely on the left side of the body and there was

greater inertia and fatigue. The patient had decided to stop visiting the psychologist. He started a new hobby, singing, because playing the saxophone was no longer possible. He cycled and played tennis, enjoyed his grandchildren, and had a good quality of life.

In April 2017, he was admitted to hospital because of a seizure and a post-ictal left hemiparesis. During admittance he suffered from recurrent seizures; the dose of valproic acid was increased and levetiracetam was added. The patient temporarily, during one week, received corticosteroids. The paresis of the left leg improved; however, a paresis of the left arm remained. An MRI did not show any tumor recurrence.

In April/May and August 2018, the patient was admitted twice, because of a deterioration in functioning. He repeatedly fell and was not able to get up. Coordination of the left leg was hampered and his strength was diminished. The MRI as compared with earlier scans showed a new small nodular enhancement that increased just a few millimeters in August. There was no leptomeningeal enhancement and we planned a follow-up MRI 3 months later. It was not necessary to prescribe dexamethasone, because of the absence of edema on the MRI. The patient was admitted to a geriatric rehabilitation clinic. After several urinary tract infections, the patient was again admitted to the hospital for pneumonia. Despite the fact there still is no convincing tumor recurrence, the patient is no longer able to live at home.

Neurological impairment

Impaired neurological function in glioma patients is dependant on tumor location. It is a broad concept, including different symptoms such as, aphasia, hemiparesis, hemianopia, and sensory problems that result in less coordination in movements. Patients with brain tumors may present themselves with focal deficits, and neurosurgical treatment may relieve these impairments. During the course of the disease, patients may deteriorate, with an increase in neurological impairment at the moment of progression. It is of interest that even without a recurrent or growing tumor on an MRI, impairment may become more apparent during the course of the disease, as the patient from the case study shows.

The patient from the case study was diagnosed with a right hemiparesis, which improved after initial treatment, and deteriorated during the course of the disease, without any signs of tumor recurrence. Fourteen years after the diagnosis, the patient was no longer able to live at home, because of neurological impairment as a late effect of the tumor,

related symptoms, and their treatment. Patients often address their concerns towards the NS who is responsible for the assessment of their needs, the management of side effects, and good patient education. Dexamethasone can be prescribed to help decrease the impairment due to tumor surrounding edema. Corticosteroids control peritumoral vasogenic cerebral edema and ameliorate neurological symptoms but it is known that they have many side effects, which also influence HRQoL and cognitive functioning. The incidence of corticosteroid toxicity is related to the cumulative dose and the duration of treatment. Myopathy is a well-known neurological side effect and typically produces proximal extremity weakness (particularly in the legs). Tapering or discontinuing steroids along with physical therapy might relieve these effects; however, recovery usually takes weeks to months. Physical and occupational therapy, to help adjust to impairment and maintain independence as long as possible is recommended.[10–11] Endocrine side effects of dexamethasone include hyperglycemia and Cushing's syndrome, which are usually reversible after steroid discontinuation. In patients with pre-existing diabetes, the insulin requirement may increase. Ultimately, prescribing corticosteroids will no longer have an effect on improvement of neurological impairment, due to tumor growth. In the end of life phase, they will be tapered and/or stopped, when the patient is no longer able to swallow medication.[12]

Fatigue

Fatigue is the most prevalent symptom associated with cancer and can have a broad impact on physical, emotional, and cognitive function. Fatigue can be associated with the cancer itself, or specific kinds of treatment, such as radiotherapy and chemotherapy. Depending on the patient sample and methodology used, prevalence of fatigue in patients with cancer is estimated to be between 60% and 90%. Fatigue was ranked most important among patients with 10 of 11 cancer types—of which primary brain tumors was one—when asked to rank lists of common concerns.[13] Expert clinicians in this study reported that most cancer-related fatigue was either treatment-related or both disease- and treatment-related with the exception of hepatobiliary cancers. Patients with brain tumors within this study listed within their top five patient-rated symptoms: lack of energy (fatigue) (44.0%); frustration at being unable to do things; inability to enjoy life; nausea; seizures.

In primary brain tumor patients, fatigue is a common symptom with 40%–70% reporting fatigue during the course of their illness. Fatigue may be perceived by patients as physical (e.g., muscle weakness) or

mental (e.g., lack of motivation, lack of energy), or a combination of both. The pathophysiology underlying fatigue is not well understood; it is often underreported, underdiagnosed, and undertreated. Fatigue is typically assessed through patient self-reporting;[14] applying supportive (nursing) interventions may improve HRQoL. Analysis of dimensions of fatigue and comorbidity and demonstration of possible metabolic and other causes such as psychosocial factors, referral to physical therapy, and time management are helpful in diagnosis and management of fatigue.

The patient from the case study presented with inertia. He reacted slowly and was less motivated to perform activities and work. After his surgery and subsequent treatment, he was doing well, and regained his motivation to work although he worked fewer hours. During the years that followed, he had a good quality of life; nevertheless, his story tells us that his performance slowly decreased. Three years after the initial diagnosis the patient was not able to work, act, and perform at the level he and his wife were used to. Seven years after diagnosis the patient and his wife were happy that there was no tumor recurrence, but life was not the way it was before the diagnosis. In the years following, he was less able to perform daily activities and eventually was no longer able to live at home. We referred the patient to a psychologist, a physiotherapist, and an occupational therapist. The spouse was also referred to the psychologist to help her cope with the situation.

Neurocognitive disturbances

Neurocognitive function is frequently impaired in cancer patients, in primary and secondary brain tumors as well as in systemic malignancies. Although recent research shows that factors other than chemotherapy (radiotherapy, hormonal therapy) can adversely impact cognition of breast cancer patients,[15] symptoms of cancer-related cognitive impairment as a late effect of chemotherapy include memory impairment, loss of concentration, speech and psychomotor deceleration, attention and learning coordination problems, and disturbance of executive functions. The symptoms may be transient but are often long-lasting, the latter negatively affecting functionality and quality of life.[16] However, in tumors arising from brain tissue, neurocognitive disorders may be present before the brain tumor diagnosis, suggesting that the tumor itself contributes to impaired cognition. The impact of radiation therapy and chemotherapy on neurocognitive function and quality of life is a critical consideration in the management of patients with lower-grade glioma with a good prognosis. Research on improvement of cognitive disturbances evaluated the use of

pharmacological agents such as methylphenidate and modafinil; however, there was no benefit seen for either psychostimulant.[17–18] A study of a cognitive rehabilitation program showed an effect on short-term cognitive complaints and on longer-term cognitive performance and mental fatigue.[19] Cognitive and behavioral interventions might improve cognitive disturbances and mood disorders in glioma patients and need a multidisciplinary approach.

The patient from the case study received chemoradiation and six adjuvant chemotherapy (temozolomide) cycles. He tolerated the treatment well, but suffered later in the course of the disease from fatigue, loss of initiative, and mood disturbances. These late effects, might be caused by the treatment, but it is not possible to exclude the attribution of the tumor itself, because the patient had initially—before any tumor treatment—presented with inertia. The NS frequently spoke with both the patient and his wife, and offered supportive care. Beside, other healthcare professionals aimed at improving HRQoL by offering therapy to help improve daily structure.

During and after the brain tumor treatment many factors play a role in the development or deterioration of cognitive disturbances and mood disorders: the presence of cerebral edema, the occurrence of seizures, the use of anti-epileptic drugs, neurosurgery, radiotherapy, chemotherapy, and corticosteroids.[16] With the recent development of modern irradiation techniques, the survival of patients has increased and mid- to long-term side effects have become more visible; this has been described as leukoencephalopathy, which has been defined by changes in white matter (e.g., demyelination), microvascular changes, and degeneration that are responsible for cognitive disturbances.[20]

Seizures

Brain-tumor patients may suffer from symptomatic epilepsy, caused by the brain tumor. A first seizure in an adult patient always necessitates an MRI, to help diagnose the cause of epilepsy. Tumor resection may positively influence the occurrence of seizures and gross total resection appears to be a strong predictor of postoperative seizure freedom.[14] Seizure recurrence after a long period of seizure control may signal progression or recurrence of glioma.[21] Radiotherapy and chemotherapy may also have a positive influence on the occurrence of seizures; however, some patients will always need anti-epileptic drugs (AEDs) to prevent them from having seizures. Late side effects of AEDs include cognitive impairment, myelosuppression, and liver dysfunction, many of which appear to be

more common in brain tumor patients. Overall, 24% of brain tumor patients on AED therapy experience side effects severe enough to warrant a change or discontinuation of AED therapy.[15]

The patient from the case study suffered recently from recurrent seizures without tumor recurrence, each seizure—and admittance to the hospital—lessened his ability to live independently because of decreasing physical performance. Beside, each new seizure might cause anxiety, because it reminds the patient of his tumor, and may predict tumor recurrence. The NS offers support, is a key contact with a low threshold, to guide the patients and caregiver in case of epilepsy. Good patient education by the NS aimed at compliance with AEDs, as well as coordination of AED care by discussing adjustment of AEDs if necessary, are a responsibility of the NS. In case of suspected tumor recurrence, an earlier MRI to evaluate the tumor will be arranged.

Recommendations

Patients with glioma may suffer from late effects of treatment, resulting in decreased HRQoL. Beside neurological impairment, cognitive disturbances, fatigue, and seizures, they face an incurable disease, with possible coping problems and mood disorders. The patient from the case study gives us an insight into a unique story—as each glioma patient does—of a glioblastoma long-survivor, different from most glioblastoma, and perhaps more comparable with low-grade glioma, due to the "favorable" course of the disease. In neuro-oncology practice, most glioma patients are guided througout the disease by specialized nurses, who are in close contact with the patient and caregivers, may become confidential advisers and counselors, assesses supportive care for patients with brain tumors, monitors and manages the symptoms of the disease and the side effects of treatments, and is in a position to communicate occurring problems with responsible physicians.

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CHAPTER 3.5

PALLIATIVE CARE

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Abstract

Increasing complexity in cancer and its treatment gives a more prominent role to palliative care, providing holistic care, and the assessment of problems in the physical, psychological, social, and spiritual domains. Palliative care has been particularly associated with advanced disease; however, a palliative approach can be provided from earlier in the disease progression and may allow an improved quality of life, improved symptom management, and less aggressive treatment, particularly in the later stages. It may even improve length of life. Palliative care should be provided by all involved in the care of patients—listening to their needs and wishes, facilitating communication and considering all aspects of the person's care. Some people may need more specialist palliative care involvement, when the problems are more complex.

The role of palliative care will also include allowing patients, and their families, to discuss all aspects of their care, including the risks and benefits of treatment and helping in these difficult decisions. Advance care planning will allow the patient the opportunity to express their views about future care, so that these can be respected if they become less well and are less able to make decisions themselves.

At the end of life, there is an increasing need to reconsider the continuation of treatment, as the aim of management is to maintain comfort and quality of life. This may include consideration of the stopping of treatment and withdrawal of some treatments, such as feeding, hydration, and ventilatory support.

The aim of care for all patients should be to maintain and improve quality of life and allow the patient to be fully involved in the decisions about their treatment and lives. Palliative care allows these issues to be considered throughout the disease progression, so that the patient can maintain the best quality of life and, if not cured, to die peacefully.

Keywords: Palliative care, quality of life, advance care planning, end of life, risks and benefits, communication

The role of palliative care

Palliative care is defined by the World Health Organization as:

> An approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering, early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. (WHO, 2002)[1]

Palliative care therefore aims to provide a holistic approach for patients and their families and in the UK this may be within an inpatient hospice, at home (including in care homes), in a day hospice or in hospital, with a Hospital Palliative Care Team. There is a multidisciplinary approach including medical, nursing, and other professionals, often together with volunteers.

Although these principles underpin all palliative care, there are differences in how the terminology is understood, both within the UK and in other countries. “Hospice care” is sometimes used interchangeably with palliative care but this is not always so. For instance in Germany a palliative care unit within a hospital aims at intervention in crisis and management of symptoms, whereas in-patient hospice care is mainly at the end of life.[2] There is a similar differentiation in the USA, particularly because in order to receive funding for hospice care, the patient should be within the last six months of life and have stopped any other medical intervention.[3]

There has also been discussion of the levels of palliative care and the European Association for Palliative Care (EAPC) White Paper on Palliative Care suggested three levels of provision:

- Palliative care approach: this should be part of all patient care, ensuring good communication with the patient and their family,

shared decision making and goal setting, and symptom management. All services should provide this basic care.
- General palliative care: this is provided by primary care professionals and specialist services caring for patients with life-threatening illness. Palliative care may not be the entire focus of their role but they should have additional expertise, acquired from special education and training.
- Specialist palliative care: this is provided for patients with more complex issues, which may not be covered by other services. The team would have this as their main activity and have received specialist training and continuing education.[2]

Thus, there is often confusion as to what care is provided by whom. This can lead to further confusion in the development of services. There is a need to provide care for patients and families at different levels, but with close collaboration between all the professionals involved. There is also a move to use a public health approach, including patients, families, professionals, communities, governments, and society, to improve care, particularly at the end of life, for all people with needs, regardless of diagnosis.[4]

Discussions of the balance of treatment

Chemotherapy may cause many different symptoms affecting all body systems. Moreover, many people will experience different side-effects, and in a study of breast, lung, and colorectal cancer patients, 86% reported at least one side-effect, 27% of which were severe, and 10% reported one to three side-effects, 10% reported four or five side effects, and 67% reported six or more side effects.[5] These side effects commonly are:

- Fatigue 85%
- Pain 75%
- Constipation 74%
- Diarrhea 74%
- Dyspnoea 71%
- Mucositis 71%
- Rash 71%
- Vomiting 63%[5]

There are also effects on the bone marrow, causing anemia and neutropenia, which may lead to life-threatening illness. The liver and renal

function can be affected by some chemotherapy. As there has been increasing possibilities for the management of bone marrow toxicity, using growth factors and bone marrow transplantation, the use of chemotherapy may have increased and led to an increased risk of neurotoxic effects.[6]

There are certain issues within the nervous system that may be seen with some chemotherapy treatment:

- Encephalopathy—acute and chronic;
- Stroke-like syndrome;
- Pseudobulbar palsy;
- Memory/attention deficits;
- Peripheral neuropathy;
- Chemotherapy-related cognitive dysfunction— "chemobrain."

There may also be an increased risk of other neurological issues, as chemotherapy may control visceral disease, and neurological control is less, and there may be an increased risk of seizures, focal signs and symptoms, increased weakness and fatigue, personality change, intracranial pressure effects with the extension and deterioration of a primary cerebral tumor or metastases or development of brain metastases, leptomeningeal metastases, or paraneoplastic syndromes.

There are also less obvious effects of continued treatment, whether by chemotherapy or radiotherapy. There may be increasing disease progression and an increasing risk of neurological sequelae. For instance, a person with breast cancer may develop brain metastases and be at risk of cognitive change, change in personality or seizures. These may develop independently of any treatment but be a result of progressive disease. Thus, there may be a complex discussion about the risk of serious disease progression, as well as treatment side-effects, when considering further management options.

All these side effects, both acute and chronic, are more pronounced as the patient deteriorates and the end of life approaches. The patient may also be experiencing symptoms and other issues due to the general deterioration in their condition and the deteriorating disease state, with increasing cancer burden. This period may last several months to one year; over this time, there needs to be a very careful balancing of the risks and benefits of further treatment, as the side effects may impinge on the quality of life, and even the length of life, with little benefit for the person.

Decision making and treatment discussion

The decision making is complex, involving balancing the benefits of treatment and the risks of side effects. This may be clearer when considering chemotherapy as first line definitive treatment if response rates are high. As the disease progression continues the benefits and risks are often more finely balanced. Decisions on adjuvant treatment, given to reduce the risk of recurrence after definitive surgery or radiotherapy, are often very nuanced: if the risk is already low then even highly effective treatment can deliver only a small absolute risk reduction.

The aim of treatment later in the disease should be for palliation—helping with the management of symptoms, aiming to improve quality of life, and, on occasions, providing extension of life.[7] However, for a person with advanced disease, who may be experiencing many symptoms from the disease itself, or previous treatments, the risk of further side effects and sequelae of treatment may be greater. Moreover, there are concerns that treatment could lead to serious infection or other issues and actually lead to an earlier death than if no treatment was given.

Patients have many fears when facing a diagnosis of cancer, in particular when the disease is at an advanced stage. The balancing of risks and benefits is difficult; studies have shown that the people who are more likely to ask for treatment to continue are younger, have young children, have a higher educational level, live with a partner, and (in this European study) be of non-European ethnicity.[8] In Japan, it was found that many people had chemotherapy near to death with a mean time of 100 days from the completion of chemotherapy to death, and 12.6% had treatment within 30 days of death.[9] The people who were more likely to continue treatment were younger (under 45 years old) and male with a lower and poorer performance score. Physicians also seemed to have an effect and those patients who had not been told about palliative care were more likely to continue. Thus, decision making seems to be related to characteristics and the feelings of the individual but this is influenced by the information and discussion by professionals.

Oostendorp et al.[10] studied the use of a decision aid for people with breast and colorectal cancer considering second-line chemotherapy. Many wanted information about treatment—94% wanted to know about adverse effects, 91% about tumor response, and 74% about survival.[10] The psychosocial characteristics of these participants could not identify clearly those who wanted more information, although it did seem that people with a lower fighting spirit, reduced cognitive avoidance, and a higher deliberation decision-making style, and those who perceived that there had

been a clear benefit of first-line chemotherapy, were more likely to ask for information.[10]

How these discussions are held can influence the result. There is some evidence that oncologists may not always explain the full details of adverse effects and Ramirez found that in the treatment of childhood cancers the acute side effects were discussed but late effects, which often would be neurological, were rarely mentioned.[11] Lack of clarity in these discussions generates problems for other members of the professional team. The nurse who gives the chemotherapy may find it very hard to continue with treatment, and faces conflicts if the patient and family insist on treatment when it seems that this could be deleterious and when they do not feel that their concerns are heard by patients, families, and oncologists.[12] Giving treatment to a very ill patient, and fearing that this not only would not benefit the patient but also could be harmful, may lead to moral distress.[13]

Patients' understanding of treatment regimes and the associated benefit and risk is often unclear. A survey of over 100,000 US patients who died within one month of diagnosis showed that over 27% received cancer directed treatment.[14] The characteristics of those patients who were more likely to choose treatment were younger age, lower comorbidity score, and private insurance. This may reflect that many patients do not realize that any treatment, for advanced disease, presenting late in the disease progression is at best palliative—69% of patients with metastatic lung cancer and 81% of patients with metastatic colon cancer did not understand that chemotherapy was unlikely to cure the cancer.[15]

It is important to ensure that patients and their families are aware of all the issues—the benefits and the risks—if they are to make a truly autonomous decision. There is always individual variation but the professional team should help patients with the decision in a shared approach. A crucial part of the palliative approach is to ground this in a holistic assessment including physical, psychological, social, and spiritual aspects. In this way, the views of the patient and family can be fully appreciated and decision making can be best facilitated.

Involvement of palliative care in early decision making

The early involvement of palliative care increasingly is widely advocated. The American Society for Clinical Oncology (ASCO), for instance, recommends that palliative care should be provided alongside oncology care for any patient with advanced cancer.[16] Studies looking at the effectiveness of palliative care vary in methodology and in quality

(including adequacy of sample size, recruitment, attrition, contamination of control groups, randomisation problems, and issues in assessing and detecting differences in quality of life). However, overall there is increasing evidence that palliative care is helpful and is certainly not harmful to patients.[16–19] There is increasing evidence that symptoms are better managed, quality of life improved, hospitalizations reduced, costs may be reduced, and treatment is less aggressive.[20]

A study in 2010 compared early palliative care involvement with standard oncological care with palliative care referral timed according to clinical judgment for people with non-small-cell lung cancer. The intervention group had improved quality of life, experienced less depression, received less aggressive treatment regimes, and lived longer—11.6 months compared to 8.9 months for the control group.[21] Other studies have shown improvement in the quality of life with increased discussion by patients of their wishes if they were dying and less distress.[20] Moreover, a trial in Italy has shown that early involvement of palliative care increased hospice care and admissions to the hospice and reduced chemotherapy in the last 30 days of life—18.7% compared to 27.8% in the control group.[22]

Palliative support with decision making may enable patients to make better decisions about chemotherapy as the disease progresses, with a reduced risk of serious adverse effects and premature death. The decision-making process may be enabled by allowing time for discussion, and listening to the concerns of the patient and wider family. This may be particularly important for some patients, for instance those who are predisposed to choose further treatment with little prospect of benefit.

The involvement of palliative care earlier in the disease—and often soon after diagnosis—may enable these decisions to be made more effectively, as suggested by the ASCO Guidelines. This decision support may in part explain the observed survival advantage for the early palliative care group in the Temel [20] study. There is a need to establish a shared decision-making process, where patients, families, and professionals are able to discuss and decide on the most appropriate treatment, taking into account all aspects—both positive benefits and the potential risks.

Risks of treatment and the issues of discussion of future care

Any decision to offer, or to accept, treatment involves balancing burdens and benefits in light of factors that are specific to the patient. The benefits

and burdens are complex. Benefits can be categorized into different kinds of benefit and different ways of evaluating benefit.

1. Kinds of benefit
    a. Additional survival
        i. Long-term cure. This is a goal of some treatments for some cancers in some patients, with variable probability and always subject to some degree of uncertainty. The only exception is where the probability is zero, that is, where there is no chance that the proposed treatment will achieve a cure. In this case, it should not be offered with this goal in mind. In quantitative terms, it is reflected by longer-term measures of the rate of survival, or in other words by the tail of a mortality graph such as a Kaplan-Meier plot.
        ii. Extension of survival without prospect of cure. This goal may be achieved by delaying disease progression, by reducing the burden of disease and therefore changing the baseline from which that progression will occur, or sometimes by slowing its rate. In quantitative terms it is usually reflected by relatively short-term measures of the rate of survival such as one year survival, although the time point at which the difference in survival is best measured may depend on the expected rate of progression and mortality without the proposed treatment. Either pattern may result directly from the effect of the treatment, or indirectly by debulking the tumor sufficiently to allow more effective surgery or radiotherapy.
    b. Symptom control.
        i. Depending on tumor type and the site of the disease, there may be physical symptoms that are reduced, in severity or impact, by a response to treatment. The effect may be measurable but may be confounded by other treatments for symptom control or by uncertainty about the course without treatment. The effect will take at least as long as the tumor response and may lag behind it, for instance if initially masked by side effects. Examples include
            - Pain in primary or secondary tumors of bone, liver or brain
            - Breathlessness in thoracic tumours with airway obstruction or pleural effusion or in cancer in any site

where the symptom is mediated by systemic metabolic effects.
- Symptoms of ascites (pain, discomfort, fullness, nausea, vomiting, constipation) in peritoneal disease.
- Asthenia (fatigue, weakness, slowness) and related symptoms.

ii. Symptoms that might have occurred because of disease progression may be prevented if there is sufficient response. Measurement of this effect is limited by the uncertainty about whether the symptom would have happened without treatment.

c. Quality of life—measured on a suitable rating scale or reported subjectively by the patient—may be improved, or anticipated deterioration may be avoided. Again, there may be confounders if other things are being done to support quality of life.

d) Doing something. Some patients and some families report psychological benefit from the feeling that something is being done to treat the cancer, even if it does not work. The toxicity from most cancer treatment and the increasing evidence for the survival effect of early supportive and palliative care (thought to be mediated partly by avoiding toxic treatment in those for whom response is unlikely) mean that where treatment is not expected to be effective the focus of the desire to "do something" should be on safer non-chemotherapy options. Drug treatment should not normally be given for the psychological benefit alone, although it may be a useful side benefit in those treated on other grounds.

2. Kinds of burden

a. Physical harm

i. Death. Although treatment is often given with the goal of prolonging life, whether by achieving long-term remission or by delaying anticipated progression, there is often a risk of shortening life through treatment toxicity. Careful patient selection and advice about being vigilant for early signs of toxicity can help reduce the risk. Evaluating risk is particularly difficult in the adjuvant setting, where patients with a fairly low probability of later recurrence have to balance a small reduction in the absolute risk of long-term recurrence against a small probability of early treatment-related death.

ii. Side effects. Most treatment regimes have a significant risk of side effects that may affect the patient's quality of life. Some, such as chemotherapy-induced nausea and vomiting, are self-limiting; others, such as peripheral neuropathy caused by some drugs, are later in onset but cumulative and can be irreversible. The likelihood, severity and immediacy of these side effects are all features that will influence the evaluation of risk.
iii. Time spent on treatment. Many regimes have to be given in a hospital setting, increasingly in a day unit but in some cases on an inpatient ward—usually because of long infusion times or a need for monitoring; sometimes because of the patient's general condition, although poor general condition will often preclude continuing treatment. Patients considering treatment with the goal of additional survival duration may want to consider whether so much time will be spent having treatment and related appointments that it outweighs the benefit. Those having treatment to reduce symptoms may find this offset by the way hospital attendance can exacerbate some symptoms, particularly fatigue.
iv. Financial and social cost. In most health care systems, there are some treatments that are available only if the patient is able to contribute to the cost. These are often treatments with the weakest evidence or the lowest cost-effectiveness. The financial burden is often compounded by the psychological and social burdens of having to sacrifice other expenditure and spend time and energy, which may be scarce, in fundraising for a treatment with a low probability of benefit. Some patients and families later regret the missed opportunities of the things they were not able to do toward the end of the patients' life because they were too busy having treatment. Others consider these burdens to outweigh the benefits.
v. Uncertainty. Patients' burden of decision making is particularly influenced by uncertainty. The evidence available is often hard to apply to a particular patient's situation. Deciding to have treatment often seems to raise the stakes; in other words, it can increase both the probability of a good outcome (better disease control, longer survival) and, paradoxically, the probability of a poor

outcome (side effects, premature death). The uncertainty therefore makes decision-making itself more burdensome. This burden is only partly mitigated by provision of good information but can be further reduced by supporting people in making decisions that are true to their values.

3. Ways of evaluating. Benefits and burdens are subject to both quantitative and qualitative evaluation. These are complementary and inter-dependent; both are necessary and neither overrides the other. The expertise needed for them is asymmetric between doctor and patient, each party having particular knowledge of some areas and less knowledge of others.
    a. Quantitative. Measurement of the effect of treatment—whether a beneficial effect on survival, symptoms, or quality of life, or harm—is usually quantitative: what probability of response, how much additional survival, what effect on the frequency or severity of symptoms, what risk of early death, what side effects. This is a necessary reflection of how evidence of benefit is gathered in trials and is useful in informing people about what benefit the treatment might offer and what burden it might entail. It is a domain where clinical expertise is decisive. It is needed:
        i. to understand the available evidence about what goals are attainable, what treatment might help, and with what probability, as well as what probability there is of which harms;
        ii. to apply that evidence to a particular patient in view of all that is known about them; and
        iii. to understand the degree and nature of uncertainty in each point.
    b. Qualitative. Patients' and families' thinking about treatment is about more than quantitative measures and includes questions of meaning and importance. The qualitative domain often involves patients making a distinction between an effect and a benefit by asking, "If the treatment works, is that beneficial to me? If it causes problems, how harmful are these to me?" What goals does the patient have? How does the goal of additional survival sit alongside other goals concerning quality of life and time with family? These goals may have been radically changed by the cancer diagnosis. For some patients a small chance of prolonged survival is highly valued; for others even a longer extension is outweighed by other factors. Similarly, while

cancer treatment studies often report effects on health-related quality of life, the effect in each patient depends on what most strongly influences that person's quality of life, which varies markedly. In this domain, it is the patient's expert perspective that is decisive, rather than clinical expertise.

4. Balancing benefits and burdens. Given this range of benefits and burdens, and the different ways in which they might be evaluated, there is a need to balance them carefully. It is tempting to move quickly to a decision; but clinicians, patients and families should be encouraged to engage in careful evaluation first. Steps to support this include:
   a. Good information about
      i. what is proposed;
      ii. the nature of the intended benefit;
      iii. the size and likelihood of the benefit that can be expected;
      iv. the nature of the burdens;
      v. the size and likelihood of the burdens;
      vi. the degree of uncertainty around each of these points.
   b. Support and facilitation to understand and reflect on this information before making a decision.
   c. Opportunities for the patient, with support from those close to them if they wish, to explore this in the context of their goals and values.

One model proposed by Baker[23] suggests that the benefits and burdens are seen as weights at opposite ends of a beam and the patient's exercise of autonomy, grounded in their goals and values, as the fulcrum or pivot. How they position it will influence the decision that is made so that different people with the same cancer offered the same treatment will rationally reach different decisions about how to proceed, not because one of them has made an unwise decision but because different decisions are right in different lives.

Advance care planning

The involvement of patients and families in the making of decisions about treatment, and balancing the benefits and risks, is important throughout the disease progression. However, as the person approaches the end of life it may be more difficult for the patient to make decisions about the continuation of treatment and the withdrawal of treatment and to ensure that their wishes are clear.

Many people have specific wishes about how they would like to be treated at the end of life:

- place of care;
- place of death;
- who is with them as they die.

And about what interventions they would wish or not wish to receive, such as:

- antibiotic therapy;
- cardio-pulmonary resuscitation;
- parenteral fluids;
- specific wishes related to their cultural or religious affiliations;
- music they may wish to have played when they are very ill or at their funeral.

As someone deteriorates it may be difficult for the person to express their wishes and make a clear decision. This may be simply due to fatigue or because of a loss of capacity to make decisions due to cognitive change, communication problems such as dysphasia or dysarthria, or severe weakness and drowsiness or loss of consciousness as death approaches. Thus, it is important to facilitate people to make their views known before they lose the ability to make these decisions, so that their wishes are respected. This makes it easier for decision makers and those close to patients to know later that decision are aligned with the patient's preferences and that their goals are met if possible.

Advance care planning allows the expression of the person's preferences about treatment to be identified, recorded, and made available if they lose the ability to make decisions for themselves. It has been defined as "a process that supports adults at any age or stage of health in understanding and sharing their personal values, life goals and preferences regarding future medical care. The goal . . . is to help ensure that people receive the medical care that is consistent with their values, goals and preferences during serious and chronic illness."[24]

The ways that decisions may be recorded will vary from country to country, as there may be specific legislative measures; nevertheless, forms of recording these include:

- A non-specific "advance statement"—this may be recorded by the person, with their views on treatment but with no specific reference

to any disease process or situation. For instance, they may express their wish not to be "kept alive artificially" and this information would be helpful in aiding professionals faced with decision making but would not necessarily be legally binding or decisive. It may express refusals or requests but it cannot demand a particular treatment.

- A specific Advance Directive—this may relate to a specific disease or an anticipated outcome, and would often, according to local legislation, be legally binding. For instance, a person may state that they do not wish to receive Cardio-Pulmonary Resuscitation (CPR), even if this may lead to their death, or request that specified treatments are withdrawn or stopped under certain specified circumstance—such as the cessation of all chemotherapy treatment if the person can no longer make the decision themselves or has increased problems with communication. It is known in some jurisdictions as an Advance Decision to Refuse Treatment; this, like many forms of advance directive, is used to refuse but not request.
- The designation of a health care proxy, who would be able to make the decision on behalf of the person, if they are unable to make the decision themselves. For instance, a partner or child could be defined as the proxy and if the person is unable to make a decision the proxy would be asked to make the decision on their behalf. In some jurisdictions, this designation is done via an advance directive.
- An End of Life Care Plan, Advance Care Plan, or Future Care Plan may be considered by some people to explain their wishes for their care at the end of life, such as music to be played, food they would wish to have or refuse, any religious rituals they would wish before or at the time of death, any cultural issues they wish to be respected. This may also include their wishes as to whether to continue or stop chemotherapy treatment. Such a plan need not be binding, and some patients prefer it for this reason because they prefer not to tie their doctors' hands in situations they cannot fully foresee. It would normally be respected if possible, and should always be considered by the professionals involved in care.
- A Do Not Attempt Cardio-pulmonary Resuscitation (DNACPR), often known as a "No-code," may be completed by the professionals involved. The completion is a medical decision, usually in collaboration with the person and their family. A person

may request this to be completed and the professional team should respect the decision if this is made by someone with capacity.

- Preferred place of care and preferred place of death may be discussed and recorded. Professionals might assume that they are similar for all patients, but the anecdotal impression that many patients may wish to be cared for at home but wish to die elsewhere is corroborated by findings that these are different decisions and should not be confused.[25] The discussions may be complex as there may be differences in the views of the patient and family; if it is possible without disproportionate burden on family caregivers, the patient's views should be respected.

The discussion of advance care planning can be complex. Many patients, families, and professionals are reluctant to discuss the future, even though they may realize that death may occur. There are fears that a discussion may be self-fulfilling and death will ensue quickly or that the discussion of these issues will be distressing. However, many people do wish their own voices to be heard and to retain some control over their care, even if they are unable to express their wishes themselves at the time. Training of professionals may be necessary to enable them to be more comfortable with these discussions, and to cope with and manage appropriately any distress.[26]

End of life care

The term "end of life" is used variably to mean anything from the last year or so of life to the last hours to days, or to mean the final deterioration without prospect of reversal, even where duration of survival is recognized to be uncertain. Any of these meanings is legitimate but given the different meanings it is important to signify the intended meaning in a particular context in order to avoid the risks associated with misunderstanding. [27]

As a person comes towards the end of their life the aims of any management may change, with life prolonging effects probably no longer attainable and increasing focus on a palliative approach—minimizing symptoms, maintaining the quality of life, and supporting all involved—patient, family, and professionals. Recognition of this shift will influence decisions on chemotherapy. Continuing deterioration on treatment usually signifies that it is not working, and deteriorating general condition makes it increasingly unlikely that any chemotherapy will work. The burden of toxicity also increases with the deterioration of the condition.

The recognition of the end of life phase may be difficult, particularly as more patients receive palliative chemotherapy and other anti-cancer treatments later in the disease progression. However, there may be indications that the situation has changed, and it may be apparent from the patient, family, or those professionals who are in regular contact with the patient that the disease has progressed and another approach is necessary.

Clinicians' prediction of survival, even when refined by the insights of a multiprofessional team, is often inaccurate and there is a tendency to overestimate future survival. There are tools that may be helpful:

- The Gold Standards Framework criteria provide a multi-step decisional approach to identify patients approaching the end of life in the document "Proactive Identification Guidance 2016."[28] This toolkit is aimed at helping professionals within the primary care setting screen the patients they see and enter into the palliative care register those who are at risk of death in the coming months. The risk is assessed by considering the surprise question: "Would you be surprised if this patient were to die in the next 6 to 12 months?" If the answer is "no," this may reflect a high degree of uncertainty or a likelihood of deterioration. It should prompt further assessment of the patient with advanced disease to understand the clinical picture and the desired choices of care, and the presence and intensity of the special need for supportive/palliative care. There is also the assessment of specific clinical indicators related to the main diagnosis that can indicate that the disorder is end stage. These indicators are also listed for neurological conditions like amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, stroke, and dementia. This approach helps identify, assess, and plan for living well and dying well.
- The Supportive & Palliative Care Indicators Tool (SPICT™)[29] is another prognostic tool. For all patients it is suggested that if two or more indicators are found, this is an indicator of deteriorating health. These indicators are poor or deteriorating performance status, two or more unplanned admissions to hospital in the past 6 months, 5–10% weight loss over the past 3–6 months, and a BMI less than 20, persistent and troublesome symptoms despite optimal treatment of the condition, living in nursing care home or requiring care at home, and the patient requesting palliative care or the withdrawal of treatment. For neurological patients there are specific indicators: progressive deterioration in physical and/or cognitive

function despite optimal therapy, speech problems with increasing communication difficulty and/or progressive dysphagia, recurrent aspiration pneumonia, breathlessness, or respiratory failure. The tool may be used to help identify people at risk of deteriorating and dying and then facilitate a holistic, palliative care-needs assessment and care planning (http://www.spict.org.uk/).[29]

- General indicators of deterioration towards end of life in neurological disorders were found to be swallowing problems; recurring infection; marked decline in physical status; weight loss; significant complex symptoms, including pain; infection in combination with cognitive impairment; and cognitive difficulties (NEOLCP 2010).[30–31]

These tools may enable professionals to work with patients and families to anticipate deterioration and a need for end of life care. This will enable further discussion about the care and the wishes of the person and family, such as:

- Place of care and death—it is important that discussion separates these issues as some people may wish to be cared for at home but do not wish to die there, and a misunderstanding may lead to a sudden emergency admission very near to death;[32]
- DNACPR/"No code" orders;
- Withdrawal or discontinuation of plans for further treatment, such as stopping further chemotherapy;
- Discussion about feeding/hydration as the person deteriorates, as it may be less appropriate to continue feeding or start parenteral hydration in the dying patient—as there is little evidence that this reduces symptoms, extends life, or is helpful at this time (NICE 2015);[33]
- The involvement of palliative care services, if they have not been involved earlier;
- Provision of equipment to enable care at home, such as a wheelchair, specialized bed, hoist, commode;
- The involvement of extra nursing and social care, to provide care at home and enable family to remain as family rather than 24-hour caregivers;
- The provision of medication to cope with a sudden deterioration—such as injections of an opioid, such as morphine, midazolam as a relaxant, levomepromazine as an anti-emetic and an anticholinergic, such as glycopyrronium bromide or hyoscine hydorbromide/scopolamine for

chest secretions. These are then available for any professional to give if there is a sudden deterioration, even if this is out of hours.[34]
- Discussion of the plan in case of a sudden deterioration—including preparation of the family so that they are aware of the actions they can take, and that information is made available for professionals who may be called out of hours, including ambulance services, which may be especially important if specific crises such as major hemorrhage are anticipated;
- Support of the patient and family caregivers as they face this deterioration;
- Support for all caregivers—including those providing personal/social care so that they are prepared and know the wishes of the patient and family if there is a sudden change.

Thus, the recognition of the later stages and approach of death is important to allow unnecessary or inappropriate treatment to be stopped and appropriate management plans to be arranged. This may facilitate the patient's wishes to be ascertained and, as far as possible, adhered to. However, there is a need for all the professionals involved in the care of patients receiving chemotherapy and other cancer treatments to be aware of the possible deterioration and to communicate clearly with patients and families about the possible disease progression. This anticipation and communication helps serve the need to balance the benefits and risks of management and to enable the person to maintain quality of life and to live and die with dignity. Leaving the consideration and discussion of these issues until the last moment leads to inappropriate admission to hospital, increased use of intensive treatment, such as intensive care, inappropriate and unsuccessful attempts at resuscitation, and families being unable to be with their dying loved one.

Psychosocial and spiritual aspects of care

Patients receiving chemotherapy often face psychological challenges, particularly when they are deteriorating and may be facing the end of life phase of their disease progression. They may be fearful of the disease itself, as the diagnosis of a cancer engenders fear, and people will have their own particular issues based on their previous experience or experience of family or friends and related to their own previous psychological wellbeing—such as previous anxiety, depression, or other mental health issues. The treatment may have increased these fears or lead to further areas of concern—such as coping with side effects.

Family members may also be affected. They may share the same fears and concerns, as well as being fearful of the issues faced by their loved ones. At the same time, the patient may have fears for their family—such as the concerns of a husband as to how his wife will cope if he dies, or practical issues of how a spouse may cope alone with the care of children. These issues may in the background of ongoing family issues—many families face problems with communication or with relationships over many years. These pre-existing factors do not usually resolve in the face of a cancer diagnosis and may be heightened under the stress of disease progression, treatment that may cause side effects, and increasing uncertainty and anxiety about the future.

Spiritual concerns are common whether or not there is a declared faith or belief system. Spirituality has been defined by the EAPC as "the dynamic dimension of human life that relates to the way persons (individual and community) experience, express, and/or seek meaning purpose and transcendence, and the way they connect to the moment, to self, to others, to nature, to the significant and/or the sacred."[35]

Thus, "faith" refers not only to religious beliefs but also to wider views of life; concerns about these deeper issues may influence decision making. An openness to discussing concerns in the spiritual domain is important when difficult decisions are faced, such as the commencement, continuation, or withdrawal of treatment. All professionals should be able to listen and respond to these discussions, although spiritual counselors/advisors or chaplains or relevant religious leaders may need to be involved for some people with more specific or complex needs (Lambert 2016).[36]

Conclusions

Palliative care has an important role in the care of people with cancer and may be very helpful for patients facing neurological issues. All professionals should provide a palliative care approach and those caring for people with cancer should have increased skills—in particular ensuring good communication with the patient and their family, shared decision making and goal setting, and symptom management. These aspects are all essential in helping patients make decisions about treatment and coping with neurological side-effects of treatment.

As a patient deteriorates, the role of palliative care remains important, supporting the patient and their family as they face deterioration and death. More specialist palliative care services may be helpful providing support at home or in a hospice/specialist palliative care unit. Treatment should be reassessed and it may be important to stop any

treatment that is not providing benefit and may be increasing the symptom burden or risk. The support of the patient and family is important at this time. The wider professional team may also need support to cope with these changes and allow the most appropriate care and treatment to be provided. In this way patients, and their families, may be supported and their quality of life maintained throughout the disease progression, until death.

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CHAPTER 3.6

THE DEVELOPMENT AND IMPORTANCE OF PATIENT SUPPORT GROUPS

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Abstract

Patients with cancer are exposed to the cancer, the treatment, and often the social and psychological sequelae. Despite improved health organizations, increasing care and partnership as well as patient participation, patients often need communication, practical help, and reassurance. Over the past decades, support groups (SG) have increasingly been established to help with practical issues. Furthermore, the management and interpretation of symptoms and signs are important for patients and care givers. SGs provide a valuable resource.

Keywords: Cancer, patient, support groups, NGO, late effects

Introduction

In preparing this chapter, I remembered a remark I read on the internet, that patient support groups (SGs), who were initiated in the US after World War II and slowly entered Europe subsequently, were often seen as "herds of wild patients." Fortunately, over the past few years this has been changing, and the relation between physicians and health professionals (HP) and patient SGs is increasingly characterized by joint targets, cooperation, and trust. This climate is necessary to provide help and reassurance in many ways.

Being diagnosed with cancer is a dramatic change for an individual. Often people feel helpless and abandoned. Daily life needs to be restructured and is now dominated by visits to doctors, investigations,

and therapy. Cancer treatment has improved, and surgery, chemotherapy, and radiation therapy often control the disease with preservation of good QL (quality of life), in some instances even healing the patient. In these situations, communication and the exchange of experience between patients and caregivers is of eminent relevance.[1] Support groups are platforms that provide such an environment. Patients and caregivers can openly discuss the disease and their concerns. This can be done without time constraints. Lack of time is often a road block to effective communication with physicians. This is regrettable, as good communication between patients and physicians is very helpful. It is important for individuals to learn, that other patients share concerns, fears, and worries. Patients realize that they are not "solitary cases." Experiences improve the individual situation and also empower patients in their fight against cancer.[2]

Support groups also organize lectures given by experts, and enable patients to receive information, as well as give them the chance to inform themselves and ask questions to experts. As such, the support groups are an important part of patient care. Patients experience reassurance regarding treatment ("Der mündige Patient"), and it can also improve compliance and quality of live. Often it is a relief for patients to discuss their side effects with others.[3] Side effects, despite being part of effective cancer therapy, have a negative effect on patients' zest for life as well as life quality.

As an example, we want to discuss a few relevant aspects of chemotherapy induced neuropathy (CIPN), a condition that frequently occurs as a result of chemotherapy. Neuropathies not only cause sensory loss, numbness, and sometimes paraesthesia, but also can interfere with the activities of daily living. Sensory loss in the fingers and hands can induce clumsiness, resulting in impairment in performing fine motor tasks, such as buttoning shirts and tying shoe laces, and in gait difficulties and falls. Often, it also leads to temperature misperceptions (e.g., touching a cold object), which can be painful. Activities of daily life can be seriously impaired. We would like to demonstrate some patient perceptions and symptoms in two case vignettes.

Case Vignette 1: "it is only a side effect"

My neuropathy story starts in 2003. Thalidomide, which I received at this time to treat my multiple myeloma (MM), has this side effect and also the MM damages the peripheral nerves. Unfortunately, this side effect was not mentioned by my doctor, and also I was not instructed to communicate

with him when I felt sensory symptoms. My gait deteriorated, and I had to be careful not to stumble over pavement edges.

The tingling in my toes varied in intensity. In the morning it often seemed to disappear, whereas it emerged during the day. The symptoms increase when I have the flue or fever. In the cold, my fingers are also strongly affected, and they turn white and cold. Picking out coins from my purse takes a long time. Going shopping and paying at the cash register takes some time, and also needs patience from the other customers behind me.

This handicap also fosters the positive and social aspects of others. For instance, when trying to close the zip on my coat, people sometimes offer help. The sad thing is, as patients we often hear: there are no remedies against neuropathy, except the recommendation "perhaps try pregabaline." At present I use an inflatable cushion when napping. I rest my feet on this in the morning in the bathroom, when I am at my desk, and whenever I have the possibility. It seems to do good. And yet I know, that many patients are worse and have more severe symptoms.

Case Vignette 2

When receiving chemotherapy, in this case oxaliplatin, one feels how the nerve endings are damaged. The feeling is tingling, like ants, similar to the feeling when the hand becomes numb. From one chemo to the next, the sensory impression is that of numbness in the feet. Also calf cramps, and twitches, as well as restlessness occur. Cold and heat can be misperceived and painful. Unfortunately, there has been little effort made to explain the symptoms of neuropathy, and the impression is that some people recover fully while others don't.

In my case sensory perception has not recovered fully, although through exercise and rehabilitation improvement can be noted, and daily life is not much affected. The exercises I do are simple and can be done easily. In general, they should stimulate the nerve endings and improve function. One exercise is to move the feet over a rough cloth (e.g., a towel), sometimes the toes or the heel. Another is to roll the feet on a ball with knobbles. One more is to brush the fingers with a brush to stimulate the nerves. Only a few patients know that simple exercises can help.

Interpretation

Both these case vignettes describe patients with peripheral neuropathy induced by chemotherapy. Although the symptoms seem predominately

sensory, there appears to be some unsteadiness and impairment of motor dysfunction in the legs. The first case vignette also describes sensory loss in the hand followed by a reduction of fine and coordinated movements; thus, it also describes a loss of "fine motility" in the daily routine, which induces a slowing of movements and delays in (daily) tasks. The second person reports sensory loss and what he perceives as pins and needles, and also actively describes exercises that seem to be helpful. Both vignettes point out that the patients were unaware of the side effects, or that several issues had not been discussed with them, when receiving cancer therapy.

In one of our SG meetings, a young man who had received chemotherapy described sensory exercises with cherry cores, which helped. Sometimes simple procedures can help. Often patients' sensory symptoms are perceived as minor, in the face of the general situation resulting from tumor treatment. Symptoms often exceed numbness and result in impairment of functionality, also causing ataxia and neuropathic pain. Tools such as questionnaires could be used as a screening method to identify patients developing sensory symptoms.

Both case vignettes illustrate that sensory impairment can be quite troublesome and can impair the functions of daily life. There are also other topics, such as fatigue after radiation; although RT procedures are often short, the side effects can be long lasting. Patient information is often superficial, and does not explain these effects in detail. A good conversation—attentive listening to patients' complaints—is important and one of the key tasks of support groups.

"Together we are strong" is the motto of support groups; as Goethe writes in *West–Eastern Divan*, "For I have been a human, and that means I have been a fighter."

How can support groups improve situation for patients who have side effects?

In many encounters with patients who had long-term experience with cancer, we found that often a long-term follow up was missing. This does not refer to routine medical check-ups, but the lack of a competent health care professional, who could be contacted about problems occurring after treatment, or about persisting side effects.

Patients often feel left alone and are uncertain how to continue their lives or to prevent a relapse or recurrence. Some problems out of many include: Can I travel a long distance? Can I receive vaccinations for these journeys? What drugs need to be avoided after chemotherapy? How can I deal with sexual problems and problems in my relationship?

In recent years in Austria, onco-rehabilitation has been established in several centers.[4–5] This rehabilitation not only treats symptoms, but also helps patients re-enter their professional lives. Unfortunately, not all patients know about these possibilities and the impression is that persons who have participated are quite enthusiastic about the program, feel well informed, and are prepared to continue.

We, as support groups are eager to inform patients about these possibilities. From my personal perspective (my husband died in 2006), my husband would have been eager to take up this opportunity. Holidays after cancer therapy in a conventional resort or hotel do not cover the needs of these patients.

It is useful to listen to affected patients, as they are often in a state of despair, and to listen to their needs and wishes. They may result not only in increased quality of life but also may reduce costs. Further, models of online support need to be provided[6] and social support needs to be available.[7]

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CHAPTER 3.7

ACCESS TO CANCER CARE IN RESOURCE-LIMITED COUNTRIES

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Abstract

Non-communicable diseases are relentlessly rising globally. Cancers are the typical example with a clearly disproportionate increase in prevalence and mortality in low- and middle-income countries (LMICs). Cancer access to care is a major challenge in developing countries. Despite a lower incidence of cancer in these areas compared with high-income countries, mortality is significantly higher and obviously associated with younger age. Cancer-care programs based on prevention are difficult to implement in such a context. Limited budgets, lack of awareness, and knowledge of prevention, cancer risks, and precancerous conditions are also associated with this situation. Despite the efforts of the World Health Organization (WHO), few guidelines are applicable for cancer control in low-resource settings. Even when diagnosis is accurate, access to treatment represents another barrier. When cancer is identified at a late stage, palliative care is expensive and often not available. In this chapter, we aim to describe cancer care in limited-resource areas and to discuss several factors and considerations that may compromise the success of cancer-control programs in LMICs and possible conceivable remedies for these issues.

Keywords: cancer, malignancies, low-income countries, limited resources, Africa, Asia, Latin America, African American, prevention, screening, treatment, access to care, palliative care, neurology, neuro-oncology

Introduction

Cancer is a chronic disease representing one of the greatest health challenges today. According to the 2018 World Health Organization (WHO) report, cancer is the second leading cause of death globally and was responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer. It is increasingly affecting countries worldwide, including those of low income. The current 2020 World Bank Country Classifications defined low-income countries as economies with a Gross National Income (GNI) per capita of $1,025 or less in 2018, lower-middle income as countries with GNI per capita ranging from $1,026 to $3,995, and upper-middle income countries as economies with GNI ranging from $3,996 to $12,375 (Annex 1). Approximately 70% of deaths from cancer occur in low- and middle-income countries (LMICs). This might reflect not only poor access to oncology therapies in these countries with limited resources, but also the lack of adequate diagnosis infrastructures and health care policy. The global burden of cancer is growing. Healthcare expenditure is becoming a heavy burden on countries' budgets worldwide, especially in low-income countries. Prevention was always considered a pillar of healthcare in oncology; however, focus on treatment is still a priority in this field. Limited infrastructure for diagnosis and treatment remains the main barrier in countries with scarce resources, in which good results regarding mortality and morbidity are also required. Late-stage presentation and inaccessible diagnosis and treatment are common. In 2017, only 26% of low-income countries reported having pathology services generally available in the public sector. More than 90% of high-income countries reported that treatment services are available, compared with less than 30% of low-income countries. Only 1 in 5 LMICs have the necessary data to drive cancer policy. In fact, the aim of a health care policy is to maximize the health of the population within the limits of available means and within an ethical framework based on values such as fairness and solidarity. Oncology in general, and neuro-oncology especially, has been revolutionized with the rapid advancement in the field of neurosurgery and the advent of new non-invasive techniques. These matters are further highlighted when it comes to neurosurgical practice in low-income countries. In the past five decades, major breakthroughs have been realized in controlling cancer. However, for patients in LMICs, most of these advances are only an aspiration and a hope for the future. Indeed, the greatest challenge faced in oncology today is how to reconcile small, incremental and significant improvements in the management of cancer

with the exponentially increasing costs of new treatments. Currently, emerging economies are attempting to address this important issue of access to cancer medications. In this chapter, we aim to describe cancer care in limited-resource areas, with a focus on screening, diagnosis, and treatment, and to discuss several factors and considerations that may compromise the success of cancer control programs in LMICs and possible conceivable resolutions to these issues.

Body

Studying cancer epidemiology in low-income countries is challenging but necessary to understand the determinants of growing cancer rates in these countries. Infrastructure for screening and diagnosis procedures are always lacking in these areas. According to the Global cancer statistics of 2018, the GLOBOCAN estimates that there will be 18.1 million new cases and 9.6 million cancer deaths worldwide in 2018.[1] Cancer rates in limited-income countries are increasing due to a raise in life expectancy and modifications in lifestyle. Risk factors for cancers such as smoking, obesity, and inactivity are the main incriminated causes. The 18.1 million cases that occurred in 2018 are predicted to rise to 22.2 million by 2030 mostly in LMICs.[2] Infection-related cancers affecting the stomach, liver, and cervix are the most prevalent. However, lung, breast, and colorectal cancer rates are also rising in many low-income countries because of the increase of related risk factors, mimicking Western countries. Thus, developing countries are undergoing an epidemiological transition leading to a "double burden" due to both infectious diseases and chronic diseases such as cancers. Screening and diagnosis tools are different between high income countries and low incomes ones. Effective low-cost cancer control options are validated for some malignancies by the WHO but are not available in low-resource areas. Disparities in cancer care and outcome are obvious between high- and low-income countries. Many factors contribute to cancer disparities and include health insurance difficulties, health education insufficiency and obsolete health cultural beliefs.

Cancer prevention efforts in limited-resource areas

The main interventions on which cancer prevention is based are: modifications in daily lifestyle, cancer vaccines for infection-related cancers, cancer screening to diagnose precancerous conditions, and the diagnosis of cancer at an early stage when it is possibly treatable.

Behavior modification programs

Tobacco prevention and cessation

Tobacco is the principal known cause of cancer. Thus, limiting tobacco use is the most obvious axis of prevention of cancer worldwide. The increasing rates of tobacco-related cancers are due to the escalating prevalence of smokers worldwide, especially among women. Decreasing tobacco consumption by half, by 2020, will lead to a reduction of 180 million tobacco-related deaths.[3] Thus, effective tobacco-control strategies are urgently needed. All over the world, basic interventions have been conducted such as mass-media campaigns, raising tobacco prices, and reducing the cost of anti-smoking cures. Programs to control tobacco consumption have been implemented in many countries, for example Tunisia, Brazil, Thailand, Chile, Jamaica, Madagascar, and Suriname. As a result of a 10% increase in tobacco price, a decrease in consumption by 8% has been obtained in LMICs.[4]

Physical activity

Physical activity can lower the risk of developing cancers by 20 to 30%. Researchers have suggested that reducing fat overload in the human body, inflammation, and insulin resistance are the main possible mechanisms supporting the role of physical activity in cancer prevention.[5] Promoting physical activities as a part of cancer prevention programs for low-resource communities is very interesting because it does not cost. This intervention was tested for African American women and resulted in authentic weight loss and improvement in other metabolic outcomes. One of these programs is the Deep South Network for Cancer Control. In this collaboration, researchers, health care professionals, and volunteers from the rural US South (Alabama and Mississippi) aimed to promote healthy interventions on weight management, healthy diet, and physical activity.[6]

Cancer vaccines

Cervical cancer is the chief malignant disease for which prevention requires vaccination. Vaccines for HPV to prevent cervical cancer and vaccines for the hepatitis B virus to prevent liver cancer are widely available. For cervical cancer, 79–83% of new cases worldwide were diagnosed in developing countries in 2008.[7] The HPV vaccines have demonstrated high vaccine efficacies against HPV infection and cervical

cancer precursors. It is in use in most high-income countries. In low-income countries, HPV vaccination is limited mainly due to the high costs and logistical difficulties. Some middle- and low-income nations provide the HPV vaccine, such as the Philippines and Malaysia. However, in others, vaccines are only part of a pilot phase, as in India and Thailand. In Tunisia, inclusion of the HPV vaccine in the national vaccination calendar from 2020 is scheduled and will be for girls aged 12 to 14 years. In Algeria, the National Cancer Plan advocates the introduction of vaccination against the HPV virus soon.

Hepatocellular carcinoma is one of the five leading cancers in the developing regions. Geographic distribution of this malignancy overlaps with that of chronic Hepatitis B virus (HBV) infection, such as in East and Southeast Asia, Middle and West Africa, the southern parts of East and Central Europe and the Amazon basin.[8] The link between HBV infection and hepatocellular carcinoma is well established. Universal Hepatitis B vaccination is the most effective and safe preventive intervention. Since 1991, the WHO recommended that all countries add hepatitis B vaccination to their national immunization programs. Unfortunately, based on its recent report, only 75% of all countries vaccinate for hepatitis B. Many low-income countries such as those in Southeast Asia and sub-Saharan Africa do not use the vaccine.

Early detection and screening for cancer

Access to cancer screening

Effective management of cancer relies on early detection in precancerous conditions. The principal aim of cancer screening is detecting precancerous lesions or cancer at a preclinical stage to improve disease outcomes. Cancer-screening procedures are difficult to achieve in low-income nations because of limited resources and the complexity of implementing screening programs. In limited-resource countries, the WHO recommends screening programs for cervical, breast, and colorectal cancers. Screening for stomach cancer is also suggested for Asian countries with low resources and high incidence.[9] As a consequence of a pilot project in Malaysia, the proportion of women with advanced breast cancers (stage III/IV) decreased from 60% to 35% and that of cervical cancer decreased from 60% to 26%.[10] In India, screening efforts led to an increase in the proportion of diagnosis of early breast cancers from 74% to 81%.[11]

Cervical cancer screening

Visual inspection with acetic acid was evaluated in cross-sectional and randomized controlled trials conducted in limited-resource regions. This method was tested as an alternative to Pap smear cytology and was sensitive and easy to implement in basic settings. Moreover, it is not expensive and the results are immediate. Visual inspection with acetic acid was adopted in many LMICs, like Bangladesh, India, Zambia, and Morocco, in national cervical cancer screening programs.[12]

A cross-sectional large study from 11 multicentric studies conducted in India and Sub-Saharan African countries, including 58,000 women aged between 25 and 64 years, revealed that the Pap smear had a low sensitivity of 57%.[13] Human papillomavirus (HPV) detection was recommended by the WHO as the first test for cervical cancer screening because of its high sensitivity in all countries. Lack of knowledge and awareness of cancer screening is the main problem in LMICs. As a consequence, 90% of Tanzanian women and about 85% of Ethiopian women had never been screened for cervical cancer.[14]

In the Maghreb, cancer detection programs were introduced in Morocco, Algeria, and Tunisia. In Morocco, in 2010, the Ministry of Health, in partnership with the Lalla Salma Foundation for Prevention and Treatment against Cancer, conducted a pilot screening program for cervical cancer. This project started in Témara and then spread throughout Morocco in 2013. Prevention against cervical cancer is based on an inspection acetic acid procedure in women aged 30 to 49 years. In Algeria, a national program to screen cervical cancer was implemented in 1997 and was based on cytodiagnosis (cervico-vaginal smear). After that, a national strategy led to the opening of a screening unit in 48 *willayas* (provinces). The National Cancer Plan was introduced in 2015. In Tunisia, cancer screening is primarily based on conventional cytological examination in women aged 35 to 59 years. A screening test is performed at five- or three-year intervals for women at risk.[15]

Breast cancer

Breast cancer, the most prevalent female cancer worldwide, is linked to an increase in the disease burden of over 35% between 1990 and 2010.[16] In countries with low resources, it concerns younger patients and the disease is always at an advanced stage when diagnosed compared with high income countries.[17]

This explains the high rates of mortality, which reach 40% in African low-income countries. In fact, in Africa, for example, breast cancer incidence tends to be low, but breast cancer mortality is high. The low financial resources are responsible for these epidemiological data.

In Latin America, 115,000 women are diagnosed with breast cancer yearly and 37,000 die as a consequence of the disease. Aging is recognized as the main risk factor for breast cancer. In Mexico, geographic disparities with regard to breast cancer diagnosis were noted. Breast cancer distribution and severity was proportional to poverty and to the existence of barriers to breast cancer care.[18]

Breast cancer prevalence and incidence are expected to increase in Latin American countries. Mammography screening is not performed as recommended. Most diagnosed cases are detected in the symptomatic phase when a tumor is palpable. However, screening with hormone receptors and biologic markers are more common in practice in the Latin American region. The results of early screening in those countries are disappointing. About 35% of patients are diagnosed when the disease is already in the metastatic stage.[19] In Jordan, breast cancer screening and early diagnosis was also problematic. About 70% of diagnosed cases between 2000 and 2003 were at stages 3 or 4. Late diagnosis is related to ignorance and misconceptions. In Tunisia, the screening program started with small experiences. A breast cancer screening program was conducted in the Ariana province by volunteers, started in 2003 and lasting for five years. Fifty women were diagnosed with cancer among 8,244 screened.[20] In Sfax (southern Tunisia), a mammography screening pilot program was conducted between 2004 and 2010 by the founders of the Dar El Amal association for women aged over 45 years. The cancer rate was therefore 5.6% in prevalence and 6.3% in incidence.[21] Since 2015, breast cancer screening has been supervised by the National Office of the Family and Population and the Basic Health Care Directorate. Annual clinical breast examination in all women aged 30 and above has allowed early detection of breast cancer. Implementation mammography screening programs in low-income countries require heavy investments. Added to that, the WHO recommended clinical breast examination as an alternative to mammography. This last method was used as a breast cancer screening test in Bangladesh, China, Ghana, India, Morocco, and Tunisia, and reduced mortality due to cancer.[22] Breast ultrasound is an interesting screening tool. In conjunction with mammography, it is more sensitive compared with mammography only in women with dense breasts without any palpable lumps. However, the test has lower specificity and depends on radiologist experience.

Colorectal cancer

The highest rising rates of colorectal cancers are observed mainly in countries with a low socio-economic development index. This cancer can be prevented or diagnosed at an early stage by detecting and removing precancerous growths or early cancers with a colonoscopy. Colorectal cancer screening is recommended for those older than 50 years. Many programs in African American populations were implemented in the United States. The results were encouraging and mortality was reduced by 42%.[23] Despite this, systematic population-based screening is not yet feasible in all low-income countries except Latin America and the Mediterranean region. Screening methods vary from one country to another. In Europe, most organized screening programs use noninvasive tests like blood and stool tests, rather than colonoscopies. The fecal immunochemical test is of interest to adopt because it is simple, objective, and reproducible. Then, if patients test positive for the fecal immunochemical test, they should get a colonoscopy. This method has been realized in Thailand.[24] Most Asian countries do not have colorectal screening programs, except Japan. Efforts are limited to some pilot programs in Taiwan and in Hong Kong, respectively, through fecal-occult-blood testing and colonoscopy. In Japan, the fecal immunological test has been the screening tool used in the national colorectal screening program since 1992.

In Tunisia, the national screening program is not established in systematic common practice. Only a multi-center pilot project was implemented. Screening was via fecal-occult-blood test. Colonoscopy was planned if a positive fecal-occult-blood test was received. Currently, screening of colorectal cancer is part of the cancer projects for 2010–14 and 2015–19.[25]

Lung cancer

Screening for lung cancer is controversial. It should be limited to individuals at high risk of developing the disease. False positive diagnosis and unnecessary invasive testing is frequent in this context. The National Lung Screening Trial (NLST) demonstrated that low-dose computed tomography is more sensitive in detecting lung tumors than chest radiography. Ambiguity remains over the appropriate population to screen and a standardized radiological screening test. Barriers to validate one test or another are due to the cost effectiveness of available screening tools and adverse effects such as radiation.

Focus on neuro-oncology

The global burden of central nervous system (CNS) cancer has increased over the last three decades. Incidence rates of CNS cancer are higher in Europe and North America compared with Africa and Asia. CNS tumors are relatively rare and represent approximately 2–3% of all malignancies; however, they significantly affect young and middle-aged people compared with other malignancies. Advances in diagnostic tools and therapeutic strategies are the main explanation for the improved outcome. However, disparities are the rule between high- and limited-income countries. Few data are available on access to diagnosis and care of CNS tumors in low-resource countries. According to a review dealing with brain tumor research in low-income areas, CNS malignancies are underestimated and are not considered among the leading cancers. Awareness of brain tumors in this region is limited. Recently, the International Network for Cancer Treatment and Research (INCTR) Cancer Registry Program, established in 2012, has been coordinating an African Cancer Registry Network (AFCRN).

To our knowledge, there are no specific screening or diagnosis programs for CNS malignancies in these areas. Infrastructure is limited, as are the number of trained personnel healthcare. For example, only 9 to 30 neurosurgeons work in Nigeria out of a population of 140 million.[26]

Access to cancer therapeutics

Access to cancer treatment in low- and middle-income countries

In addition to the prevention of new cancers through the reduction of risk factors, strategies are needed to close the gap between developing and developed countries in cancer treatment and survival. In resource-limited countries without specialized services, experience has shown that much can be done to prevent and treat cancer by deployment of primary and secondary caregivers, use of off-patent drugs, application of regional and global mechanisms for financing and procurement, and inclusion of cancer treatment in national health insurance coverage. These strategies can reduce costs, increase access to health services, and strengthen health systems to meet the challenge of cancer and other diseases. In 2009, the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries was formed to insure the proposal, implementation, and evaluation of strategies to advance this agenda in LMICs.[27] Four key priorities have been identified to promote health services for cancer

control and data acquisition. The first of them is the capacity to build oncological health services, research, policy, and planning relevant to LMICs.[9] In Africa, important strides have been made in cancer centre development in Algeria, Egypt, Ghana, Morocco, South Africa, Tanzania, and Tunisia. The National Cancer Institute in Cairo and the Moroccan cancer centre have been major catalysts for human resources in Africa. Morocco has 11 public-sector cancer centers and is an exemplar of cancer centre development in Africa, especially in supporting human resource development in Francophone African countries such as Burkina Faso, Chad, Gabon, Mauritania, Niger, and Senegal. Tunisia provides cancer services through a comprehensive cancer centre in Tunis and cancer units in 24 university hospitals. However, Algeria, Egypt, Morocco, South Africa, and Tunisia account for 80% of all cancer centers and cancer treatment facilities in Africa. Large and populous African countries such as the Democratic Republic of the Congo, Nigeria, and most Francophone African countries have substantially underdeveloped cancer centers.[28] The second priority is the development of high-quality health data sources, such as population-based cancer registries, to identify the process and outcome of cancer management to ensure that they are iterative and achieve quality cancer control. Unsurprisingly, the majority of LMICs do not have adequate cancer registries. In the International Agency for Research on Cancer report on global cancer incidence, only 1% of Africa, 4% of Asia, and 4% of South and Central America have population-based data sufficient for inclusion, compared with 80% of North America. The third priority is to elaborate more oncology-related economic evaluations in LMICs. An estimated 0.1% of total health care expenditure should be dedicated to health services and policy research in LMICs; however, on average, the amount currently spent is approximately 0.007% of total health care expenditures in LMICs. The last of the key priorities is the exploration of high-quality models of cancer control in LMICs as opposed to the extrapolation of experiences from high income countries.[9]

Cancer treatment means in low- and middle-income countries

A correct cancer diagnosis is essential for adequate and effective treatment because every cancer type requires a specific treatment regimen that encompasses one or more modalities, such as surgery, radiotherapy, and chemotherapy. Cancer treatment requires a multimodal and tailored approach because not all cancers are biologically similar. Determining the goals of treatment and palliative care is an important first step, and health services should be integrated and people-centered. Data from LMICs

unfortunately are limited when it comes to the current status of cancer care and infrastructure.[9]

Surgical resection

Used in conjunction with chemotherapy and radiation, surgery often has the most important role in cancer treatment plans in LMICs.[32] Unfortunately, access to surgical services is not an option for the majority of the world's population. An estimated 5 billion people lack access to safe, affordable surgical services when needed, not to mention appropriate accompanying anesthesia care. In addition, an estimated 33 million people globally per year face financial ruin from payments for surgery and anesthesia.

The Lancet Commission on Global Surgery published a landmark initial report entitled Global Surgery 2030 that highlights the current deficiencies and implores policymakers, implementers, and funders to include core indicators and associated targets for universal access to safe and affordable surgical and anesthesia care by 2030.[9] Particularly in low-resource settings where patients present with later-stage disease, sophisticated, easy-to-use tools to perform surgical excision or tumor resection are essential. Real-time optical imaging of the surgical site can provide immediate feedback to clinicians on post-resection margins. HRME is an example of a small, portable device that has the potential to be used for margin determination during a procedure. It offers the surgeon critical histologic information and could lead to fewer repeat procedures by ensuring more complete tumor resection.[29] Also of utmost importance is addressing cultural barriers and societal norms in several LMICS that may limit the acceptability of and participation in surgical procedures. If not addressed, these may impede successful implementation of key aspects of cancer control programs.[9]

Medical therapy and chemotherapy

Currently, LMICs face the dual challenge of addressing long-term issues such as implementing preventive care and health education programs for their populations and how to finance and provide their population with increasingly expensive cancer therapies. Limited data have been reported on the prevalence of the use of newer, innovative cancer medications in emerging markets. In a review by Lopes et al. published in 2013, the authors examined how LMICs using generic and biosimilar drugs, expanding participation in clinical trials, implementing universal health-

care schemes to pool resources, and using compulsory licensing schemes as well as increasing multiple-stakeholder public–private partnerships could lead to improved access to cancer medications for their citizens.[30] Alongside overall infrastructure considerations, attention must be paid to cancer therapy availability, accessibility, efficacy, safety, and post-therapy monitoring and follow-up. Unfortunately, data that inform therapeutic decision making for cancer management in high-income countries might not always be applicable in LMICs. Some LMICs are unable to perform rigorous clinical trials to assess their own therapeutic outcomes. Hence, little information exists to guide therapeutic management of diagnosed cancers. Although the exact availability and types of anticancer therapies in LMICs are unknown, a WHO survey found that only 22% of African countries and 43% of Southeast Asian countries report availability of anticancer therapy, with the specific therapies not specified, while the reported availability exceeds 90% in Europe. Even when therapy is available and effective, cost remains an overriding concern. A report by the WHO found that 20% to 60% of health expenditures in developing and transitional countries are for medicines, which is significantly more than in developed countries.[9] In Kenya for example, chemotherapy is available, but because of the high cost of drugs and the consequent inability of the National Hospital Insurance Fund to cover the cost of cancer treatments, it is inaccessible to most patients. Most drugs in the WHO essential medicines list are not available, and there is no national or regional purchasing arrangement. Rather, hospitals and other providers procure drugs directly from industry, decreasing the purchasers' bargaining power. For cancer drugs, of 52 present in the UICC's revision of the WHO essential medicines list, only 18 are present in Kenya's essential list.[31]

While a range of types of chemotherapy treatments are available, intravenous chemotherapy can require the use of an infusion pump to carefully control dosage over time. Currently in development, a low-cost infusion pump called AutoSyP offers a laboratory accuracy of fluid delivery within 4% of the programmed flow rate. The device can be assembled for approximately $500, which is a viable price point for hospitals in LMICs.[29] Although universal coverage is needed for adequate access to cancer medications in LMICs, its establishment requires political will to manage myriad challenges. The majority of LMICs, mainly in Africa, still lack such universal coverage programs. Generic and biosimilar off-patent medication drug development is a long and expensive process. Little has been published on the prevalence of use, safety, efficacy, and economic implications of generic oncology medications, especially in LMICs. Using data from a retrospective series of patients who were

treated with generic oxaliplatin and irinotecan in India, no evidence of decreased clinical outcomes was identified, but the estimated yearly cost savings are nearly $64 million. Physicians and patients in LIMCs often choose to participate in clinical trials as a means of accessing medications that would otherwise not be covered in their low-resource health-care systems. Although this positive effect of increasing clinical trial participation is evident in emerging markets, many challenges must be addressed. These issues include ethical matters, such as the adequacy of informed consent, financial compensation, and the potential conflicts of interest for all involved in the trial, as well as a potential lack of adequate oversight from regulatory authorities and potential ethnic differences in treatment results. New payment system LMICs can also gain access to expensive drugs through price discrimination, which is an important concept in economics and businesses consisting of charging different prices for the same product in different markets or segments of a market. For example, Novartis, has a worldwide access program for imatinib, which has helped tens of thousands of patients gain access to the medication in >80 countries. Roche has begun marketing some of its products under different brand names in India in the hopes of decreasing parallel imports and political backlash while increasing overall sales. Finally, the challenge of access to cancer medications in LMICs can only be effectively addressed through a combination of public and private efforts.[30]

Radiotherapy

Given its central role in the treatment and cure of malignancy often encountered at an advanced stage in LMICs and in its palliative potential, radiation therapy will be a requirement and a key component in cancer care in LMICs.[32] Unfortunately, the accessibility of radiotherapy is still inadequate to meet the needs of those who would benefit from services in LMICs. Previous studies estimated that the supply of radiotherapy machines in Africa was sufficient to meet only 18% of radiation needs, and 22 African and Asian countries did not have access to radiotherapy at all. Developing countries have one radiotherapy machine per 7 million people compared with one per 250,000 people in developed countries. Furthermore, 5 million new people annually are estimated to need radiation therapy in LMICs.[9] For instance, there are only two cobalt radiation machines available for public patients at one of the two tertiary referral centers in Kenya. These machines are overstretched, and appointments for radiotherapy are booked up eight months in advance. For

private patients, there are four linear accelerators in Nairobi. Those who can pay out of pocket or with private insurance coverage are able to get prompt radiotherapy when needed.[31] On the other hand, in lower-resource settings where human resource capacity in health systems is already limited, severe shortages in equipment and trained staff present significant challenges. Therefore, a major component of appropriately designed tools for radiotherapy is a focus on task-shifting to less specialized levels of healthcare professionals. The application of automated radiotherapy treatment planning has great potential to promote this task-shifting and address staffing shortages. Using real-time software and cloud-based capabilities, researchers are developing automated treatment planning algorithms for cervical, breast, and head and neck cancers.[29] If not present at the outset, there must be a clear plan and timeline to obtain this capability within the first few years. A recent series of articles organized by Zeitman addresses the potential role and responsibility of radiation oncology for global cancer health. Datta et al. provide a detailed description of the infrastructure and human-resources shortages using data from GLOBOCAN, the International Agency for Research on Cancer. Suggested remedies include capacity building, networking, and to challenge industry for low-cost, affordable, low-maintenance equipment. Some authors discuss the shortages in Africa and the pros and cons of cobalt and linear accelerators, both of which have roles.[32]

Cancer treatment indications in low- and middle-income countries: Examples

In addition to the previously detailed preventable cancers with risk factors (tobacco for lung cancer, head and neck cancer, and bladder cancer; Human papillomavirus infection for cervical cancer, head and neck cancer; Hepatitis infection for hepatocellular cancer) and cancers that are potentially curable with early detection and treatment, including surgery such as cervical, breast, and colorectal cancers, other cancers are amenable to treatment in countries with low and middle incomes. Cancers that are potentially curable with systemic treatment, and for which early detection is not crucial, include Burkitt's lymphoma, large-cell lymphoma, Hodgkin's lymphoma, testicular cancer, acute lymphoblastic leukaemia, soft-tissue sarcoma, and osteosarcoma. On the other hand, Kaposi's sarcoma, advanced breast cancer, ovarian cancer, and chronic myelogenous leukaemia are cancers that are often well palliated with systemic treatment.[27]

Cervical cancer treatment

In addition to the high burden of disease, a disproportionate number of cervical cancer deaths—nearly 90%—occur in LMICs. With scant screening services available for cervical cancer and a lack of public health awareness of cancer symptomatology in sub-Saharan Africa, a substantial number of patients are diagnosed with advanced-stage disease. In eastern and southern Africa, prevalence and prognosis are compounded by the high frequency of HIV, with HIV-positive women four to five times more likely to develop cervical cancer.[33–34] Timely access to appropriate cancer care may also be limited in many LMICs. Cervical cancer treatment is stage dependent and often includes surgical resection, chemotherapy, radiotherapy, or a combination of these treatments. Cervical cancer is curable, even with locally advanced disease. For locally advanced disease, concurrent chemoradiotherapy followed by brachytherapy has been the standard of care in the United States since the late 1990s. The American Brachytherapy Society (ABS) with participants from LMICs (Bangladesh, Botswana, Brazil, India, Malaysia, Pakistan, Philippines, Thailand, and Vietnam) has made recommendations for guidelines modification that are appropriate for use in resource-limited settings.[33]

Breast cancer treatment

Women in LMICs face various barriers to breast cancer care, from accessing early detection programs to receiving timely diagnosis and appropriate treatment. This situation is reflected in breast cancer five-year survival outcomes, which are 40–60% in LMICs versus 84% in North America. The poor breast cancer survival in LMICs can be attributed to advanced-stage presentation and poor access to systemic therapy.[35] The Breast Health Global Initiative guidelines for the early detection and appropriate treatment of breast cancer in LMICs have been specifically designed to improve breast cancer outcomes in these regions. Optimal management of breast cancer requires a multidisciplinary team. Surgical treatment is often the only modality of treatment available in LMICs where modified radical mastectomy is the most common operation performed.[36] More intensive efforts and collaboration are required in the field of education and training to create greater numbers of skillful and thoughtful surgical oncologists in developing countries in future years.[37] As for chemotherapy and radiotherapy, more resources are needed. Endocrine therapy is available but requires accurate assessment of estrogen receptors status. Targeted therapy with trastuzumab is generally unavailable due to

cost.[36] In some LMICs, there might be an important concern about the non-cost effectiveness of early detection programs when women are not prepared to proceed to diagnosis and treatment, as happened in the Philippines, where 42% of women who had a breast lump detected in a clinical breast examination study refused any further steps toward diagnosis and treatment. Fortunately, the relatively inexpensive essential and generic chemotherapy and hormonal therapy with tamoxifen still constitute the backbone cost-effective systemic therapy for most patients with breast cancer in LMICs.[37] Moreover, there is a need to develop more clinical trials tailored to the socioeconomic conditions of LMICs. For example, herceptin's efficacy and survival advantage in treating breast cancer has been proven in well-developed prospective clinical trials. However, only a meager percentage of the population of LMICs can afford herceptin, which, according to world standards, must be taken for one year in an adjuvant setting. However, another study, from a Finnish group, suggests that only nine weeks of herceptin use shows a disease-free and overall survival advantage (hazard ratios, 0.42 and 0.41). Although the study does not illustrate the difference between the herceptin arms, it presents the possibility for a shorter duration of this costly treatment regimen, which almost 85% to 90% of patients with breast cancer in LMICs cannot afford. Obviously, the cost of nine weeks of herceptin will be more affordable. Conducting such trials in LMICs will help poor and needy patients and will reduce the cost of cancer care in already fragile health care systems.[38]

Focus on treatments in neuro-oncology

Studies of cancer care for nervous tumors or paraneoplastic neurological syndromes in LMICS are scarce. Most of them concern pediatric populations. In fact, central nervous system (CNS) tumors are the most frequent solid tumors in children[39] and the most common cause of cancer-related death in this population. In high-income countries, pediatric cancers are cured at a rate of 80%. This rate does not hold for LMICs due to under diagnosis, poor clinical assessment, and barriers to access of higher levels of care and multi-disciplinary treatment facilities. In a study conducted in Nepal, the most common type of tumor was ependymoma and a more uniform distribution was observed among four of the more commonly found tumor types—astrocytoma, medulloblastoma, and ependymoma—when compared with findings in other LMICs. In Nepal, these four tumors combined accounted for 52.8% of the CNS tumor burden, a percentage comparable to all other LMICs (range: 50.7–92.7%)

with the exception of Uganda (12.4%), in which 40% of the tumors were unclassified. Delayed presentation and treatment found in all studies in LMICs likely negatively affects the survival of children in LMICs with CNS tumors.[40] Another major challenge in the management of CNS tumors in the pediatric population in LMICs is therapy abandonment. In a recently published systematic review and meta-analysis by Seah et al. exploring the magnitude and predictors of this issue, the available abandonment rates ranged from 0% to 59%, from 38 studies (2497 children in 14 countries) and were higher in lower-middle-income countries than upper-middle-income countries. Common predictors for abandonment included distance to treatment centers, financial hardship, and prognostic misconceptions.[41]

Access to cancer palliative care

Palliative care is treatment to relieve, rather than cure, symptoms caused by cancer and improve the quality of life of patients and their families. Although palliative care is an underused resource in high-income countries, it is an all-too-often unavailable resource in LMICs. Unfortunately, of the 40 million people in need of palliative care, nearly 80% reside in LMICs, a number likely to increase in the coming years. The majority of cancers in LMICs are diagnosed in the advanced stage with limited therapeutic options, even in the event that they are available and affordable.[9] In Kenya for instance, related to available resources, there are more than 50 palliative care centers, including free-standing hospices, rural community palliative and hospice centers, religious mission hospitals, public tertiary referral centers, government hospitals, and private hospitals. Pain control remains a major challenge as a result of the cost of narcotics (morphine costs approximately US$3 per gram), the lack of availability of pain medications, and the variable level of awareness of pain management among health care workers.[31] Similar to the scant emphasis on prevention, palliative care is systematically underfunded, particularly in LMICs, despite the fact that 50% of cancer cases are not cured. Although palliative care does not need high-cost technology and is widely applicable, the lack of access to palliative care in poor countries remains a major public health problem and a human rights issue.[34] As such, the WHO recognizes palliation as the fourth key principle of adequate cancer control in LMICs. Morphine and other opiates critical to adequate relief from malignant pain are highly regulated and even unavailable in some countries as a result of government bans. According to a Human Rights Watch report in 2008, India's morphine supply was

adequate to cover only 4% of people who needed it. In addition to these restrictive regulations, societal and cultural beliefs around pain and opiate use, the prominent shortage of professionals trained in palliative care, and an overall lack of awareness and appreciation of the role of palliative care in terminal illness are all factors hampering access to these palliative options.[9] Affordable technologies adapted to the context of LMICs could be an option for these countries. For instance, pain control using low-cost, reliable drug delivery systems such as infusion pumps with the ability to reliably function without consistent access to power while delivering accurate drug dosages makes it a promising option for cancer care units seeking cost-appropriate solutions for infusion of pain medication. Other tools to improve quality of life, such as stents for esophageal cancer patients, can play a role in providing late-stage presenters with drastic benefits in the final months of life. Self-expanding metal stents are an example of a low-cost intervention tool that can be tailored to a particular patient, markedly improving hydration and nutrition in LMICs.[29]

Focus on palliative care in neuro-oncology

For patients with neuro-oncological conditions, the burden for palliative care is double because of their cancer combined with their neurological symptoms. In fact, Miyasaki et al. showed that the symptom burden in advanced Parkinson's disease (PD) for instance is similar to that in metastatic cancer. Patients with brain cancer have distinct symptom profiles including more cognitive problems, seizures, and communication deficits than patients living with other types of cancers. In clinical experience regarding spiritual well-being, neurology patients experience their disease as something intrinsic to their person, which clearly differs from patients with cancer who see "the cancer" as something outside themselves. In neuro-oncology, the association of both conditions could be even more challenging. Caregivers of neurology patients also have similar, if not higher, rates of distress and burnout as caregivers of patients with cancer. Moreover, palliative physicians who are largely trained in internal medicine may be less comfortable with neurologic illnesses other than cancer than with the combination of the two.[42]

Discussion

In this chapter, we undertook a general analysis of the situation of access to cancer care in countries with limited resources. The main publications in this field were studied to draw the current picture of cancer

epidemiology and management in a large area of the world represented by LMICs. Although the burden of infectious diseases is significant in those communities, chronic pathologies such as cancers are growing exponentially, especially those that are precisely associated with infectious risk factors. Awareness and access to care related to cancer is very limited and even unavailable in some countries. Malignancy prevention, diagnosis, and therapy are not a priority for most LMICs governments. Obviously, poor outcome and increasing mortality rates are the result. Basic infrastructure, screening, and diagnosis tools and treatments are lacking. Prevention and management of risk factors of various cancers is the first step in cancer care programs. These interventions are costly and require knowledgeable and experienced personal health care. Despite this difficult situation, some countries are trying to implement programs to prevent, screen for, and treat the most frequent cancers in their populations. Prevention of leading cancers like gynecologic cancers, lung cancer, and liver cancer was based on vaccines, reduction of tobacco consumption, healthy food, and physical activity. These interventions are easy to carry out because they are not costly, except for vaccines. Infection-related cancers like cervical cancer were notable for screening because of their prevalence in LMICs. Visual inspection with acetic acid and cytodiagnosis were the main methods used in North African countries. Breast cancer was the target in many LMICs. Annual breast examination in women aged 30 and more was the main screening method, which was validated by the WHO. Mammography associated with breast ultrasound is sensitive but expensive. Screening for colorectal cancer was made via fecal-occult-blood test in some Asian and African countries. Colonoscopy was indicated when this latter was positive. Early diagnosis of lung cancer remains problematic because it is invasive and involves radiation. Four key priorities have been identified to promote health services for cancer control and data acquisition including the capacity to build oncologic health-service research, policy, and planning relevant to LMICs, the development of high-quality health data sources, oncology-related economic evaluations, and the exploration of high-quality models of cancer control in LMICs. All three mainstays of cancer treatment, i.e. surgery, chemotherapy, and radiotherapy as well as palliative care suffer major shortages in LMICs. However, several remedies are conceivable such as using generic and biosimilar drugs, expanding participation in clinical trials, implementing universal health-care schemes to pool resources, using compulsory licensing schemes, and increasing public–private partnerships. Neuro-oncological cancer care in LMICs is very understudied in world literature. Although they have serious effects, CNS

tumors remain under-diagnosed in countries with limited resources. Advances in neurosurgery techniques have not revolutionized this field in LMICs because technical platforms are unavailable. Neuro-oncology is still a limited domain with neither structured infrastructure nor established care programs in LMICs.

Conclusions

Cancer control represents a health priority all over the world especially in LMICs where the disease wreaks havoc. Investment in cancer prevention and control on the broader scale is required now more than ever in the face of an aging population in LMICs and rising cancer incidence and mortality. Attention should be paid to all four areas identified by the WHO as being integral to the success of cancer control programs: risk factor modification and prevention, early diagnosis, treatment, and palliation. Prevention remains the main cost-effective axis in cancer care in LMICs. In fact, several cancers in LMICs are preventable or their risk is significantly attenuated either by the eradication of or vaccination against carcinogenic infectious agents or by avoiding carcinogenic exposures, such as tobacco smoke or air pollutants from indoor cooking. However, lack of awareness, cultural and religious beliefs, inadequate infrastructure, and logistics are the principal barriers against this. Research focused on understanding and addressing these barriers may be informative and effective. The epidemiology of cancer is broadly shared between limited-income countries. Breast cancer, cervical cancer, colorectal cancer, and lung cancer are the most frequent. There are already a few implemented programs for screening and malignancy prevention. Early detection of cancer remains a challenge when strategies and infrastructure are lacking. The WHO recommended many instructions in the field of cancer care and prevention. However, personal health care in LMICs could not follow guidelines. The diagnosis of cancers is made at a late, often metastatic, stage. Therapeutic and palliative care is not always affordable. Any cancer control effort would benefit from rigorous testing in LMICs because evidence for interventions shown to be beneficial in resource-replete settings are not universally extrapolatable to resource-constrained settings. Policy makers need to realize that cancer screening could minimize mortality rates and improve life quality in LMICs. Recently, some LMICs countries showed an effort in cancer care focused on prevention and innovation more than adapted therapeutic schemes. However, as a complex and growing health problem globally, and in LMICs in particular, cancer should be a priority for governments and requires revolutionary

interventions and the integration of multiple sectors that not only include but also extend beyond health care delivery.

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