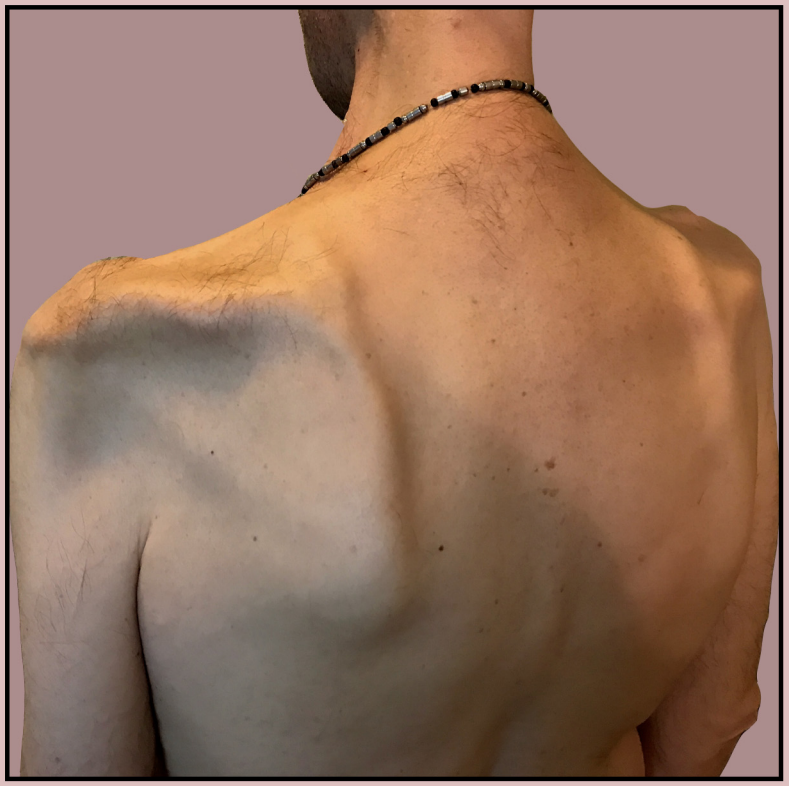

Effects of Cancer Treatment on the Nervous System, Volume 2

Edited by

Wolfgang Grisold, Stefan Oberndorfer, Guido Cavaletti and Riccardo Soffietti

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PART 1:

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

CHAPTER 1.1

NEUROSURGERY AND "BRAIN TOXICITY" INCLUDING NOVO TTF

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Abstract

Neurosurgical resection of brain tumors represents an indispensable treatment option in the multimodal management of patients. In recent years there is clear evidence that the maximum safe resection of brain tumors correlates with the patient prognosis. The neurosurgical goal to achieve maximum safe resection is especially challenging for neurosurgeons in gliomas due to their diffuse infiltrative growth pattern into the normal brain and the lack of a definite tumor margin. Therefore, complete resection of brain tumors, especially diffusely infiltrating gliomas, bears the risk of postoperative neurological deterioration ("brain toxicity"). To minimize the risk of a new postoperative neurological deficit, several advancements were introduced into the neurosurgical field to optimize surgery of brain tumors and markedly increase the safety of these neurosurgical procedures in recent decades. First of all, neuronavigation with multiple preoperative image data is nowadays the current standard for preoperative planning and intraoperative image guidance during brain tumor surgery at most neurosurgical centers worldwide. Intraoperative magnetic resonance imaging (MRI) is a powerful imaging tool that is able to detect residual brain tumor tissue during surgery independent from brain-shift; it is not, however, widely available due to its high costs. Additionally, functional imaging techniques such as fiber tracking/diffusion tensor imaging, functional MRI and

transcranial magnetic stimulation are powerful techniques to visualize brain function during the preoperative investigation of tumors in eloquent brain regions. To localize and monitor the brain function during surgery of eloquent brain tumors, intraoperative monitoring and brain mapping/stimulation are powerful techniques to prevent injuring sites of motor, language and sensory function. In this book chapter, we also focus on “brain toxicity” of specific substances that support the neurosurgeon during resection of brain tumors, locally applied substances that bypass the limited permeability of the blood–brain barrier and tumor treating fields. Overall, “brain toxicity” of these substances and tumor treating fields is relatively low, however, specific side effects have to be considered.

Keywords: Brain tumors, gliomas, epileptic seizures, neurotoxicity, tumor treating fields

1. Neurosurgery of brain tumors

More than 120 different types of central nervous system (CNS) tumors are distinguished by the World Health Organization (WHO) (David N. Louis, MD Hiroko Ohgaki, PhD Otmar D. Wiestler, MD Webster K. Cavenee, 2016). These tumors are further divided, according to their behavior, into non-malignant and malignant tumors as well as primary and secondary CNS tumors. Diffusely infiltrating gliomas represent the most common primary brain tumors in adults and these tumors are further classified into slowly growing low-grade gliomas (LGG; WHO grade II) and rapidly growing high-grade gliomas (HGG; WHO grade III and IV). Within the subgroup of diffusely infiltrating gliomas, glioblastoma (GBM) is the most frequent and aggressive CNS tumor with a devastating patient prognosis. Since gliomas are characterized by indefinite tumor margins and glioma resection is thus particularly associated with the risk of potential “neurotoxicity,” this chapter will focus on diffusely infiltrating gliomas.

Neurosurgical resection or the biopsy of brain tumors represents an essential treatment option in multimodal management. After surgery, the histopathological tumor diagnosis is established according to the criteria set by the WHO. In recent years, further characterization of brain tumors with the assistance of molecular markers has gained more and more importance in routine clinical practice for postoperative treatment decisions. Depending on the histopathological diagnosis and the molecular markers, either postoperative treatment such as chemotherapy and/or radiotherapy is initiated or a follow-up treatment with regular imaging studies is conducted in patients suffering from brain tumors (Stupp et al., 2005). Over recent years,

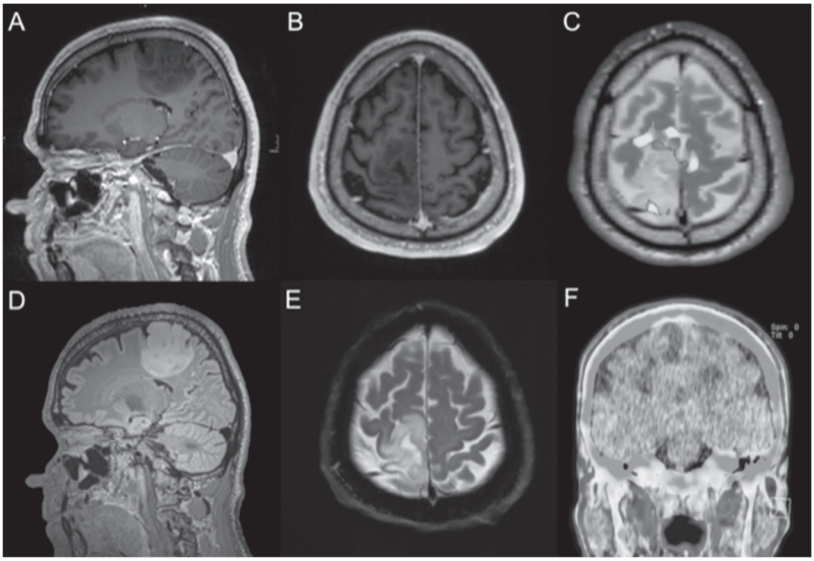

Figure 1: Preoperative investigation of brain tumors with structural MRI, functional MRI and positron emission tomography. (A) Sagittal and (B) axial contrast-enhanced T1-weighted images demonstrate a parietal/postcentral lesion with non-significant contrast-enhancement that is hyperintense on (D) sagittal FLAIR and (E) axial T2-weighted sequences. (C) Functional MRI is able to localize motor function of the lower extremity that is in close proximity to the anterior tumor margin according to T2-weighted images. (F) Positron emission tomography is capable of identifying an intratumoral region (red) of increased tracer uptake that might already be a sign of focal malignant transformation of an initial low-grade glioma.

several studies have been conducted with the purpose of clarifying the value of the extent of tumor resection in different brain tumors (Hollon, Hervey-Jumper, Sagher, and Orringer, 2015; Sanai and Berger, 2008; Sanai, Polley, McDermott, Parsa, and Berger, 2011; Soffietti et al., 2010). According to these studies, clear evidence now exists that complete resection of the vast majority of brain tumors is associated with an improved patient prognosis as compared to incomplete tumor removal (Sanai and Berger, 2008). In diffusely infiltrating gliomas, complete tumor resection is also beneficial as it prolongs the time period for the malignant transformation of initial LGG. Consequently, the neurosurgical aim is maximum safe tumor removal with preservation of neurological function whenever possible (Sanai and Berger, 2008; Stummer and Kamp, 2009;

Tonn and Stummer, 2008; Vogelbaum et al., 2012). In contrast, a neurosurgical biopsy is preferentially conducted in selected patients with deep-seated brain tumors or suspicion of a CNS lymphoma. According to the Response Assessment in Neuro-Oncology (RANO) criteria, the aim of surgery in LGG is the complete resection of the abnormality on preoperative T2-weighted/Fluid attenuated inversion recovery (FLAIR) sequences (Chukwueke and Wen, 2019). In other tumors such as HGG and brain metastases, the aim of surgery represents the complete safe resection of the contrast-enhancing tumor according to preoperative MRI.

1.1 Challenges of brain tumor surgery

Since neurosurgical resection is the primary treatment for the majority of patients with brain tumors, these tumors pose a special challenge for neurosurgeons in the preoperative planning phase as well as during the procedures (Sanai and Berger, 2008). In this sense, neurosurgical resection of LGG and HGG is especially challenging due to their characteristic diffusely infiltrative growth pattern into the normal brain. Furthermore, the most common primary brain tumors frequently show only slight differences in the macroscopic appearance as compared to the normal brain parenchyma, and thus insufficient visualization of the tumor margin is frequently observed during surgery (Martin et al., 1998). Therefore, these limitations might lead to incomplete resection of brain tumors with associated unfavorable patient prognosis. In diffusely infiltrating gliomas, incomplete tumor resections are reported in the literature in up to 88% of the cases (Sanai and Berger, 2008; Smith et al., 2008; Sanai et al., 2011; Capelle et al. 2013). Although considered as well-demarcated tumors, incomplete resections in brain metastases are also reported in approximately 25% of cases with available postoperative MRI (Kalkanis et al., 2010; Kocher et al., 2011; Patchell et al., 1998).

1.2 Potential perioperative neurological deficits (“Neurotoxicity”)

Maximal safe neurosurgical resection is considered to be the gold standard for the initial treatment in the majority of brain tumors. Nonetheless, neurosurgery for brain tumors is associated with potential perioperative morbidity and mortality. The rate of perioperative morbidity ranges from 9% to 40% as well as the mortality rate in neurosurgical procedures which must be taken into account (Cinotti et al., 2018; Trinh et al., 2015; Wong et al., 2012). During the perioperative period, a large diversity of postoperative complications might occur that are mainly

dependent on the tumor localization and the tumor type. Since brain tumors are frequently localized in the proximity of functional brain structures such as cortical motor or speech areas and the visual pathway, complete tumor removal bears the risk of new postoperative neurological deficits. This has a special relevance in diffusely infiltrating gliomas due to the lack of a distinct tumor margin.

Common neurological deficits after brain tumor surgery include sensory/motor deficits, visual perceptual deficits, impaired cognition and epileptic seizures (Mukand et al., 2001). Moreover, cranial nerve palsy, aphasia, dysarthria, dysphagia, ataxia and diplopia might occur after resection of brain tumors. Further intracranial complications comprise infarction, hemorrhage, postoperative peritumoral edema, intracranial hypertension and hydrocephalus (Trinh et al., 2015; Wong et al., 2012). Additionally, adverse medical conditions such as deep venous thrombosis and pulmonary embolism, pulmonary complications as well as renal and cardiac complications, and local or systemic infections may occur. Moreover, the removal of brain tumors located in the skull base can bear the risk of cerebrospinal fluid leak through insufficient dural closure as dural repair may be challenging in these cases.

Also, the urgency of surgery (elective or emergency surgery) plays an important role in the occurrence of postoperative complications such as intracranial hematoma, which have a higher incidence in emergency patients. Furthermore, it is well established that the neurosurgical institution and the performing neurosurgeon have major impacts on postoperative patient outcome (Trinh et al., 2015). The fact is that high-quality institutions with well-experienced neurosurgeons, who have improved access to advanced surgical resources, significantly reduce the risk of increased postoperative mortality and morbidity.

1.2.1 Epileptic seizures

Epileptic seizures represent common initial symptoms in patients with brain tumors, especially patients suffering from diffusely infiltrating gliomas. Interestingly, epileptic seizures are a favorable prognostic factor for survival in patients with LGG (Chang et al., 2008; Lote et al., 1998; Schaller and Rüegg, 2003). Chang et al. (2008) referred to their data of 332 LGG patients in which epileptic seizures had a high impact on the patients' quality of life (QOL). Furthermore, surgical resection and a short preoperative history of seizures reduced the number of seizures in this patient group postoperatively. In detail, 90% of these patients were seizure-free or had "meaningful improvements" after surgery. In contrast,

a long history of preoperative therapy of refractory epileptic seizures and simple partial seizure types showed an increased tendency to poor postoperative seizure control. The authors further illustrated that freedom from seizures after surgery and a return of epileptic seizures over time was associated with tumor progression. Pallud et al. argued that not only epileptic seizures but also antiepileptic drugs (AED) might result in cognitive impairment (Klein et al., 2003; Pallud et al., 2014; Ruda et al., 2012).

2. Techniques to minimize neurological deficits

Routinely, resection of brain tumors is performed with the assistance of an advanced neurosurgical microscope. In recent decades, several advancements were introduced into the neurosurgical field to optimize surgery of brain tumors and markedly increase the safety of neurosurgical procedures by minimizing the risk of new postoperative neurological deficits.

2.1 Neuronavigation

One of the greatest advancements in neurosurgery in recent decades was the introduction of neuronavigation systems. In this sense, Roberts et al. reported the first application of a neuronavigation system during resection of brain tumors approximately thirty years ago (Roberts et al., 1986). Such navigation systems are capable of including imaging data acquired in the preoperative course and thus facilitate the preoperative approach to planning and precise localization of brain tumors and adjacent brain structures during tumor resection. Primarily, only single image data such as computerized tomography (CT) or one selected MRI sequence - mostly contrast-enhanced T1-weighted MRI images - was usually integrated into neuronavigation. The advanced neuronavigation systems are nowadays also capable of integrating multiple image data that are co-registered mostly with standard MRI. As a consequence, navigation with multiple imaging data such as positron emission tomography (PET), multivoxel magnetic resonance spectroscopy (MRS) and functional images is feasible (G. Widhalm et al., 2011). Therefore, neuronavigation systems are nowadays an essential component of neurosurgical procedures in brain tumors and are considered as standard in the neurosurgical daily routine in most neurosurgical centers worldwide. However, loss of cerebrospinal fluid after craniotomy, brain edema and gravity effects result in distinct changes in brain structure during resection of brain tumors, which is called “brain-

shift." This well-known phenomenon in neurosurgery might lead to a progressive inaccuracy of the neuronavigation system and can reach up to 2.4 cm (Georg Widhalm et al., 2010). Thus, precise localization of brain structures as well as the tumor margin, especially at the end of surgery, is frequently not possible since the neuronavigation is based on preoperatively acquired imaging data.

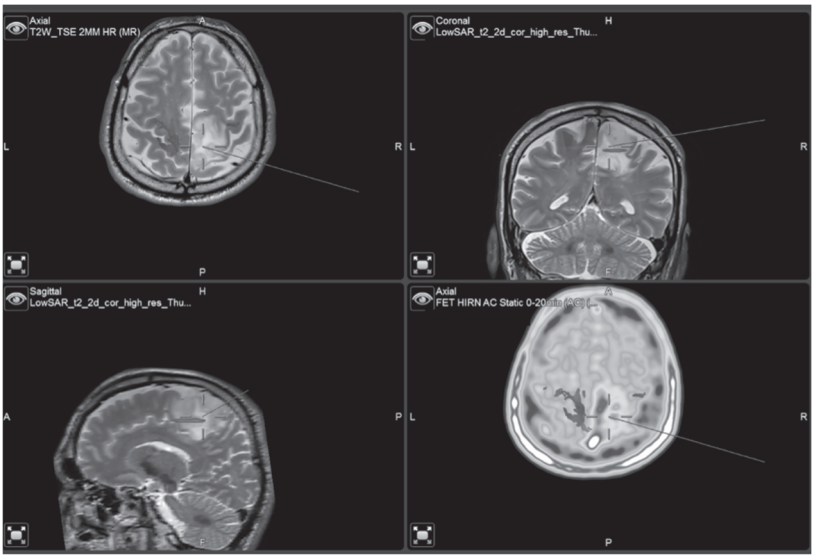

Figure 2: Intraoperative application of neuronavigation with multiple image data. Navigation-guided resection of a left parietal/postcentral glioma with non-significant contrast-enhancement with multiple image data including T2-weighted sequences, fiber tracking/diffusion tensor imaging and positron emission tomography (*right below*).

2.2 Intraoperative imaging

Generally, the extent of resection after brain tumor surgery is investigated by postoperative MRI performed in most centers within the first 72 hours to detect a potential residual tumor (Albert et al., 1994). In the case of a large and unexpected residual tumor, a second surgery has to be taken into consideration. Thus, the acquisition of image data during surgical resection of brain tumors would be the ideal way to detect and subsequently remove residual tumor tissue in the same procedure. In this sense, in 1999 Black et al. first described the use of intraoperative MRI

during surgery of brain tumors (Black et al., 1999). In 2011, Senft et al. demonstrated in a randomized, controlled trial that significantly more patients in the intraoperative MRI group had a complete glioma resection compared to the control group (96% vs 68%) (Senft et al., 2011). In this sense, intraoperative MRI provides the advantage of an immediate intraoperative update of imaging information. The new MRI sequences on the one hand can be used to evaluate the extent of resection during surgery and on the other hand can be uploaded into the neuronavigation system. This very useful feature provides the neurosurgeon with regenerated imaging information intraoperatively. In the case of residual tumor tissue being visible on the intraoperative MRI images, surgery can be continued safely, based on the advantage of a compensated brain-shift. Consequently, this innovative method is useful at increasing the rate of complete resections of brain tumors. Due to the disadvantages of this technique, such as prolonged operation time and high expense, intraoperative MRI is not widely available.

2.3 Functional imaging

Furthermore, diffusion tensor imaging (DTI), functional MRI (fMRI) and transcranial magnetic stimulation (TMS) are powerful techniques to visualize brain function during the preoperative investigation of tumors in eloquent brain regions. First of all, DTI data is capable of visualizing relevant white matter tracts such as the corticospinal tract or arcuate fascicle in the proximity of a brain tumor (Nimsky et al., 2006). Secondly, fMRI investigates brain activity and is capable of detecting changes associated with blood flow. As a result, eloquent brain regions especially relevant for motor and speech function can be identified with the assistance of fMRI (Hall et al., 2005). Finally, TMS represents a new and promising method for preoperative mapping of functional brain areas similar to direct intraoperative cortical electrical stimulation (Picht et al., 2016). Primarily, TMS has been demonstrated to be a reliable method for preoperative mapping of the motor cortex of brain tumors localized in, or in the proximity of, the precentral gyrus with a high accuracy. In recent years, TMS has also increasingly been investigated for precise preoperative mapping of brain areas relevant for speech function.

All these above-mentioned functional imaging data can be integrated into the neuronavigation and intraoperatively applied to limit the resection of brain tumors in or adjacent to eloquent brain regions. Consequently, navigation with functional imaging data is a useful tool to minimize the risk of a new postoperative neurological deficit, which is again limited by

the decrease of accuracy due to brain-shift.

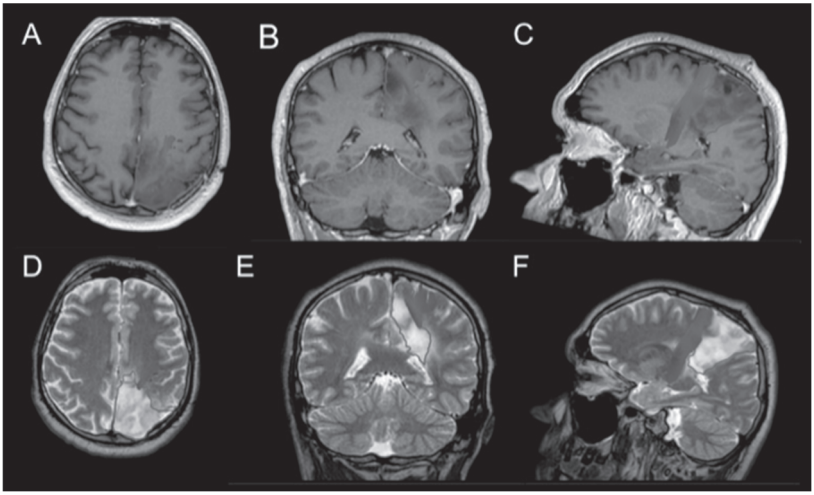

Figure 3: Intraoperative use of navigation with fiber tracking data to increase the safety of brain tumor surgery. Navigation with fiber tracking data using (A, D) axial, (B, E) coronal and (C, F) sagittal contrast-enhanced T1-weighted images (*above*) and T2-weighted images (*below*) to limit resection of brain tumors in and near the central motor region and minimize the risk of postoperative neurological deficits.

2.4 Intraoperative monitoring and brain mapping

To localize and monitor the brain function in eloquent brain tumors, intraoperative monitoring and brain mapping/stimulation represent powerful techniques to prevent injuring sites of motor, language and sensory function. Intraoperative monitoring refers to the constant reassessment of neurological function by using direct excitation of neural pathways during the brain tumor resection while the patient is anesthetized. The two most frequently applied methods during neurosurgical procedures are motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs). By direct stimulation of brain regions involved in the motor- and/or sensory pathways, it is possible to monitor the functional integrity in "real-time" in order to reduce postoperative neurological deficits by avoiding damage to those eloquent areas.

Current limitations of intraoperative monitoring alone revolve around eloquent areas, such as language regions, that are not solely integrated in either the motor and/or the sensory system. In such cases, the so-called “brain mapping/stimulation” during awake surgery is a powerful method to precisely identify functional language areas not involved in the sensory and/or motor system after dura opening and prior to the tumor resection. During the different steps of tumor resection, the neurosurgeon repeatedly stimulates suspected language areas to examine the patient’s language performance in an awakened state. In case of a significant deterioration of language function, the tumor resection should thus be terminated to avoid a permanent postoperative neurological deficit. Recently, a meta-analysis found that the intraoperative use of brain mapping/stimulation results in fewer postoperative late severe neurological deficits as well as more complete tumor resections compared to surgeries without brain mapping/stimulation (De Witt Hamer et al., 2012).

2.4.1 Intraoperative occurrence of epileptic seizures

Intraoperative monitoring and brain mapping/stimulation during surgery of brain tumors localized in eloquent areas might lead to epileptic seizures/abnormalities on EEG monitoring. With regard to awake craniotomies, these possible consequences for the patient have to be considered by the neurosurgeon. Dineen et al. reviewed in a recent study the most important consequences of epileptic seizures during awake craniotomies (Dineen et al., 2019). According to their data, the authors observed a high risk of aspiration and breathing problems based on pharmacologically caused respiratory depression due to the absence of airway protection in awake patients. As a result, the postictal and/or post-therapeutic status of the patient (somnolence, confusion, dysphasia) can impede the intraoperative mapping after medical seizure treatment during awake surgery. Further studies also described a possible increase in the essential mapping thresholds due to postictal cortical depression with possible false localization of eloquent brain areas (Blume et al., 2004; Karakis et al., 2015). Dineen et al. further investigated in their study in 544 consecutive functional mapping cases relevant factors for the appearance of epileptic seizures during surgery and found that the risk of intraoperative seizures can be markedly reduced by preoperative administration of an AED loading dose (Dineen et al., 2019).

3. Toxicity of Perioperatively and Locally applied substances

In recent decades, specific substances were introduced in the neurosurgical field to support the neurosurgeon during resection of brain tumors. Furthermore, new approaches with the local application of specific substances in brain tumors were also developed that bypass the limited permeability of the blood–brain barrier (BBB) in order to increase the therapeutic agent concentrations in brain tumors.

3.1 5-Aminolevulinic Acid (5-ALA)

Intraoperative visualization of tumors with the assistance of fluorescence represents an innovative technique for improved visualization of tumor tissue during surgery. Since 1992, 5-aminolevulinic-acid (5-ALA) has been increasingly applied as a fluorescent dye for such fluorescence-guided procedures in different surgical disciplines. After oral administration of primarily non-fluorescing 5-ALA, this dye leads to intratumoral accumulation of fluorescing protoporphyrin IX (PpIX) in specific tumors. With the assistance of a modified neurosurgical microscope including a xenon light source and longpass filter, specific brain tumors can be visualized during surgery independent of brain-shift by their characteristic red fluorescence under violet-blue excitation light. As a consequence, this innovative technique supports the neurosurgeon, especially to improve the definition of the margin in brain tumors. In 2000, Stummer et al. described that 5-ALA fluorescence-guided surgery of HGG resulted in an increased rate of complete resections of the contrast-enhancing tumor area compared to historic data with conventional white-light procedures (Stummer et al., 2000). In 2006, Stummer et al. described a randomized multicenter phase III trial that found a significantly higher rate of complete resections (65% and 36%, respectively) and prolonged six months progression-free survival (41% and 21%, respectively) in HGG surgically treated with 5-ALA fluorescence-guided surgery compared to conventional white-light resections (Stummer et al., 2006). Based on these convincing data, the use of 5-ALA was approved in the European Union for resection of HGG in 2007. Ten years later, 5-ALA was also approved by the Food and Drug Administration (FDA) in the United States. Nowadays, 5-ALA fluorescence-guided surgery is widely used at many neurosurgical centers worldwide for improved resection of HGG. In recent years, the 5-ALA fluorescence technique has also been increasingly used in brain tumors other than HGG for improved intraoperative visualization of

anaplastic foci in radiologically suspected LGG, meningiomas, metastases and lymphomas (Kiesel et al., 2018; Marhold et al., 2019; Millesi et al., 2016; Georg Widhalm et al., 2010, 2013).

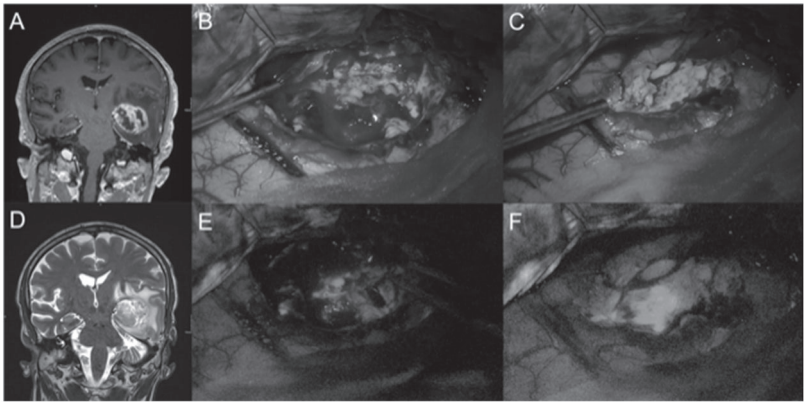

Figure 4: Fluorescence-guided surgery using 5-ALA in a patient suffering from a glioblastoma. Coronal T1-weighted image shows a contrast-enhancing lesion in the left temporal lobe (D) with a hyperintense “infiltration zone” on T2-weighted sequences. (B) Conventional white-light microscopy demonstrates tumor tissue with distinct macroscopic abnormalities (E) that can be visualized by strong 5-ALA fluorescence under violet-blue excitation light. (C) The region near the tumor border reveals no clear macroscopic abnormalities under white-light microscopy, (F) but tumor tissue can still be detected with visible 5-ALA fluorescence.

3.2 Neurotoxicity of 5-ALA

In general, 5-ALA is a well-tolerated fluorescent dye and adverse effects are rare in routine clinical practice. However, some potential side effects of 5-ALA must be considered. First of all, 5-ALA results in activation of its fluorescing metabolite PpIX, not only in the brain but in the skin as well. Thus, 5-ALA is a potential phototoxic substance that might lead to skin and subcutaneous tissue disorders such as photosensitivity or photodermatosis. However, 5-ALA and its metabolites are eliminated quickly from the body (t½ = 50 minutes), therefore, the risk of skin photosensitivity is limited to one or two days (Regula et al., 1995). Consequently, patients should avoid contact with sunlight and should remain ~~are kept~~ in a darkened room for at least 24h after 5-ALA administration.

Furthermore, 5-ALA might lead to an increase in liver function parameters/enzymes or an elevation of blood bilirubin and hepatobiliary disorders. Moreover, in patients suffering from renal or hepatic dysfunction, 5-ALA metabolism is slower and the risk of phototoxicity may be increased due to the fact that 5-ALA is usually excreted within 24 hours by the kidneys and sometimes by the liver (Utsuki et al., n.d.). Therefore, patients with risk factors with regard to hepatobiliary conditions or preoperatively elevated hepatic enzyme levels require closer monitoring after surgery until physiological levels are established. Furthermore, in patients suffering from porphyria the administration of 5-ALA is contraindicated.

By administering the standard dose of 5-ALA (20 mg per kg bodyweight) no further severe side effects usually occur. Rarely, hypotension or gastrointestinal disorders such as nausea, vomiting and diarrhea might occur in patients after 5-ALA administration. However, in many patients suffering from hypotension, this condition was already present before oral 5-ALA intake (Chung and Eljamel, 2013). Furthermore, gastrointestinal disorders after 5-ALA administration might also be caused by other drugs applied during the perioperative course or general anesthesia, which are known to cause postoperative side effects such as nausea and vomiting.

3.2.1 5-ALA based photodynamic therapy (PDT)

In recent decades, local photodynamic therapy (PDT) showed promising results in the treatment of primarily recurrent HGG and has been performed with various substances. However, this innovative treatment approach was limited for a long time by its considerable risk of treatment related adverse effects due to the restricted selectivity in tumor cells. PDT based on 5-ALA relies on the principle of the preferential accumulation in the mitochondria of HGG cells (Castano et al., 2005). In short, activated by irradiation at a specific wavelength, this photosensitizer inducts reactive oxygen species (ROS)-mediated apoptosis, which is a programmed cell death mechanism in tumor cells (Bonnet et al., 2007; Michelakis et al., 2008).

A previous study investigated the impact of 5-ALA and its ability to induce ROS-mediated apoptosis of tumor cells (Sugiyama et al., 2014). The findings demonstrated the potential of 5-ALA as a selective antitumor photosensitizer for PDT (Ueta et al., 2017). Nowadays, two main applications of 5-ALA based PDT are used. On the one hand, irradiation is executed with a balloon diffuser in the resection cavity immediately after

5-ALA fluorescence-guided resections. By this approach, no additional 5-ALA administration is required. On the other hand, stereotactic interstitial PDT (iPDT) is performed preferentially with cylindrical diffusers, which deliver light irradiation directly inside the tumor tissue.

3.2.2 Neurotoxicity of PDT

Due to its high tumor selectivity, 5-ALA in PDT evokes only minor adverse effects, such as short-lasting phototoxicity, therefore displaying relatively safe therapeutic properties as a photosensitizer. The major advantage of 5-ALA for safe PDT is the quick photobleaching effect of the active metabolite PpIX (Stepp and Stummer, 2018). Thus, especially in tumor cells containing only a little photosensitizer, even prolonged irradiation and extremely high doses of light cannot induce phototoxic effects as long as the intensity is low enough to avoid thermal damage. Since cells of the normal brain parenchyma accumulate none or only minimal amounts of PpIX, there is no risk of phototoxic damage to the normal brain. Nevertheless, there exists evidence that 5-ALA based PDT directly interferes with endothelial cells within the brain, thus leading to a mediated opening of the BBB (Semyachkina-Glushkovskaya et al., 2017). The amount of these endothelial cells is only small (<1%), but the effects of 5-ALA based PDT on the BBB might lead to induction of local, transient edema in the surrounding normal brain tissue (Ito et al., 2005; Stepp and Stummer, 2018). This adverse effect must be considered during treatment planning and management in the context of steroid administration to minimize the 5-ALA PDT induced edema.

3.3 BCNU Wafers

Another interesting and locally applied approach is the implantation of biodegradable polymers impregnated with carmustine (bis-chloroethyl nitrosourea, BCNU) in the tumor resection cavity of HGG. BCNU wafers (Gliadel®; Eisai, Tokyo, Japan) are usually used in addition to the standard therapy of surgery, radiation and chemotherapy for treatment of HGG. One of the advantages of the therapy with BCNU wafers is the supply of high doses of local chemotherapy at the tumor cavity, bypassing the BBB (Shibahara et al., 2018). In 1995, Brem et al. initially studied the applicability and safety of BCNU wafers for patients with a GBM (H Brem, Ewend, et al., 1995; H Brem, Piantadosi, et al., 1995; Henry Brem et al., 1991). In 2003 Westphal et al. published a phase 3 trial of local chemotherapy with BCNU wafers in patients with primary HGG and

found that the median survival rate for the BCNU wafer plus radiation group was 13.9 months, whereas 11.6 months was reported for the placebo wafer plus radiation group (Westphal et al., 2003). In the following years, subsequent studies analyzed the therapy with BCNU wafers especially in combination with temozolomide (TMZ) and radiation therapy. In these studies, the median survival rate showed an extension of up to 21 months (Affronti et al., 2009; Bock et al., 2010; McGirt et al., 2009; Noël et al., 2012; Pallud et al., 2015; Sonoda et al., 2017). In 1997, Gliadel® gained FDA approval for the treatment of recurrent GBM and in 2003 for newly diagnosed HGG.

3.3.1 Neurotoxicity of BCNU Wafers

In 2016, Ashby et al. published a literature review analyzing patients with a newly diagnosed HGG after implantation of BCNU wafers combined with standard radiotherapy and adjuvant TMZ and also reported the occurrence of side effects (Ashby et al., 2016). According to this review, the most frequent adverse events were myelosuppression (10.2%), neurological deficits (7.8%) and healing abnormalities (4.3%). Furthermore, epileptic seizures, fatigue and gastrointestinal disorders were also reported. However, systemic carmustine levels usually showed only low amounts and thus these adverse events might also be based on the systemic toxicity of standard adjuvant therapy.

3.4 Convection-Enhanced Delivery (CED)

In recent decades, convention-enhanced delivery (CED) was introduced as another promising local treatment approach. In the 1990s a group of researchers led by Edward Oldfield of the National Institute of Health was the first to describe and develop CED (Bobo et al., 1994; Lonser et al., 2002; Nguyen et al., 2003). CED allows local delivery of targeted agents in the brain bypassing the BBB. In this sense, one or more catheters are inserted through a standard burr hole into the brain/tumor area with navigational guidance. Subsequently, an infusion pump is connected to the catheter and specific drugs are delivered via infusion directly into the targeted area. The advantages of this innovative technique are to provide high local drug concentrations inside the tumor. Still, the most frequently applied agents are those which cannot be transported easily through the BBB. However, further studies and developments, e.g., regarding catheter technology and prolonged delivery are warranted to

benefit from such a promising and innovative technique and take advantage of its full therapeutic capability.

3.4.1 Neurotoxicity of CED

A previous review analyzed clinical trials of the last two decades with regard to the safety and tolerability of various agents for CED including antibodies, targeted toxins, interleukins, chemotherapeutic drugs, targeted radioisotopes, and vaccines (Shi and Sanche, 2019). In this review, the authors classified CED related toxicities as immediate (within hours of the placement of catheters), early (hours to days after CED) and late (days to weeks after infusion) side effects. In detail, immediate side effects are induced by physical damage to the brain tissue as well as cerebral hemorrhage through catheter placement and might cause symptoms such as headache, epileptic seizures and neurological deterioration. Early side effects are usually caused by mechanical stress through the infusion of fluids and the most common symptoms include headache, epileptic seizures, worsening of neurological symptoms, shivering, and mild fever. Late side effects include mainly neurological symptoms due to toxicity from the delivered drugs.

Furthermore, the authors of the aforementioned review article also distinguished between local and systemic toxicities. (1) Local toxicities (common and severe) include “neurotoxicity” that is mainly based on inflammatory reactions, tissue necrosis and perifocal edema. Depending on the tumor size and localization, patients with “neurotoxicity” show symptoms of headache, seizures, nausea, pyrexia, sensory disturbance, upper motor neuron lesion, aphasia/speech disorder, and memory impairment. However, tumor debulking or craniotomy was necessary in only a few cases to treat cerebral edema and intracranial hypertension (Rand et al., 2000). Mostly, edema can be well controlled by the use of corticosteroids. Certainly, the severity of local toxicity is dependent on the type of the infused substance. Further studies also described local infections after catheter placement that were usually, however, well controllable by antibiotics (Carpentier et al., 2010; Pöpperl et al., n.d.; Tanner et al., 2007). Systemic toxicities (rare and transitory) include general toxicity with symptoms such as fever, fatigue and erythema as well as gastrointestinal symptoms. Other studies also observed hematological changes and liver enzyme perturbations (H Brem, Ewend, et al., 1995; Carpentier et al., 2006, 2010; Laske et al., 1997; Souweidane et al., 2018).

4. Tumor Treating Fields (TTF)

The application of "tumor treating fields" (TTF) constitutes a new adjuvant therapeutic modality in the treatment of GBM that exposes the tumor to localized low-intensity alternating electric fields at a frequency of 100-300 kHz (200 kHz used in GBM). The exact mechanism of action is not completely understood; however, preclinical in vitro data suggest growth inhibition by mitotic arrest at metaphase/anaphase due to microtubule subunit misalignment (Fonkem and Wong, 2012; Stupp et al., 2012; Wick, 2016). In addition to cell cycle interruption leading to caspase-independent autophagy and necroptosis, recent preclinical analyses also showed a reduced potential of glioma cells for migration and invasion that might contribute to growth control. To apply the electrical field to the tumor, four transducer arrays with a total of thirty-six electrodes are placed directly to the scalp. Prior to transducer placement, the head needs to be shaved and transducer arrays are changed once or twice a week to provide optimal electric field transmission. Transducers are connected to a control unit with integrated exchangeable batteries that last for two to three hours each. The currently available (second commercially available) TTF unit (Optune® NovoTTF-200-A System, Novocure, Israel) weighs approximately six pounds (2.7 kg) and is designed to be carried by the patient in a shoulder bag (Kinzel et al., 2019; Stupp et al., 2017). Ideally, continuous application of the field over twenty-four hours a day should be obtained and study protocols required patients to wear the device for at least eighteen to twenty-two hours daily.

Results of randomized phase III trials are currently available for the use of TTF in recurrent GBM and as maintenance therapy in newly diagnosed GBM. In the initial examination of TTF against chemotherapy according to physicians' choice in recurrent GBM, no benefit in overall survival (primary endpoint) was observed (Stupp et al., 2012). However, in a subsequent trial comparing TMZ + TTF to TMZ alone after completed adjuvant concomitant radiochemotherapy in newly diagnosed GBM, the addition of TTF demonstrated a marked improvement in median overall survival (20.9 months vs. 16.0 months) at the interim analysis, resulting in the trial's premature closure (Stupp et al., 2017; Wick, 2016).

FDA approval for the Optune® device was granted in 2011 for the treatment of recurrent GBM and extended to newly diagnosed GBM in 2015 (Mehta et al., 2017). Contraindications of Optune treatment include implanted active medical devices such as pacemakers, brain stimulators and CSF shunts, unreplaced skull defects or bullet fragments as well as known sensitivity/allergy to the hydrogels used in the transducer array

placement. Further trials in other tumor entities are currently being performed, including other CNS neoplasms such as brain metastases, meningioma and oligodendroglioma (Wang et al., 2019).

Despite the promising results with regard to prognosis and safety, application of TTF currently remains subject to controversial discussions. Concerns regarding TTF arise from insufficiently understood mechanisms of action and methodological concerns, especially the lack of a placebo-control (i.e. sham device) and a higher level of care in the intervention group (Wick, 2016). Furthermore, the considerable therapy costs of approximately €21.000 per month were repeatedly mentioned as a major drawback of TTF treatment and a recent analysis deemed the technique not cost-effective by conventional thresholds at the current price (Bernard-Arnoux et al., 2016; Weller, 2018; Wick, 2016). However, a future decline in treatment costs may lead to improved cost-effectiveness as well as the availability of TTF.

4.1 Neurotoxicity of TTF

The toxicity profiles observed in the clinical trials showed no increased risk of systemic adverse effects with a lower rate of typical therapy-associated events (i.e. infectious, gastrointestinal, hematologic) as compared to active chemotherapy control. The most common and relevant side effects associated with TTF are skin reactions of varying severity at the transducer sites. Total rates of dermatologic adverse events in clinical trials were 19% (3% severe) and 54% (2% severe) respectively, while smaller series reported incidences of up to 90% (Kirson et al., 2007, 2009; Mrugala et al., 2017; Stupp et al., 2012, 2017). Treatment recommendations for the typically observed dermatological adverse events (dAE) such as dermatitis, erosions and ulcerations are provided by the device manufacturer. While recommended treatment of mild dAE (Grade 1) is based on topical steroids and antibiotics, moderate dAE (Grade 2) reactions mostly require systemic treatment and adapted array placement. In the case of severe dAE (Grade 3) reactions treatment interruption should be considered.

Further symptoms initially more frequently reported in the TTF treatment arm as compared to chemotherapy alone in the interim analysis included mostly transient unspecific neurological signs such as mild anxiety, headaches, insomnia and confusion (Stupp et al., 2015). However, no increased incidence of these neurological symptoms was observed in the final trial results.

Altogether, TTF is a promising treatment modality in GBM treatment that should be further investigated to answer the questions currently leading to its low acceptance as a standard of care (Weller, 2018; Wick, 2016). It is of note, however, that all concerns currently raised address primarily the effectiveness of TTF, while no evidence suggests a significant risk of severe (neuro-) toxicity (Stupp et al., 2012, 2017; Weller, 2018; Wick, 2016).

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Chapter 1.2

Radiotherapy including Hyperthermia and Brain Toxicity

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Abstract

Radiation therapy (RT) remains the cornerstone of the treatment of brain tumors and head and neck cancers but is associated with a high risk of disabling (sometimes life-threatening) neurotoxicity that may impact the quality of life of the patients. The enlargement of the indication of RT, the development of techniques such as radiosurgery and the improvement of prognosis with more aggressive therapeutic strategies have increased the population exposed to neurotoxicity, especially the long-term

survivors. Thus, neurological complications of RT, involving the neuroanatomical and functional structures included in the irradiation field, have garnered increasing interest. Radiation damage may be direct to the central nervous system or secondary to vascular or endocrine lesions, or to the development of a radiation-induced tumor. The time of occurrence of radiation-induced toxicity is related to the renewability potential of the tissue involved. The main purposes of this chapter are to review the clinical presentation, the incidence, the physiopathology of the RT-induced adverse neurological effects, and to detail the current recommendations for diagnosis and treatment.

Keywords: Radiotherapy, neurotoxicity, risk factors, pseudoprogression, radionecrosis, leukoencephalopathy,

Introduction

Throughout recent decades, radiotherapy has moved to occupy a central position in the management of most head and neck and brain tumors, and it has undoubtedly contributed to the improvement of the outcome of those patients. The drawback, though, is that irradiation can cause cerebral toxicities if some brain tissue is included in the radiation field. The adverse neurological effects of RT are usually classified according to the time course in relation to irradiation and include acute disorders (days to weeks), early-delayed complications (1–6 months) and late-delayed complications (more than 6 months) (Table 1). There is a correlation between the volume of irradiated brain tissue and the risk of cerebral toxicity. The total dose of irradiation is also a risk factor of cerebral toxicity, and the dosimetry is designed to respect the dose constraints that are regularly established for each organ by international consensus conferences (the international standards for radiation units and measurement—ICRU). The aim of the dosimetry is to deliver a curative dose to the tumoral site while sparing the adjacent healthy organs at risk. Advanced conformational techniques, such as intensity-modulated RT (IMRT), can improve the dose delivery accuracy. Stereotactic radiotherapy (hypofractionated stereotactic radiotherapy or single-fraction stereotactic radiotherapy—i.e radiosurgery) is a very high precision irradiation technique that uses a large number of converging microbeams. This enables targeting high doses of radiation to small volumes with minimum impact on the surrounding healthy tissue. On the other hand, the high dose fractionation of radiosurgery exposes the patient to a higher risk of

radionecrosis.[1] The inherent biophysical properties of photons do not allow a proper sparing of the organs at risk adjacent to the tumor. In contrast, the inherent biophysical properties of protons allow a much higher accuracy of the dose delivery.

Acute complications	< 4 weeks after RT	- Acute encephalopathy
Early-delayed complications	1–6 months after RT	- Somnolence syndrome - Worsening of preexisting symptoms - Transient cognitive impairments - Subacute rhombencephalitis
Late-delayed complications	> 6 months after RT	- Focal brain radionecrosis - Delayed cognitive dysfunction and leukoencephalopathy - SMART syndrome - PIPG - ALERT syndrome - Secondary brain tumors - Radiation-induced vasculopathy

Table 1: Main brain complications of radiotherapy.

Dose constraints vary significantly according to the brain structure considered.[2] Organs at risk follow two tolerance profiles: parallel organs and serial organs. Parallel organs are made of numerous functional units that work independently from one another, and their tolerance to irradiation depends on the volume of the organ receiving radiation. The brain is roughly considered as a parallel organ, and the dose constraints are less than 33% of the brain volume receiving 60 Gy, when the irradiation is delivered in 2 Gy-fractions.[3] Whole-brain irradiation is limited to 45 Gy in 2 Gy-fractions.[4] In stereotactic radiotherapy (1 or 3 fractions), dose

[1] Dhermain et al., 'Stereotactic radiotherapy in brain metastases'.
[2] Jacob et al., 'Cognitive Impairment and Morphological Changes after Radiation Therapy in Brain Tumors'.
[3] Paulino et al., 'Late Effects in Children Treated with Radiation Therapy for Wilms' Tumor'.
[4] Société française de radiothérapie oncologique, 'Handbook of external radiation therapy procedures 2007'.

constraints are less than 5–10 % of the brain volume receiving 12 Gy.[5] Serial organs (such as optic nerves and chiasm, spinal cord and brain stem) are made of linear functional structures and their tolerance to irradiation depends on the maximal dose deposited on even a limited segment of this organ. Dose constraints to the optic chiasm are thus 50 Gy in 10% of the volume, with a maximal tolerance dose of 54 Gy, when the irradiation is delivered in 2 Gy-fractions.[6] The tolerance to irradiation also depends on dose per fraction; late-delayed toxicities especially increase with dose per fraction. Normo-fractionation is 1.8–2.2 Gy per fraction. When the irradiation is hypo- or hyper-fractionated, the equivalent-dose in 2 Gy-fractions (EQD2) formula allows the calculation of the corresponding total dose if the irradiation was delivered in 2 Gy-fractions and with respect the dose constraints. Finally, concomitant and/or adjuvant anti-neoplastic systemic treatments may diminish irradiation tolerance. Besides the scheme of radiotherapy treatment, characteristics of the patient influence the risk of neurologic complications after radiotherapy. Notably, the very young and elderly patients (less than ten years or more than seventy years of age) are more vulnerable to radiotherapy-related complications. Indeed, survivors of childhood cancers are more likely to be allowed time to develop late-delayed complications of the irradiation, especially radiation-induced tumors. Elderly patients, given their likelihood of having organs with worse function, are more vulnerable to the toxicities of radiotherapy. Cardiovascular risk factors are also thought to be associated with complications of radiotherapy, especially late-delayed complications that are related to vascular changes. However, this correlation has been poorly reported in the literature. Finally, genetic predisposition is thought to participate in the risk of RT-induced complications as recently illustrated by an association between two SNPs and radiation-induced skin complications after breast irradiation.[7] Such studies should be conducted for radiation-induced neurotoxicity. Interestingly, concerning CNS, APOE knockout mice have been found to recover less well (reduced open field exploratory

[5] Benedict et al., ‘Stereotactic Body Radiation Therapy’; Blonigen et al., ‘Irradiated Volume as a Predictor of Brain Radionecrosis after Linear Accelerator Stereotactic Radiosurgery’.

[6] Maingon et al., ‘Les Contraintes Aux Organes à Risque En Radiothérapie Par Modulation d’intensité Des Cancers ORL’; Lawenda et al., ‘Permanent Alopecia after Cranial Irradiation’.

[7] Oliva et al., ‘Individual Genetic Variation Might Predict Acute Skin Reactions in Women Undergoing Adjuvant Breast Cancer Radiotherapy’.

activity, affected spatial working memory) from brain radiotherapy,[8] and a recent pilot study suggested that the APOE ε-4 allele may increase radiation-induced cognitive decline in glioma patients, this independently of β-amyloid deposition.[9]

I. Acute Encephalopathy

Acute encephalopathy occurs during radiation, generally within two weeks of the onset of irradiation.

The incidence of this syndrome is related to the dose per fraction and to the importance of cerebral edema prior to irradiation. Symptoms include headache, nausea, drowsiness, fever and worsening of neurological deficits. Radiation-induced blood–brain barrier disruption with increased edema is probably involved in the pathogenesis of the syndrome.

Corticosteroids are efficient at lessening the symptoms and can be administered as a preventive measure 48–72 hours before the onset of irradiation in cases of important cerebral edema. Surgical debulking before starting radiotherapy treatment also prevents this syndrome.[10]

II. Early-delayed complications of RT

These complications occur one to six months after the onset of irradiation and include somnolence syndrome, pseudoprogression, transient cognitive decline and subacute rhombencephalitis.

1. Somnolence syndrome

Somnolence syndrome is mainly characterized by hypersomnia, drowsiness and sometimes headache, nausea and fever. It occurs usually six to eight weeks following the onset of RT and starts to resolve four to six weeks later.[11] Improvement usually occurs spontaneously and resolves within one to three months. During the symptoms, neuropsychological evaluation often demonstrates attention deficits and alteration of short-

[8] Higuchi et al., 'Apolipoprotein E Expression and Behavioral Toxicity of High Charge, High Energy (HZE) Particle Radiation'.
[9] Correa et al., 'A Pilot Study of Neuropsychological Functions, APOE and Amyloid Imaging in Patients with Gliomas'.
[10] Soussain et al., 'CNS Complications of Radiotherapy and Chemotherapy'.
[11] Powell et al., 'Somnolence Syndrome in Patients Receiving Radical Radiotherapy for Primary Brain Tumours'.

term memory functions, which probably constitute the cognitive correlate of the somnolence syndrome. MRI findings are usually unchanged relative to those seen before radiotherapy.

The severity of somnolence syndrome is not predictive of later, more severe, cognitive impairments. The pathogenesis, although unclear, is thought to be due to demyelination and/or destruction of the microvasculature resulting from transient damage to oligodendroglia and all the brain parenchymal cell elements. The inflammatory response to irradiation has also been proposed to play a primary role [12]. Somnolence syndrome is experienced with varying intensity by most patients who have received whole-brain or large volume irradiation. It has been mainly reported in children with leukemia receiving prophylactic cranial irradiation.[13] None of the patient, disease or treatment characteristics are predictive for the development or severity of somnolence syndrome. A study found increased symptom severity in patients treated with accelerated fractionation.[14] A preventive and curative role of steroids has been suggested. However, the benefit of steroids remains controversial. Patients should be informed of the high frequency and transient nature of this syndrome, in order to prevent anxiety and unwarranted investigations in the immediate postradiation period.

2. Tumor pseudoprogression

Pseudoprogression can be described as an increased perilesional edema and worsened enhancement on post-contrast T1-weighted imaging occurring within the first twelve weeks after completion of irradiation, mimicking tumor progression, which improves or stabilizes without further intervention.[15] This time-dependent definition is incorporated into the tumor response assessment RANO criteria.[16] Tumor progression and pseudoprogression are indistinguishable on conventional MRI and may both be associated with a neurological focal deficit or the worsening of a preexisting one. However, in the case of pseudoprogression there is often a

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[12] Ballesteros-Zebadua et al., 'Radiation-Induced Neuroinflammation and Radiation Somnolence Syndrome'.

[13] Powell et al., 'Somnolence Syndrome in Patients Receiving Radical Radiotherapy for Primary Brain Tumours'.

[14] Faithfull and Brada, 'Somnolence Syndrome in Adults Following Cranial Irradiation for Primary Brain Tumours'.

[15] Ellingson et al., 'Pseudoprogression, Radionecrosis, Inflammation or True Tumor Progression?'

[16] Galldiks, Kocher, and Langen, 'Pseudoprogression after Glioma Therapy'.

discrepancy between the importance of the radiological changes and their clinical consequences.

The precise pathophysiological mechanism is still poorly understood. Histologic features of pseudoprogression are typically necrosis, fibrosis, gliosis, edema, demyelination (implying oligodendroglial cell loss), and vascular changes such as hyalinization, thrombosis and reduced number of endothelial cell nuclei.[17] In some cases, sheet-like infiltration by macrophages has been observed. Pseudoprogression most probably represents a subacute local tissue reaction which comprises inflammation and increased permeability of the blood–brain barrier. This last feature is due to radiation-induced damage to the tumor neovasculature endothelial cells, which are particularly vulnerable to irradiation.

Pseudoprogression is commonly described after the treatment of high-grade gliomas but may also occur after radiotherapy of low-grade gliomas or brain metastases. The incidence has increased since the introduction of radiotherapy with concomitant and adjuvant temozolomide as the current standard of care for patients with glioblastoma and is about 36%.[18] Pseudoprogression has been reported to be more common in patients whose tumors show a methylated MGMT gene promoter,[19] although this association was not confirmed by other studies.[20] In cases of pseudoprogression, radiological changes remain stable and ultimately regress on further follow-up MRI without any change in treatment. Improvement occurs spontaneously, but steroids accelerate its resolution. Hence, pseudoprogression is of considerable importance in neuro-oncology because an active treatment might be wrongly and prematurely changed with potentially negative influence on survival. The relatively high incidence emphasizes the need for a reliable diagnostic method to distinguish tumor progression from pseudoprogression when a radiological worsening is observed within twelve weeks of completion of irradiation. The present literature highlights the potential of amino acid PET (with

[17] Ellingson et al., 'Pseudoprogression, Radionecrosis, Inflammation or True Tumor Progression?'; Galldiks, Kocher, and Langen, 'Pseudoprogression after Glioma Therapy'.

[18] Abbasi et al., 'Incidence of Tumour Progression and Pseudoprogression in High-Grade Gliomas'.

[19] Brandes et al., 'MGMT Promoter Methylation Status Can Predict the Incidence and Outcome of Pseudoprogression after Concomitant Radiochemotherapy in Newly Diagnosed Glioblastoma Patients'.

[20] Wick et al., 'Evaluation of Pseudoprogression Rates and Tumor Progression Patterns in a Phase III Trial of Bevacizumab plus Radiotherapy/Temozolomide for Newly Diagnosed Glioblastoma'.

18F-FET, 18F-FDOPA and 11C-MET) and perfusion-weighted MRI (PWI) techniques measuring relative cerebral blood volume (rCBV) to detect pseudoprogression.[21] However, standardization is needed before implementing any particular quantitative PWI strategy across institutions since there is considerable variability in reported rCBV thresholds, PWI methods and post-processing software.

3. Transient cognitive decline

A transient cognitive decline can be observed within the first six months after cranial irradiation. Attention and verbal memory deficits stand in the foreground, but the speed of processing and executive functions can also be affected. It is not always observed and seems to vary according to the patient.[22] Elderly patients and those receiving concurrent chemotherapy might be more exposed. The importance of cognitive decline depends on the dose and volume of irradiation. It remains unknown whether the total dose or dose per fraction is the main contributor to cognitive decline. An individual sensibility is suggested. Moreover, a transient cognitive decline may also be driven by a depressed mood and/or a somnolence syndrome, and these three entities are often intertwined. Early-delayed cognitive decline, although persistent in some cases, does not appear to be a clear-cut predictive factor for subsequent development of long-term cognitive disorders. The pathogenesis remains unclear, although radiation-induced demyelination resulting from transient damage to oligodendroglia, as well as blood–brain barrier disruption and cerebral edema, are suspected.[23] Informing patients about these possible early transient postradiation cognitive dysfunctions which may impact their daily and professional life is useful.

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[21] Galldiks et al., ‘Diagnosis of Pseudoprogression in Patients with Glioblastoma Using O-(2-[18F]Fluoroethyl)-L-Tyrosine PET’; Wan et al., ‘The Diagnostic Performance of Perfusion MRI for Differentiating Glioma Recurrence from Pseudoprogression’; Patel et al., ‘MR Perfusion-Weighted Imaging in the Evaluation of High-Grade Gliomas after Treatment’.

[22] Vigliani et al., ‘A Prospective Study of Cognitive Functions Following Conventional Radiotherapy for Supratentorial Gliomas in Young Adults’; Armstrong et al., ‘Biphasic Patterns of Memory Deficits Following Moderate-Dose Partial-Brain Irradiation’.

[23] Buthut et al., ‘Kognitive Defizite nach Strahlentherapie von Hirntumoren’.

4. Subacute rhombencephalitis

This early-delayed complication of radiotherapy is rare but serious. It occurs between two weeks and three months after the completion of radiotherapy and corresponds to a brain stem encephalopathy following irradiation of the posterior fossa.[24] The clinical picture includes ataxia, dysarthria, diplopia, and/or nystagmus as well as auditory loss. In some cases, the cerebrospinal fluid analysis shows inflammatory changes. The pathogenesis remains poorly understood; transient radiation-induced demyelination is suspected. MRI may demonstrate white matter abnormalities appearing as T1-weighted hypointensities and T2-weighted hyperintensities, enhancing after gadolinium injection, affecting the brainstem and cerebellar peduncles.[25] Most patients recover spontaneously or with steroids over a few weeks to months, but evolution to stupor, coma and death have been reported in rare cases.

III. Late-delayed complications of RT

These complications occur more than six months after completion of radiotherapy and include focal brain radionecrosis and cognitive dysfunction related to leukoencephalopathy (Figure 1).

RADIONECROSIS: A 56-year-old woman was diagnosed with nasopharyngal carcinoma treated by surgery and focal cavum radiotherapy of 70 Gy in 30 fractions with an irradiation field including brain temporal lobes. Two years later she had a slight memory complaint. At this time a brain MRI showed T1, gadolinium-enhanced and FLAIR abnormalities.

A: Axial section of a gadolinium-enhanced T1-weighted MRI. Bi-temporal lesions with central necrosis-like hyposignal and peripheric enhancement.

B: Axial section of a FLAIR-weighted MRI. Hyposignal of the bi-temporal necrotic lesions, peripheric edema-like hypersignal.

C: Axial section of a Perfusion-weighted MRI. Low rCBV of the bi-temporal lesions.

D: Histological features, hematoxylin-eosin (H&E), 100× original magnification, from a surgical resection. Diffuse ischemic necrosis and thickening of the vessel walls due to fibrosis.

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[24] Keime-Guibert, Napolitano, and Delattre, 'Neurological Complications of Radiotherapy and Chemotherapy'.

[25] Créange et al., 'Subacute leukoencephalopathy of the rhombencephalon after pituitary radiotherapy'.

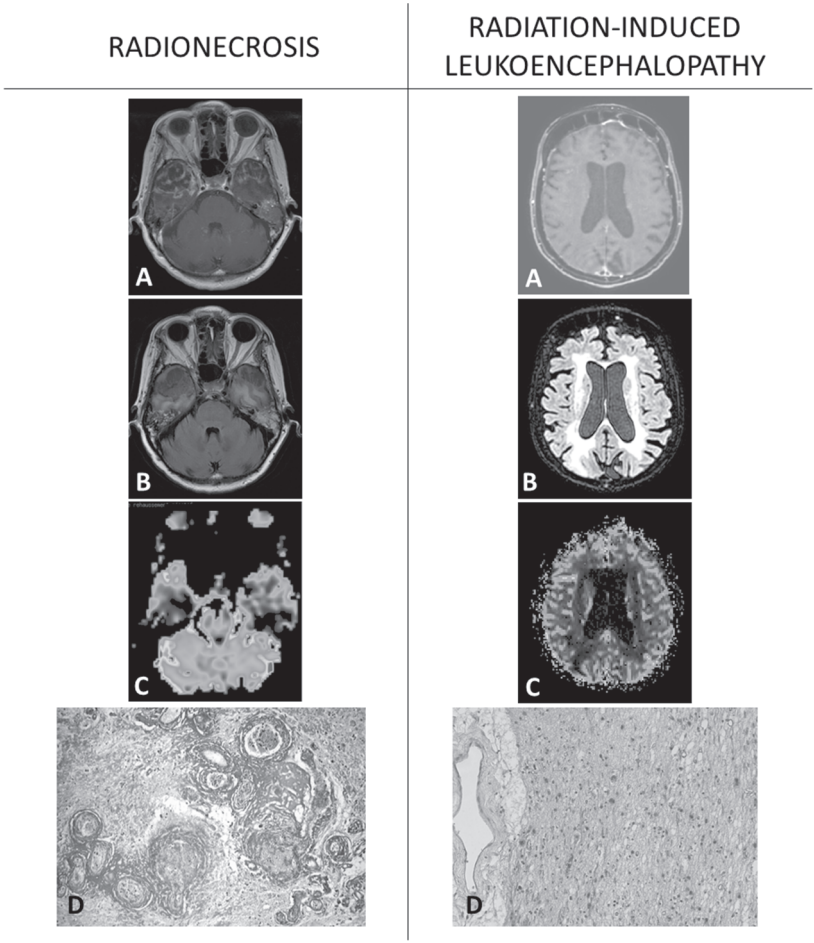

Figure 1: MRI and histological features of radionecrosis and radiation-induced leukoencephalopathy.

1. Focal brain radionecrosis

Radionecrosis generally occurs within six months to two years, but it has been observed after several decades. It may occur if some cerebral tissue is included in the radiation field (e.g., primary and secondary cerebral tumors, head and neck or pituitary tumors, meningiomas, skull

osteosarcomas). Studies report incidences from 5 to 40%.[26] The main risk factors are total dose, dose per fraction and volume of the target lesion. Age at radiation and concurrent chemotherapy also influence the occurrence of radionecrosis, in addition to individual susceptibilities that remain to be further investigated. Other combined treatment may also increase the risk of radionecrosis. A recent study showed that patients treated with an anti-PD-1 antibody concomitant with radiotherapy for melanoma brain metastases have an increased risk of focal brain radionecrosis (cumulative incidence at two years of 18%).[27] Trastuzumab, a monoclonal antibody used in overexpressed HER2 breast cancer, has also been shown to increase the risk of focal brain radionecrosis (incidence of 39.1% in patients who received trastuzumab versus 4.5% in patients who did not). The pathophysiological justification was an increased radiation-induced cytotoxicity and astrocytic swelling via the upregulation of Aqp4.[28] Stereotactic radiotherapy has become a standard of care for patients with a limited number of brain metastases. Doses per fraction are as high as 10 Gy (with hypofractionated stereotactic radiotherapy) to 24 Gy (with radiosurgery) and it increases the risk of radionecrosis, with the volume of the lesion being associated with radionecrosis risk.[29]

The pathogenesis of radionecrosis remains unclear. Ischemia secondary to blood vessel damage is involved but additional factors such as edema, gliosis and demyelination come into play. At the molecular level, VEGF seems to play a pivotal role in endothelial cell loss.[30]

Histopathological characteristics are mainly vascular damage (vascular fibrosis/hyalinization with luminal stenosis, thrombosis, hemorrhage, damaged epithelial cells) with ischemic necrosis, interstitial fibrosis and fibrinoid necrosis figure 1). An edema of the brain parenchyma due to blood–brain barrier disruption, calcifications and histiocytic infiltrates are also observed. The brain parenchyma often contains dystrophic neurons

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[26] Ellingson et al., 'Pseudoprogression, Radionecrosis, Inflammation or True Tumor Progression?'

[27] Silva et al., 'Incidence, Features and Management of Radionecrosis in Melanoma Patients Treated with Cerebral Radiotherapy and Anti-PD-1 Antibodies'.

[28] Stumpf et al., 'Combination of Trastuzumab Emtansine and Stereotactic Radiosurgery Results in High Rates of Clinically Significant Radionecrosis and Dysregulation of Aquaporin-4'.

[29] Donovan, Parpia, and Greenspoon, 'Incidence of Radionecrosis in Single-Fraction Radiosurgery Compared with Fractionated Radiotherapy in the Treatment of Brain Metastasis'.

[30] Ricard et al., 'Neurologic Complications of Radiation Therapy'.

and reactive astrocytes. In the case of gliomas, dystrophic cells, which are irradiated tumoral cells, are seen within the ischemic necrosis.

Symptoms are seizures (inaugural in 50% of cases), intracranial hypertension and/or focal neurological deficits. Such symptoms mimic tumor recurrence or progression, and radiological changes are compatible. White matter FLAIR hyperintensities are the first MRI manifestations of focal brain radionecrosis. Contrast-enhanced lesions, that may include necrotic areas, develop afterward and may evolve to a cystic appearance (Figure 1).

PET—with 18F-FET, 18F-DOPA, 11C-MET, 201Thallium or 99mTc-MIBI—may help with a differential diagnosis between tumor progression or recurrence. However, standardization of detection thresholds is still needed. MRI perfusion sequences show high rCBV for tumor recurrence and low rCBV for radionecrosis. On magnetic resonance spectroscopy (MRS), necrosis areas classically show a decrease of metabolite peaks and an increase of lipid peak without lactate peak. Despite the diagnostic contribution of PET and/or MRI, in a substantial number of cases the distinction between tumor recurrence/progression and radionecrosis remains unclear, partly because necrotic areas sometimes contain residual tumoral tissue. Hence, a definite diagnosis of cerebral radionecrosis relies in theory on neuropathological confirmation, although in practice brain biopsy or surgical resection are not systematically proposed.

The first-line treatment is steroids. A study reported 35% of patients with cerebral radionecrosis achieved a durable response to steroids.[31] If steroids fail to decrease the symptoms and the lesion is accessible, surgical resection of the necrotic mass can be carried out with good symptomatic efficiency. If the lesion is not accessible or the patient's clinical condition does not allow surgery, bevacizumab can provide radiological and symptomatic benefits.[32] Bevacizumab is also used for preventing focal brain radionecrosis when administered concomitantly to reirradiation for recurrent malignant gliomas.[33] Anticoagulants and hyperbaric oxygen therapy (HBO) have also been tested but without clear evidence of efficiency.

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[31] Lee et al., 'Clinicopathologic and Genomic Features of Gliosarcomas'.

[32] Levin et al., 'Randomized Double-Blind Placebo-Controlled Trial of Bevacizumab Therapy for Radiation Necrosis of the Central Nervous System'; Tye et al., 'An Analysis of Radiation Necrosis of the Central Nervous System Treated with Bevacizumab'.

[33] Hundsberger et al., 'Re-Irradiation with and without Bevacizumab as Salvage Therapy for Recurrent or Progressive High-Grade Gliomas'.

2. Late progressive cognitive dysfunction and leukoencephalopathy

Radiation-induced cognitive impairment is known to occur at different levels in up to 50%–90% of adult brain tumor long-term survivors after radiotherapy. The most impaired functions are attention, executive functions and speed of information speed processing.[34] These functions involve frontal cortico-subcortical networks. Hippocampal-dependent deficits in learning and memory are also reported,[35] although this remains controversial with some authors considering that cognitive changes are not hippocampal-dependent but related to executive dysfunction.[36]

The course of radiation-induced late-delayed cognitive decline is uncertain; most patients remain stable, but some patients deteriorate progressively toward dementia, which represents the ultimate stage of radiation-induced leukoencephalopathy. The incidence of radiation-induced dementia varies widely in the literature according to the series, recent studies estimate it to be less than 10%.[37] Patients present with progressive memory and attention deficits, intellectual loss, emotional lability, apathy and fatigue. Gait ataxia and incontinence are common in patients with severe evolution. Depression is frequently associated, although antidepressants do not improve cognitive function. Death generally occurs within one month to four years after the onset of the dementia stage. The late progressive cognitive impairment is associated with extensive diffuse T2 FLAIR-weighted MRI white matter hyperintensities, and this clinical and radiological picture defines radiation-induced leukoencephalopathy (Figure 1-). Lesions are predominantly anterior and may cause disconnection of the prefrontal or anterior cingulate cortices from the basal ganglia, explaining the clinical picture of executive dysfunction associated with impaired gait capacity and urinary control. Cortical and/or subcortical brain atrophy is also observed, and some patients present T2*-weighted MRI small asignal areas consistent with a cerebral small vessel disease[38] (Figure 2). Correlation between the cognitive impairment severity and the extent of MRI abnormalities remains imperfect. However, a study of pediatric medulloblastoma treated with craniospinal irradiation found that

[34] Grosshans et al., 'The Role of Image-Guided Intensity Modulated Proton Therapy in Glioma'; Asher et al., 'Cancer-Related Cognitive Changes'.
[35] Allen et al., 'Remediation of Radiation-Induced Cognitive Dysfunction through Oral Administration of the Neuroprotective Compound NSI-189'.
[36] Bompaire et al., 'New Insights in Radiation-Induced Leukoencephalopathy'.
[37] Chen et al., 'Dementia Risk in Irradiated Patients With Head and Neck Cancer'.
[38] Bompaire et al., 'New Insights in Radiation-Induced Leukoencephalopathy'.

decreased anisotropy of water diffusion in white matter was well correlated with the radiation dose,[39] suggesting the role of diffusion tensor MRI as a potential tool for the assessment of radiation-induced leukoencephalopathy.[40] In severe cases, neuroimaging shows advanced lesions of leukoencephalopathy with cortical and subcortical atrophy, ventricular dilatation and diffuse white matter hyperintensities on T2 and T2 FLAIR-weighted images.

The histopathological lesions of this radiation-induced leukoencephalopathy distinguish it from radionecrosis by a spread to large areas of white matter necrosis with a diffuse rarefaction of oligodendrocytes and myelin, inflammatory infiltrates featuring histiocytes, microglia activation, white matter vacuolation and severe vascular thickening and thromboses (Figure 1). Vascular thickening is due to fibrosis and proliferation of endothelial cells. Pathophysiological hypotheses evoking radiation-induced leukoencephalopathy as a cerebral small vessel disease has also been considered since it shares common clinical and MRI features.[41] The hippocampal region is a particularly radiosensitive region. A recent animal experimental study suggests that irradiation induces hippocampal neuronal loss in CA1 and CA3 areas, neuroinflammation and reduces gliogenesis. The hippocampal neurovascular niche and the total number of microvessels are also reduced after radiation exposure.[42] Interestingly, Gondi et al. reported that conformal avoidance of the hippocampus during whole-brain RT is associated with the preservation of memory as compared with historical series.[43] Tsai et al. reported that four months after completion of the radiotherapy, dosimetric parameters specific to the left-side hippocampus exert an influence on verbal memory.[44] Clinical trials are currently testing

[39] Khong et al., 'White Matter Anisotropy in Childhood Medulloblastoma Survivors'.
[40] Nagesh et al., 'Radiation-Induced Changes in Normal-Appearing White Matter in Patients With Cerebral Tumors'.
[41] Vigliani et al., 'Dementia Following Treatment of Brain Tumors with Radiotherapy Administered Alone or in Combination with Nitrosourea-Based Chemotherapy'.
[42] Tang, Loke, and Khoo, 'Postnatal Irradiation-Induced Hippocampal Neuropathology, Cognitive Impairment and Aging'.
[43] Gondi et al., 'Preservation of Memory with Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment during Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933)'.
[44] Tsai et al., 'Hippocampal Dosimetry Correlates with the Change in Neurocognitive Function after Hippocampal Sparing during Whole Brain Radiotherapy'.

the hypothesis of memory-specific hippocampal radiation sensitivity (NCT02360215, NCT02635009). Other structures, including the corpus callosum, frontal lobe and posterior fossa are known to be critical to cognitive functions, and the functional effects of sparing these structures would be interesting to investigate prospectively.

Radiation dose delivery accuracy has been continuously improved since the early 1990s with the emergence of IMRT. However, the inherent physical properties of photons do not allow the normal tissues surrounding the target volume to be properly spared. This often limits the ability to deliver a curative dose to the tumor without unacceptable toxicities to the surrounding normal tissues. Proton therapy has been shown to enable clinically significant radiotherapy dose escalation while preserving critical structures. A recent trial showed that measures of cognitive functions were stable for patients with WHO grade II gliomas five years after completion of proton therapy.[45] A clinical trial is currently testing the effects of dose escalation of radiotherapy delivered with IMRT or proton therapy on tumor control and toxicities (NCT02179086). Intensity-modulated proton therapy (IMPT), which combines the mechanical advantages of IMRT and the physical properties of proton therapy, appears promising for improving the tumor local control while better sparing the adjacent critical structures.

There is currently no recognized treatment for radiation-induced leukoencephalopathy although some authors have advocated the use of methylphenidate, donepezil, memantine or modafinil for symptomatic relief. Donepezil, an acethylcholinesterase inhibitor used to treat Alzheimer's disease, has been shown in a pilot study to improve attention, graphomotor speed and visual and verbal memory six months after completion of whole-brain radiotherapy in patients with brain metastasis.[46] The glutamate receptor antagonist memantine has also been shown to reduce cognitive decline when administered from the outset of radiotherapy and for a total of twenty-four weeks.[47] Cognitive and gait-oriented rehabilitation are helpful and must be started early. In patients with severe apathy and asthenia, small doses of amphetamines may be useful.[48] Promising results have been recently reported in preclinical studies using innovative approaches such as fingolimod (by restoring the

[45] Shih et al., 'Proton Therapy for Low-Grade Gliomas'.
[46] Correa et al., 'Cognitive Effects of Donepezil Therapy in Patients with Brain Tumors'.
[47] Brown et al., 'Memantine for the Prevention of Cognitive Dysfunction in Patients Receiving Whole-Brain Radiotherapy'.
[48] Meyers et al., 'Methylphenidate Therapy Improves Cognition, Mood, and Function of Brain Tumor Patients'.

pool of neuronal progenitor cells after brain irradiation), the proneurogenic compound NSI-189, and melatonine (as mitochondria-targeted antioxidant protecting hippocampal neurons against radiation effects).[49]

3. Other long-term direct brain parenchyma radiation-induced lesions

(a) SMART syndrome

The SMART syndrome (stroke-like migraine attacks after radiation therapy) has been described by Bartleson and diagnostic criteria were then revised [50]. It is defined as the association of: (i) Prolonged, reversible, unilateral cortical signs and symptoms beginning years after radiation (visuospatial deficit, confusion, hemiparesis, aphasia, seizures, headaches, migraine with or without aura); (ii) Transient, diffuse, unilateral cortical gray matter enhancement in contrast-enhanced T1 MRI, sparing white matter (Figure 2); (iii) in a patient with a history of cranial radiation, after elimination of any other diagnosis.

RADIATION-INDUCED CEREBROVASCULAR ACCIDENTS: A six-year-old boy was diagnosed with medulloblastoma. He was treated by surgery, chemotherapy (vincristine, procarbazine and methotrexate) and craniospinal irradiation (35 Gy) with a boost on posterior fossa (to 55 Gy). Twenty-six years later, he presented a sudden right hemi-hypoesthesia and a homolateral proprioceptive ataxia. MRI features revealed a cerebrovascular accident.

A: Axial section of a diffusion tensor MRI. Recent left occipital and thalamic ischemic lesions.

B: reconstruction of the TOF sequence focusing on the polygon of Willis. Occlusion of the left posterior cerebral artery (arrowhead).

RADIATION-INDUCED MICROBLEEDS: An eleven-year-old boy was diagnosed with medulloblastoma and received craniospinal irradiation (35 Gy) and a boost on posterior fossa (to 55 Gy). Thirty-six years later, he presented complex-partial epilepsy. MRI revealed several microbleeds.

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[49] Stessin et al., 'FTY720/Fingolimod, an Oral S1PR Modulator, Mitigates Radiation Induced Cognitive Deficits'; Allen et al., 'Remediation of Radiation-Induced Cognitive Dysfunction through Oral Administration of the Neuroprotective Compound NSI-189'; Liu et al., 'Ameliorating Mitochondrial Dysfunction Restores Carbon Ion-Induced Cognitive Deficits via Co-Activation of NRF2 and PINK1 Signaling Pathway'.

[50] Black et al., 'SMART'.

A: Axial section of the T2 star-weighted MRI. Left temporoparietal microbleed (arrow).

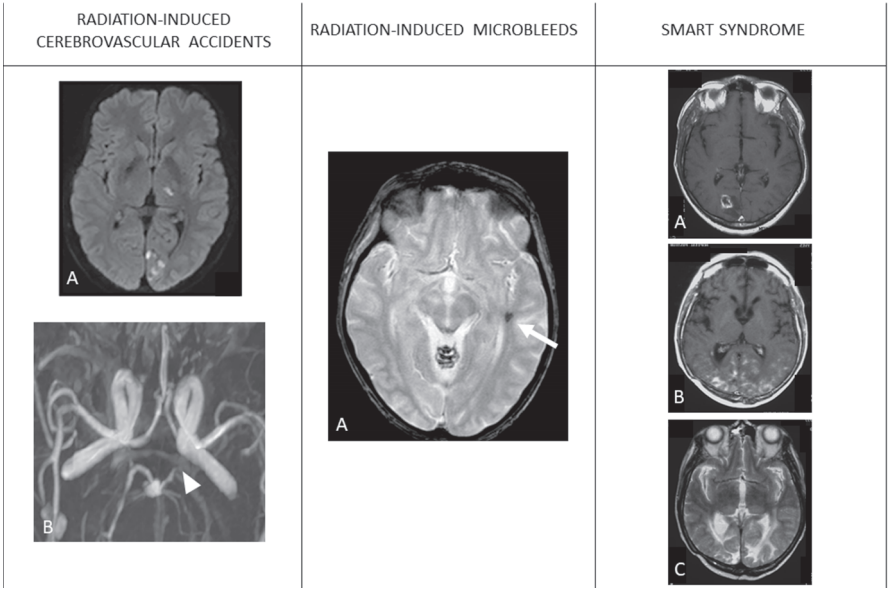

Figure 2: MRI features of radiation-induced cerebrovascular accidents, microbleeds, and SMART syndrome

SMART SYNDROME: A forty-year-old man was diagnosed with an anaplastic astrocytoma of the right occipital lobe. He was treated by surgery, a whole-brain irradiation of 30 Gy in 10 fractions and a boost of 20 Gy in 10 fractions on the tumor bed, and chemotherapy (procarbazine, lomustine and vincristine). Two years later, he developed recurrent generalized seizures, attacks of ophthalmic migraine, and recurrent episodes of confusion. Subsequently, he experienced severe headaches with episodes of aphasia and mild left hemiparesis. MRI revealed multiple enhancing nodular lesions of both occipital lobes.

A: Axial section of a gadolinium-enhanced T1-weighted pre-therapeutic MRI. Initial right occipital tumoral lesion.

B: Axial section of a gadolinium-enhanced T1-weighted MRI at the time of the most severe symptoms. Bilateral occipital gyral enhancement.

C: Axial section of a FLAIR-weighted MRI at the time of the most

severe symptoms. Bilateral occipital subcortical edema.

It can occur with both focal and whole-brain radiotherapy; most cases are reported to have received at least 50 Gy. The pathophysiology is not well understood; vascular instability, endothelial dysfunction and metabolic etiologies are postulated.[51] Black et al. report 55% of clinical recurrence. Up to 45% of patients have been reported to have incomplete recovery; in these patients, MRI findings may include cortical laminar necrosis or ischemia.[52] The evolution may be unfavorable with a progressing permanent neurological deficit.[53] A prolonged oral corticosteroid course may help patients with this condition.

(b) Peri-ictal pseudoprogression

Peri-ictal pseudoprogression (PIPG) corresponds to the appearance of new cortical and/or leptomeningeal contrast-enhancing lesions in a context of seizures, that can incorrectly suggest tumor progression [54], occurring years after radiotherapy (three to twenty-five years)[55] (Figure 2). The mechanisms underlying the MRI changes in PIPG remain undetermined, but it is speculated that the vascular response to seizures might be altered in irradiated patients, promoting the observed extensive seizure-related disruption of the blood–brain barrier. The patients could present post-ictal deficits, but full recovery within weeks to a few months is the rule. The anti-epileptic treatment adjustment may benefit patients in this condition.

(c) ALERT syndrome

ALERT syndrome (acute late-onset encephalopathy after radiation therapy) manifests itself by an acute but long-lasting (four to twenty-four days) impaired consciousness, progressing to coma within twenty-four to seventy-two hours, and possibly accompanied by motor deficit, aphasia, headache, and visual hallucinations.[56] MRI can show multiple bilateral areas of subcortical patchy enhancement and focal leptomeningeal

[51] Ramanathan et al., 'Unusual Case of Recurrent SMART (Stroke-like Migraine Attacks after Radiation Therapy) Syndrome'.
[52] Black et al., 'Stroke-like Migraine Attacks after Radiation Therapy (SMART) Syndrome Is Not Always Completely Reversible'.
[53] Bompaire et al., 'SMART Syndrome'.
[54] Rheims et al., 'Peri-Ictal Pseudoprogression in Patients with Brain Tumor'.
[55] Rheims et al.; Dunn-Pirio, Billakota, and Peters, 'Postictal Magnetic Resonance Imaging Changes Masquerading as Brain Tumor Progression'.
[56] Di Stefano et al., 'Acute Late-Onset Encephalopathy after Radiotherapy'; Di Stefano et al., 'Stroke-like Events after Brain Radiotherapy'.

enhancement but can also show no modification and EEG recordings objectify bilateral or diffuse slow abnormalities with unilateral predominance. ALERT syndrome occurs years after whole-brain radiation therapy (nine months to seventeen years in the first description). The pathogenesis could be related to post-irradiation inflammatory endothelial damage that preferentially targets small vessels, or to mitochondrial damage. The evolution is favorable under corticosteroids, but neurological deficits may persist; relapses can occur when tapering down chronic steroid therapy.

4. Radiation-induced brain tumors

Evidence for radiation-induced brain tumors has been known for a long time. The precise role of RT in the development of a tumor in any given case is difficult to determine, in great part because these tumors lack distinctive features compared to unirradiated patients. Cahan et al.[57] proposed diagnostic criteria for radiation-induced brain tumors: (i) the tumor must occur within the irradiated field; (ii) a sufficient latency period must exist between radiotherapy and tumor diagnosis; (iii) the radiation-induced tumor must be proven to be of a different histological type than the original one; (iv) the patient must not have any pathologies favoring the development of tumors. Activation of oncogenes or inactivation of tumor suppressor genes via DNA strand breaks has been hypothesized as the main mechanism driving the development of secondary tumors after RT.

Lee et al. assessed the relative risk of developing a radiation-induced tumor in an extensive review.[58] In children, they reported approximately 600 CNS tumors attributed to cranial radiation. The most commonly reported secondary CNS tumor was a meningioma, which had a latency period of two to twenty years from cranial radiation. Gliomas were reported to develop in around five to ten years. The reported twenty-year cumulative incidence of radiation-induced CNS tumors ranged from 1.03% to 28.9%. Radiation seems to increase the incidence of secondary CNS tumors by 7 to 10-fold. In adults, they reported 395 CNS tumors, the most commonly reported being a meningioma. For meningiomas, the latency period ranged from 0.8 to 42 years, with most occurring more than ten years after radiation. The latency for gliomas ranged from six to

[57] Cahan et al., ‘Sarcoma Arising in Irradiated Bone’.
[58] Lee and Wernicke, ‘Risk and Survival Outcomes of Radiation-Induced CNS Tumors’.

twenty-six years, and most occurred less than ten years after cranial radiation. The thirty-year cumulative incidence ranged from 2.7% to 8.5%. However, this increased incidence may not be attributed to radiation alone, as in the absence of radiation, patients with a brain tumor already have an increased risk of subsequent CNS tumors.

Cases of radiation-induced CNS tumors after radiosurgery have been described, but they remain rare. For example, Hasegawa et al. reported 1% of radiation-induced CNS tumors (glioblastoma, and anaplastic oligodendroglioma) after Gamma Knife Radiosurgery for arteriovenous malformations.[59]

(a) Radiation-induced meningiomas

Yamanaka et al. reviewed 251 cases of radiation-induced meningiomas.[60] A single lesion was present in 73.3% of cases and 11.9% had multiple lesions (not reported for the remaining 14.7%). The most represented histological subtype was meningothelial meningioma (30%). The latency period between radiotherapy and the onset of meningioma was correlated with the grade, with grade III tumors occurring earlier (12.9 years vs 21.9 years for grade II and 24.8 years for grade I). Grade II and III meningiomas and multiple meningiomas were more common for patients who had received more than 15Gy, and the latency period was shorter for these patients. A 0.81:1 female/male ratio was found, whereas spontaneous meningiomas usually display a female predominance with an approximate female/male ratio of 1.7:1. There is an overlap in the mutational spectrum of sporadic meningiomas and radiation-induced ones, but NF2 inactivation and chromosome 22q deletions seem to be far less frequent in radiation-induced meningiomas.[61]

(b) Radiation-induced gliomas

Yamanaka et al.[62] reviewed 296 radiation-induced gliomas. The gliomas were mostly of grade IV (58.8%). The mean radiation dose delivered to the primary lesion was 28.5 Gy for grade II, 39.3 Gy for grade III, and 37.2 Gy for grade IV gliomas. Approximately 10% of cases developed secondary gliomas following radiotherapy treatment with less than 16 Gy. The latency period between radiotherapy and diagnosis of glioma was nine years on average. It appears that these tumors manifest

[59] Hasegawa et al., 'Long-Term Outcomes for Pediatric Patients with Brain Arteriovenous Malformations Treated with Gamma Knife Radiosurgery, Part 2'.
[60] Yamanaka, Hayano, and Kanayama, 'Radiation-Induced Meningiomas'.
[61] Shoshan et al., 'Radiation-Induced Meningioma'.
[62] Yamanaka, Hayano, and Kanayama, 'Radiation-Induced Gliomas'.

similar alterations of PTEN, EGFR and TP53 to sporadic gliomas[63] but do not depend upon the classical molecular pathways implicated in gliomagenesis such as IDH1/2 mutation.[64]

(c) Radiation-induced sarcomas

Yamanaka et al. systematically reviewed reports of radiation-induced central nervous system sarcomas.[65] The median latency period between radiotherapy and the onset of sarcomas, regardless of histological type, was 12.4 ± 8.6 years. The average irradiation dose delivered to the primary lesions was 51.4 ± 18.6 Gy. The latency period was longer for patients who received less than 15 Gy. The characteristic karyotype of radiation-induced sarcomas is a rearrangement of chromosome 3p;[66] compared to primary sarcomas, radiation-induced osteosarcomas have higher proliferative activity, and higher frequencies of p53 overexpression and mutations.[67]

5. Radiation-induced vasculopathy

The late vascular complications of cranial irradiation include cerebrovascular accidents (hemorrhagic and ischemic), lacunar lesions, vascular occlusive disease including moyamoya syndrome, and vascular malformations. Clinical expression of radiation-induced vasculopathy is highly variable in terms of mode of installation (acute, subacute, progressive) and severity of symptoms (ranging from asymptomatic to severely disabling).

Vascular injury after radiation usually begins with progressive endothelial loss, which is followed by formation of thrombi and hemorrhage. Long-term morphological changes consist of endothelial proliferation, basement membrane thickening, adventitial fibrosis, and vessel dilatation.[68]

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[63] Brat et al., 'Molecular Genetic Alterations in Radiation-Induced Astrocytomas'.
[64] Nakao et al., 'Radiation-Induced Gliomas'.
[65] Yamanaka and Hayano, 'Radiation-Induced Sarcomas of the Central Nervous System'.
[66] Mertens et al., 'Radiation-Associated Sarcomas Are Characterized by Complex Karyotypes with Frequent Rearrangements of Chromosome Arm 3p'.
[67] Huvos et al., 'Postradiation Osteogenic Sarcoma of Bone and Soft Tissues. A Clinicopathologic Study of 66 Patients'.
[68] Murphy et al., 'Review of Cranial Radiotherapy-Induced Vasculopathy'.

(a) Cerebrovascular accidents

Increased incidence of cerebrovascular accidents among adults treated by fractionated radiotherapy for pituitary adenoma has been reported and has been estimated at 12–21% at 20 years. However, the link between this increase of incidence and radiotherapy remains uncertain, as the risk is also increased in patients treated with surgery alone.[69] In children, this increased risk of cerebrovascular accidents seems clearer: the Childhood Cancer Survivor Study reports a Risk Ratio in the leukemia group of 6.4 (cumulative incidence of 0.73% at 25 years), with strokes occurring at a median interval of 9.8 years and a Risk Ratio of 29 (cumulative incidence of 5.6% at 25 years) in the brain tumor group, strokes occurring at a median interval of 13.9 years.[70] The risk of radiotherapy-related stroke increased in a dose-dependent fashion, with increased risk appearing above 30 Gy and highest risk above 50 Gy (Figure 2). The location of tumors relative to vascular structures impacts the likelihood of long-term effects: due to proximity to vessels, optic pathway glioma is a risk factor for vasculopathy, as well as craniopharyngioma.

(b) Large and medium intra- and Extracranial artery injury

Many cases of large intra- and extra-arterial stenosis, as late complications of radiotherapy, were described in the 1990s, often located in unusual places for common atherosclerosis. Most authors suggested that atherosclerosis in large arteries, accelerated by irradiation, had caused atherothrombotic stroke. A vessel wall MRI study of five patients with radiation-induced narrowing of the intracranial internal carotid arteries found circumferential arterial wall thickening and enhancement in all cases,[71] suggesting an inflammation of the vessel wall. It has been observed that the larger the diameter of an irradiated artery is, the longer the latency is between RT and the onset of vasculopathy, a fact that might explain the shorter latency of RT-induced vasculopathy in children. Proton beam therapy could be a risk factor of large-vessel vasculopathy: in a series of 115 pediatric brain tumor survivors, three of the ten patients developing arteriopathy received proton beam therapy, compared to only one of the one hundred and five patients without arteriopathy; and these

[69] Murphy et al.

[70] Bowers et al., ‘Late-Occurring Stroke among Long-Term Survivors of Childhood Leukemia and Brain Tumors’.

[71] Mandell et al., ‘Intracranial Vessel Wall MRI’.

three patients developed arteriopathies with a latency smaller than average.[72]

(c) Radiation-induced Vasculopathy with Moyamoya pattern

Moyamoya syndrome refers to a progressive occlusion of the arteries of the circle of Willis with subsequent development of smaller collateral vessels; it can cause both ischemic and hemorrhagic cerebrovascular accidents, as well as transient ischemic attacks or focal seizures. This complication is particularly frequent in children treated for optic chiasm glioma (in a series of sixty-nine children, 19% developed signs of vasculopathy after a median latency of 36 months)[73] but not only in those treated for this: from over 1800 ALL (acute lymphoblastic leukemia) patients who received 18 or 24 Gy prophylactic cranial radiotherapy, the cumulative incidence of moyamoya was 0.46 % at eight years.[74] Increased moyamoya incidence has been associated with NF1, young age, and radiotherapy dose (significant increase for dose above 50 Gy).[75] Cases of moyamoya syndrome have also been described in pediatric patients after proton beam therapy.[76]

(d) Lacunar lesions

Lacunar lesions represent ischemic infarcts of restricted size in the deep parenchyma of the brain. A cohort of 524 consecutively treated pediatric patients with brain tumors has been studied by Fouladi et al. to assess the incidence of these lesions.[77] Of the patients treated by radiotherapy, 5.9% developed such lesions at a median interval of two years. Lacunar lesions progressed in number and size over several years but remained clinically silent, including from a cognitive point of view.

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[72] Nordstrom et al., 'Large Vessel Arteriopathy After Cranial Radiation Therapy in Pediatric Brain Tumor Survivors'.

[73] Grill et al., 'Radiation-Induced Cerebral Vasculopathy in Children with Neurofibromatosis and Optic Pathway Glioma'.

[74] Kikuchi et al., 'Moyamoya Syndrome Following Childhood Acute Lymphoblastic Leukemia'.

[75] Murphy et al., 'Review of Cranial Radiotherapy-Induced Vasculopathy'.

[76] Scala et al., 'Radiation-Induced Moyamoya Syndrome After Proton Therapy in Child with Clival Chordoma'.

[77] Fouladi et al., 'Silent Lacunar Lesions Detected by Magnetic Resonance Imaging of Children with Brain Tumors'.

(e) Microbleeds

Microbleeds are also observed in irradiated patients (Figure 2). After whole-brain irradiation (24–60 Gy), microbleeds were detected in 21% of thirty-four patients on T2-weighted imaging, and 47% on phase-sensitive magnetic resonance imaging, with a latency of three months to nine years (mean: 33 months). The frequency of microbleeds was significantly associated with radiation dose, and there were no foci observed in regions that had received less than 25 Gy.[78] Microbleeds after proton beam therapy were also observed in 81% of 100 pediatric patients with primary brain tumors, five years after treatment.[79]

(f) Vascular malformations

Vascular malformations include cavernoma, telangiectasia, and aneurysm, which can remain asymptomatic or cause intracranial hemorrhage.

- ***Cavernomas***

A cavernous malformation corresponds to a cluster of abnormally dilated blood vessels with blood-filled cavities. Such malformations occur with doses higher than 30 Gy. Their incidence after radiotherapy varies in studies from 3.8% to 43% at ten years. They occur at a median latency of six years after radiotherapy.[80] An age younger than ten years at the time of radiotherapy correlates with shorter latency and higher incidence of cavernomas.

- ***Telangiectasia***

Cranial telangiectasias are small asymptomatic lesions with low vascular flow made of dilated capillaries with a thin endothelial lining. In a group of ninety pediatric patients with brain tumors, 20% were found to have telangiectasia (median follow-up of 8.1 years).[81]

- ***Intracranial aneurysms***

An intracranial aneurysm is a localized dilation of a blood vessel caused by weakness in its wall. It can remain asymptomatic or cause a hemorrhage in the case of rupture. Post-radiotherapy aneurysms have been reported, with a median latency of 10.6 years.[82] The management of

[78] Tanino et al., 'Radiation-Induced Microbleeds after Cranial Irradiation'.
[79] Kralik et al., 'Radiation-Induced Cerebral Microbleeds in Pediatric Patients With Brain Tumors Treated With Proton Radiation Therapy'.
[80] Murphy et al., 'Review of Cranial Radiotherapy-Induced Vasculopathy'.
[81] Koike et al., 'Asymptomatic Radiation-Induced Telangiectasia in Children after Cranial Irradiation'.
[82] Sciubba et al., 'Intracranial Aneurysm Following Radiation Therapy during Childhood for a Brain Tumor. Case Report and Review of the Literature'.

vasculopathy after radiotherapy is at the moment patterned after the management of non-radiation-induced lesions, as there is limited data describing interventional techniques specifically for radiation-induced cranial vasculopathies. Strategies to decrease the risk of vasculopathies include delaying the treatment at young age, using a lower dose, and using more conformal radiotherapy.[83] Long-term stroke prophylaxis after radiotherapy may also contribute to decreasing this risk.

6. Endocrine dysfunction

Cranial irradiation can also lead to hypothalamic-pituitary dysfunction, and this can cause neurological symptoms: neurological consequences of severe hypothyroidism include encephalopathy, cerebellar ataxia, pseudomyotonia, and sometimes peripheral neuropathy. The severity and frequency of deficiencies in the secretion of anterior pituitary hormones correlate with the total radiation dose delivered to the hypothalamic-pituitary axis. Radiation-induced anterior pituitary hormone deficiencies are irreversible and progressive, such that the treatment lies in replacement therapy. In children, the GH axis is the most vulnerable, and GH deficiency generally occurs in isolation following irradiation with doses less than 30 Gy. TSH and ACTH deficiencies occur after irradiation higher than 50 Gy only. Hyperprolactinemia, due to hypothalamic damage leading to reduced dopamine release, has been described but is usually subclinical.[84] In adults, the hormonal consequences of cranial irradiation have been specifically studied in a cohort of adult-onset glioma occurring distant from the hypothalamic-pituitary axis.[85] The calculated thresholds above which individual axes were damaged in a clinically relevant way were 10 Gy for the GH axis, 30 Gy for both the gonadotropin and ACTH axes and approximately 40 Gy for the TSH axis. If the patients are not considered to be appropriate for GH replacement therapy, an endocrine screening should be required only where the dose at the hypothalamic-pituitary axis is above 30 Gy.

[83] Shih, Loeffler, and Tarbell, 'Late Effects of CNS Radiation Therapy'.
[84] Darzy and Shalet, 'Hypopituitarism Following Radiotherapy'.
[85] Kyriakakis et al., 'Hypothalamic-Pituitary Axis Irradiation Dose Thresholds for the Development of Hypopituitarism in Adult-Onset Gliomas'.

IV. Complications of hyperthermia

Hyperthermia at 39–45 °C can be used as a thermal sensitizer adjuvant to radiotherapy, notably in the management of head and neck cancers. Datta et al. reviewed six articles involving 219 clinical cases treated by thermoradiotherapy. None of the six studies reported any significant increase in toxicities with thermoradiotherapy compared to radiotherapy alone.[86]

Conclusion

Radiotherapy remains one of the most efficient treatments of cancer. Knowledge of its potential risks according to radiation treatment protocol is thus essential in order to prevent complications when possible as well as to be able to inform patients of their possible occurrence. However, the development of RT-related neurotoxicity remains largely unpredictable and seems to depend partly on individual predispositions to be elucidated that represent a major axis of research toward personalized treatment. One other challenge remains in the development of mitigation treatment for severe progressive late radiation-induced toxicities. As progress has been made in understanding the pathophysiology of radiation-induced injury and in determining "safer" radiation treatment protocols in terms of doses, volume and timing in several CNS tumors over the past few decades, some complications have become rarer. As an example, the decreased indication of whole-brain radiotherapy in brain metastases and primary CNS lymphomas is expected to be associated with a significant reduction of radiation-induced leukoencephalopathy in the future. Nevertheless, as the development of new anti-cancer systemic treatments is continuous with many benefits to patients who survive longer, great attention must be maintained on cross toxicities with radiation.

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Glossary

ICRU	International standards for radiation units & measurement
RANO	Response assessment in neuro-oncology
MGMT	O6-methylguanine-DNA methyltransferase
PET	Positron-Emission-Tomography
18F-FET	18F-fluoroethyl
18F-FDOPA	18F-fluorodihydroxyphenylalanine
11CMET	11C-methionine
rCBV	Relative cerebral blood volume
PWI	Perfusion-weighted MRI
NAA	N-acetyl-aspartate
IMRT	Intensity-modulated radiotherapy
VMAT	Volumetric modulated arc therapy
HER2	Human EGFR2
Aqp4	Aquaporin-4
MRS	Magnetic resonance spectroscopy
HBO	Hyperbaric oxygen
IMPT	Intensity-modulated proton therapy
S1P-R	Sphingosine-1-phosphate receptor
ALERT	Acute late-onset leukoencephalopathy after radiotherapy
CNS	Central Nervous System
PIPG	Peri-ictal pseudoprogression
RT	Radiotherapy
SMART	Stroke-like migraine attacks after radiation therapy

CHAPTER 1.3

CHEMOTHERAPY SIDE EFFECTS IN THE BRAIN

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Abstract

Cytotoxic chemotherapy causes a multitude of adverse effects to the brain, despite protection by the blood–brain barrier and the post-mitotic status of the parenchymal brain cells. These effects may be acute, such as nausea and vomiting, manifesting during or after chemotherapy applications and other complications ranging from seizures, acute pancerebellar syndrome, encephalopathies, neuropathies of cranial nerves to degenerative disorders such as leukoencephalopathy caused by methotrexate. The pathophysiological mechanisms of damage are diverse and not all adverse events are preventable or responsive to symptomatic therapies. Therefore, careful information before therapy and monitoring of patients regarding CNS toxicities are necessary to limit toxicities and preserve the quality of life of patients with cancer as much as possible.

Keywords: Chemotherapy, toxicity, brain parenchyma, seizures, encephalopathy, cognitive impairment

Introduction

Sensu stricto nausea and vomiting, resulting from the interaction of chemotherapeutic drugs with the chemoreceptor trigger zone in the brain stem, are the most prominent side effects of chemotherapy in the brain. Thanks to efficacious anti-emetic drugs and some prophylactic dietetic precautions, nausea and vomiting can be reduced to manageable levels and have lost most of their awfulness.

However, there are more brain toxicities related to chemotherapy as well as acute toxicities manifesting during or shortly after drug application

and also occurring months or even years later. Any new neurological symptom should be considered in this context, but other potential causes should be excluded, particularly metastatic invasion of the cancer in the brain or leptomeningeal disease, infections that occur more often in patients with immunocompromised and endocrine and paraneoplastic diseases. Subsequently, brain toxicities of chemotherapy are briefly discussed, mainly related to symptoms and sometimes to the drug most prominently associated with certain symptoms, such as ototoxicity and cisplatin and methotrexate and leukoencephalopathy. Particularly in the context of advanced cancer, notably after several therapy lines and with impaired liver function, low serum albumin, drug exposure levels and presentation times might differ from situations described in the literature and lead to hitherto undescribed adverse clinical pictures.

Most patients with cancer and their relatives express the wish to have a single physician representative for their treatment, informing them about all treatment modalities, supportive care and outcomes of their cancer. However, medical knowledge has increased so rapidly in recent decades, that a single person cannot fulfill these expectations. Moreover, it is generally expected that cancer physicians should be at their disposal whenever the patient wishes to talk. Presently cancer should be treated by a multidisciplinary team of specialists from different medical specialties, able to recognize side effects caused by the treatments they have administered. This may overstrain each member of the team, when the adverse event can be allocated to another medical specialty as, for example, neurologic side effects of cytotoxic drugs are typically part of the expertise of neurologists, albeit “caused” by medical oncologists. These issues mandate interdisciplinary cooperation for diagnostic, as well as for therapeutic, work-up and prevention. Sensitive but comprehensive information for the patients and their proxies before the start of drug therapies, including the potential side effects, supported by written or audiotaped material is mandatory to ensure patient cooperation and the identification of adverse events at their onset. The early detection of side effects helps to limit their severity, adequate supportive measures to be put in place, symptomatic treatment and/or to the cessation of the drug causing the side effects. For decades, it was postulated that brain parenchyma cells, e.g. neurons and glial cells, were terminally differentiated and no longer dividing. Moreover, they were secluded from the bloodstream by the blood–brain barrier (BBB). Adverse effects of chemotherapy on the brain seemed unlikely. Indeed, the reality is different. Effective measures against chemotherapy-induced brain toxicity were slowly developed and understanding the underlying mechanisms progressed slowly. Presently

thorough and precise information for patients on the potential adverse effects of their planned treatment, as well on potential preventive and therapeutic measures is “State of the Art.”

Chemotherapy-induced toxicity may cause many neurologic adverse events, such as headache, fatigue, sleep disturbances, cognitive deficits, seizures, encephalopathy, disturbances of vision, audition, and cranial nerve neuropathies.[1] There may be indirect effects caused by cancer and chemotherapy-associated coagulopathy or bleeding, leading to strokes or intracerebral hemorrhagic complications.

Differential diagnosis of chemotherapy-induced brain toxicity includes ruling out other causes of neurologic symptoms including diabetes mellitus, hypertension, side effects of other drugs, alcohol or drug abuse and pre-existing neurologic diseases or paraneoplastic syndromes. Interdisciplinary work-up of medical oncologists and neurologists is mandatory to establish the diagnosis of chemotherapy-induced brain toxicity.

Infections

Infections can be triggered by deficiencies of the immune system caused by chemotherapy. The activity of the immune system in cancer patients is reduced, as the cancer interacts with immune cells to continue its invasion of the organism and provokes a constant inflammatory milieu. Chemotherapy with its cyclic depletion of white blood cells and, for some substances, persisting lymphopenia over several months facilitates infections also in the brain. In tumor patients with a depleted immune system, some infections to the CNS which are predominantly seen in organ transplant recipients or patients with inborn immune defects may also appear, such as herpes simplex encephalitis or progressive multifocal leukoencephalopathy (PML).

Neuropathy of cranial nerves

Neuropathy of peripheral nerves following chemotherapy is the most common and well-known neurotoxicity. It is diagnosed mainly on peripheral sensory nerves and is one of the main causes of the reduction or discontinuation of chemotherapy. The mechanisms involved in the development of neuropathies are diverse and might be multiple for a given drug and yet not fully understood for all drugs used.

Vinca alkaloids (vincristine, vinblastine, vindesin, vinorelbin) inhibit the polymerization of ß-tubulin and impair axonal transport. Moreover,

they lower the threshold of C fibers, contributing to chronic pain. Vincristine increases a serine protease that inhibits endorphins, a second mechanism for chronic pain and a third mechanism inhibits the activation of astrocytes. By the induction of reactive oxygen species (ROS), vinca alkaloids exert toxic effects on mitochondria which could be overcome by antioxidants.[2]

Patients can develop focal cranial neuropathies with ptosis, vision loss, hoarseness and facial weakness—typically in combination with peripheral sensorimotor neuropathy and sometimes in association with autonomic neuropathy manifesting as constipation and abdominal colic.

Seizures and hyponatremia associated with SIADH have been reported rarely with vincristine neurotoxicity and abnormal secretion of antidiuretic hormones.[3]

Platinum compounds (cisplatin, carboplatin, oxaliplatin) form platinum-DNA adducts and induce apoptotic cell death that can reach neurons that are not protected by the BBB. They exert their toxicity by causing apoptosis in sensory neurons with anterograde axonal degeneration. While nephrotoxicity of platinum drugs can be attenuated or even avoided by vigorous hydration given preferentially before the drug administration, neurotoxicity cannot always be avoided.

Cisplatin-induced ototoxicity

A prominent and exceedingly important manifestation of cisplatin-induced neurotoxicity is hearing loss. Cisplatin can reach the outer and inner hair cells and neurons in the spiral ganglion of the cochlea. Children have the highest risk of cisplatin-induced hearing loss reaching 20 to 77%.[4]

When hearing loss occurs before speech development, it might impair the acquisition of language and hinder socialization. Cisplatin-induced hearing loss mainly affects the high frequency range and most often becomes manifest after a cumulative dose above 300 mg/m^2. The main mechanisms of cisplatin cochlear toxicity are the increased generation of ROS and inactivation of antioxidant systems, and also compromise of the integrity of the nuclear DNA and repair system (NDNA) and damaging mitochondria. In fact, adducts between cisplatin and mitochondrial DNA cannot be repaired and lead to loss of mitochondria and energy failure of the affected cells.[2] This might be the cause of the prolonged damaging effect of cisplatin even after discontinuation of the drug ("Coasting"). Reducing or avoiding cisplatin-induced hearing loss, without reducing its anti-tumor efficacy is a challenging task, but there are some promising

approaches such as localized delivery of highly antioxidant drugs to the cochlea.[4]

Moreover, cisplatin may impair the sense of equilibrium via the same mechanisms, contributing together with peripheral sensory neuropathy to gait disturbance and unsteadiness.

Oxaliplatin

Although oxaliplatin forms fewer DNA adducts than cisplatin, these are more prone to evading DNA repair mechanisms and thus more effective in causing DNA damage. Oxaliplatin neurotoxicity presents in two forms. Acute, reversible and transient neurotoxicity manifests with paresthesias and dysesthesias in the peri-oral region which can be provoked by cold and may increase with cumulative dose (>540 mg/m^2). Oxaliplatin slows the inactivation of axonal Na+ channels, resulting in hyper-excitability of sensory neurons.

The second, prolonged toxicity occurs late in 10–20% of patients after a cumulative dose of more than 800 mg/m^2 up to two years after treatment, and consists of jaw pain, eye pain, visual and voice changes, triggered by similar mechanisms as for cisplatin.[2]

Taxanes

Taxanes bind to the lumen of microtubules, stabilize the lattice and suppress their dynamic availability. This arrests cells in the G2/M phase and causes apoptosis of dividing cells. In neurons, the axonal transport is impaired, mainly causing sensory loss, paresthesia and pain. This toxic effect is mainly due to mitochondrial damage and to an increase of Ca^{2+} influx into neurons[2] and to an upregulation of pro-inflammatory cytokines by taxanes. Treatment against glial cell activation, using minocycline, propentophylline and thalidomide, has been effective against neuropathic pain and mechanical hyperalgesia caused by taxanes.[5]

Proteasome inhibitors

These highly effective drugs bind to the proteasome in the cytoplasm of cells, lead to the enlargement of mitochondria and endoplasmatic reticulum and activate caspases, leading to apoptosis. Bortezomib is an inhibitor of NFkB (nuclear factor kappaB) which is constitutively localized in the cytoplasm and inhibits pro-inflammatory signals. Thus, bortezomib leads to inflammation and the secretion of TNF-alpha,

generation of ROS and heat shock proteins, responsible for the development of neuropathic pain. The excessive production of ROS induces mitochondrial damage, followed by cell death. This mechanism implies that treatment with antioxidants such as vitamin C and N-acetyl cysteine might alleviate or prevent the toxic effects of bortezomib—but also interferes with the therapeutic efficacy.

Acute pancerebellar syndrome

This acute toxicity was described in 2–4% of patients receiving high dose bolus injections of 5-fluorouracil or in a lesser frequency other anti-metabolites such as cytosine arabinoside. It consisted of nystagmus, dysarthria, limb and gait ataxia and was usually reversible, but recurred at re-exposure.[6,7]

It could be followed by headache, optic symptoms, seizures and encephalopathy. This syndrome was only exceptionally described with capecitabine and thus seems to be related to a high peak dose which is avoided in newer treatment regimens.[8] Also, the neurotoxicity of fludarabine appeared to be dose dependent and mainly occurred after daily doses higher than 90 mg/m^2 and consisted of optic neuritis and cortical blindness, seizures and ataxia.[8]

Leukoencephalopathy—Methotrexate (MTX)

MTX is one of the most frequently cytotoxic drugs. It inhibits DNA synthesis by antagonizing the enzyme dihydrofolate reductase which converts folic acid into tetrahydrofolate. It is used in a wide dose range going from low, oral doses of less than 100mg used against rheumatic diseases, up to intravenous applications of several grams in therapy regimens against lymphomas and sarcomas and also for intrathecal therapy. Accordingly, there is a wide spectrum of toxicities described. High intravenous doses might be followed by acute, stroke-like toxicity with neurological deficits and seizures, vanishing after several days. The major toxicity is delayed leukoencephalopathy which develops after several months or even years after high dose MTX and seems to be preventable by folate rescue started not later than 36 hours after each application. Leukoencephalopathy manifests as a neurocognitive decline, personality changes and dementia. The MRI shows periventricular white matter hyperintensity, cerebral atrophy and ventricular dilatation. Leukoencephalopathy seems to occur more frequently and is more severe,

when MTX is given after brain radiation, possibly due to vascular damage or increased vascular permeability after radiotherapy.[1]

Encephalopathy following Ifosfamide

Ifosfamide is an alkylating agent, still widely used in chemotherapy regimens of sarcomas, Non-Hodgkin lymphomas and other solid tumors. Ifosfamide causes neurological toxicity in 20 to 60% of patients, manifesting as confusion, headache, disorientation, impaired consciousness, eventually coma, extrapyramidal symptoms and seizures. This neurotoxicity often causes the discontinuation of ifosfamide therapy.

Ifosfamide is activated in the liver by the cytochrome P-450 enzyme CYP3A4 to the active moiety ifosforamide mustard. Additional metabolites formed during this multistep process are acrolein chloroacetaldehyde, which are both able to cross the blood–brain barrier and are held responsible for the neurotoxic effects of ifosfamide. Other proposed mechanisms include depletion of glutathione in the CNS, inhibition of fatty acid metabolism and induction of glutaricaciduria.[9]

Ifosfamide neurotoxicity and potential treatment with methylene blue[10,11] has risk factors for the development of encephalopathy, which are low serum albumin, increased serum creatinine and hemoglobin, previous cisplatin exposure and use of opioids.

By reducing chloroacetaldehyde formation, acting as an electron acceptor, or by treating possible glutaric aciduria, intravenous application of methylene blue has shown to be effective against ifosfamide encephalopathy. Further measures include hydration and the administration of thiamine,[12] notably methylene blue also has potential neurotoxicity.[13]

Aseptic meningitis

Intrathecal chemotherapy with MTX and/or cytarabine is used to prevent or to treat leptomeningeal disease in leukemia, lymphomas or solid tumors. It is applied either by lumbar puncture or by an Ommaya reservoir. Side effects mimic the symptoms of meningitis with neck stiffness, headache, nausea and vomiting, sometimes fever. Rarely transverse myelopathy with back pain and motor symptoms, sensory loss and bladder and bowel incontinence can occur, all in the context of aseptic meningitis and usually reversible.

Fatigue

Several studies provide data on the prevalence of fatigue in patients with glioma before the onset of radiotherapy or chemotherapy. Fatigue was associated with impaired performance status and with shorter survival. Osoba et al.[14] pooled the QoL data from three studies and found in 488 patients that fatigue was not only the most reported symptom, they also rated it the symptom with the greatest impact on QoL. Younger patients complained more about fatigue than older patients, women more often than men.

Biological mechanisms of fatigue

The biological mechanisms leading to cancer-related fatigue are complex and not yet fully elucidated. Most studies have been conducted in rodents and human data coming from patients with frequent tumors such as breast cancer or lung cancer, but the data appear consistent and plausibly transferable to the brain tumor situation. Moreover, the brain is the perceiving organ for fatigue as well as the organ affected by the tumor and its treatment.

Wang et al.[15] measured fatigue by the MDASI[16] inventory and found that fatigue correlated with serum IL-6 and TNF-alpha levels in patients with GI cancer, whereas in patients with breast cancer fatigue showed a positive correlation with increasing CRP, but neither with IL-1 nor with IL-6 levels.[15]

Circulating levels of inflammatory cytokines have been found in patients with cancer at diagnosis, during cytoreductive treatment and thereafter and were found to be related to cancer fatigue and other behavioral symptoms such as depression, anorexia, sleep disturbance and fatigue.[17] Inflammatory cytokines are able to transmit peripheral immune signals to the brain and influence neuroendocrine function, signaling pathways and provoking epigenetic changes resulting in the persistence of fatigue years after eradication of the tumor. All conditions associated with persistent chronic inflammatory changes, such as childhood trauma, lack of social support, persistent stress, prior psychiatric illness were found to be associated with more frequent and more severe fatigue in cancer patients.[18]

The release of damage-associated-molecular patterns (DAMPs), e.g. molecules normally situated in intracellular spaces released to the extracellular space by membrane damage or cell death and leading to activation of the immune system, to neoangiogenesis and more formation

of DAMPs, is convincingly documented and experimentally proven. DAMPs are proteins, such as high mobility box1 protein, nucleic acids, adenosine, purines and uric acid, as well as ROS. They are released by cancer cell apoptosis, lack of nutrients, hypoxia, all occurring within rapidly dividing cancer cells. A major pathway to DAMP release is mitochondrial dysfunction to direct damage of cytostatic drugs to mitochondrial DNA or increased ROS.

A second mechanism linking tumor growth to fatigue has been outlined.[19] In a cross-sectional study on a hundred patients with different cancers, they found that decrease of glutamine levels was associated with fatigue. Glutamine is a prevalent amino acid and builds up more than 60% of muscular protein. It is extensively used as respiratory fuel in rapidly dividing cells such as enterocytes, lymphocytes and cancer cells. Lack of glutamine was associated with sarcopenia, but also with pro-inflammatory status, fatigue and depression.[19]

Another amino acid found associated with cancer fatigue is tryptophan, an essential amino acid that is a precursor for melatonin as well as for serotonin. Inflammatory cytokines activate the indoleamine 2,3 dioxygenase pathway (IDO) which catalyzes the degradation of tryptophan to kynurenine, the first step leading to biogenic amines responsible for circadian rhythms and for mood. Lack of tryptophan is associated with behavioral symptoms such as sleep disturbance, depression and fatigue.

Posterior reversible encephalopathy syndrome—PRES

PRES is a rare adverse event in cancer, occurring in less than 1% of patients, with acute onset of neurological symptoms such as impaired consciousness, headache, visual disturbances and seizures, typically associated with increased blood pressure and renal failure and characteristic findings in CT and MRI imaging. In MRI PRES is defined as new, mostly symmetric subcortical lesions seen in standard fluid attenuated inversion recovery sequences (FLAIR) without evidence of recent infarct or brain metastases, involving not only the posterior brain regions but also basal ganglia and other sites, showing signs of hypoperfusion in the involved areas.[20]

In imaging it comprises new subcortical hypodensities in the white matter. In more than 80% of affected patients, symptoms resolve within one week, after blood pressure normalization, but even acute fatal issues might occur in patients that develop intracranial hemorrhage or brain infarction.[21]

PRES seems to occur more frequently in females and in childhood cancer and leukemia and is less frequent in males and in patients with primary brain tumors. In a series of the Memorial Sloan Kettering institute, 55% (17/31) of patients had received any cytotoxic agent during the month before, 23% of them a targeted agent with bevacizumab (6/31, 19%) being the single drug most often implicated. Seven patients (23%) with PRES were not receiving any therapy and had been scored as "inactive cancer" at their last follow up visit.[20]

The underlying pathophysiological mechanisms are endothelial dysfunction and breakdown of the blood–brain barrier, followed by extravasation of fluid and macromolecules, exhausting the cerebral blood pressure autoregulation.[22] Fluctuating, increased blood pressure might damage endothelial cells and provoke the release of cytokines TNF-alpha, IL-1 and IFN-γ and subsequently the secretion of VEGF, leading to increased vessel permeability. Potentially, the changes of VEGF signaling pathways may cause disturbance of the availability of nitric oxide, essential for blood pressure autoregulation. Remarkably, nearly 50% of patients developing PRES have a clinical history of an auto-immune disease with potential endothelial damage caused by the disease itself or the immune-suppressive medications.

Platinum-containing drugs, cyclophosphamide, anthracyclines, vinca alkaloids, prednisone/R-CHOP regimens, and gemcitabine were the agents most commonly used in patients who developed suspected chemotherapy-associated PRES. Median onset of symptoms occurred a week after chemotherapy. The most common risk factor associated with the development of chemotherapy-associated PRES was hypertension.[23]

There is no recommended standard treatment of PRES but treating the precipitating causes is recommended. Increased blood pressure should be slowly and continuously reduced and known triggering drugs discontinued, at least until resolution of PRES. If present, hyperglycemia with its endothelial damaging effects should also be closely monitored and controlled.

"Chemobrain," chemotherapy-induced cognitive impairment (CICI)

See Chapter: 1.5

These themes appeared in the program of cancer conventions in the late 1990s. It was controversially discussed whether chemobrain existed or was a plausible way for cancer survivors to claim an invalidity pension. The affected patients complained about elusive symptoms such as deficits

in attention, memory and problems with multitasking. One could imagine that it was indeed difficult to return to work after several months of sick leave, after having faced cancer therapy with its side effects. Since most patients complaining about CICI were women with breast cancer, it was proposed that they were no longer motivated to fulfill their role.

Moreover, most cancer patients have to endure periods of anxiety and depression that impact cognitive performance. It appears plausible that any person that has faced existential problems in the face of cancer changes their values and attitudes.

From our personal experience there was the notion that patients undergoing several cycles of chemotherapy seemed forgetful and mildly cognitively impaired.

Quote:

"There were the regular complaints of the nurses of our day clinic about the patients with relapsing disease." "They come here for several years, and though we have to explain our procedures to them over and over… Some of them even don´t remember where the toilets are. Chemotherapy weakens the brain…"

At this time, the state of knowledge was that—with a few exceptions—chemotherapy drugs do not penetrate into the brain protected by the blood–brain barrier (BBB). How could the damage to the brain occur?

A convincing case of CICI was the finding in functional MRIs of monozygotic twins that differed by the experience of breast cancer treatment in one of them who had to solve the same question during MRI examination. Both provided the correct result, but the sister with breast cancer needed to activate many more brain areas than her healthy twin.[24] This case report illustrates that persons reporting cognitive changes after chemotherapy may indeed suffer from CICI, even when they perform adequately in cognitive testing. In patients with CICI, MRIs showed thinning of the gray matter in the prefrontal cortex, in the hippocampus and the cerebellum as well as white matter shrinkage.

The prevalence of CICI in breast cancer patients reaches around 60% and in childhood cancer survivors 30–40%. Its severity is variable. It may last more than twenty years as suggested by a cohort of breast cancer patients treated with cyclosphosphamide; for fluorouracil and methotrexate at least twenty years before are reported with significantly more deficits in a cognitive test battery than age-matched healthy controls.[25]

The mechanisms of CICI are still not fully understood, but there are several plausible explanations for chemotherapy-induced neuronal damage.

The integrity of the BBB may be compromised in tumor patients by inflammatory cytokines that open up tight junctions and allow chemotherapeutic drugs to penetrate the CNS. Although the drug levels measured are very low and sub-therapeutical, altered behavior was observed in test animals.[26] Neural stem cells and oligodendrocyte precursor cells (OPCs) are much more sensitive to chemotherapeutic drugs than cancer cells and are depleted even by low levels of chemotherapy. In a murine model, treatment with methotrexate reduced OPC proliferation and increased differentiation, leading to a depletion of oligodendrocytes and a thinning of the myelin sheaths, resulting in behavioral changes of the animals[27] with increased anxiety.

Moreover, 50% of chemotherapeutic drugs exert their activity by inducing ROS, able to increase the permeability of BBB. This allows not only penetration of the drugs themselves, but also of inflammatory cytokines and circulating ROS, prone to damage vulnerable brain structures containing high amounts of unsaturated fatty acids. Using a TNF-alpha null mouse model, Ren et al. could prove that TNF-alpha induces oxidative stress in the brain, damaging mitochondrial function.[28] Taking into account the constant high energy requirements of the brain and the lack of energy stores, any impact on mitochondrial function decreases energy metabolism in the brain and may result in apoptotic brain cell death, as observed in the decrease of hippocampal Cho/Cr ratio in doxorubicine treated wild type mice in contrast to preserved hippocampus in TNF0 mice.[28]

Another mechanism contributing to CICI may consist of genetic alteration of DNA repair systems. Such genetic variants in the DNA repair systems are associated with a higher prevalence of cancer, premature aging and neurodegenerative diseases.[29,30] Oxidative stress caused by chemotherapy may lead to DNA damage in glial cells and neurons, exceeding repair capacities and thus leading to apoptosis.[31]

Increased peripheral and consequently also increased brain levels of pro-inflammatory cytokines such as TNF-alpha, IL1-ß and IL-6 modulate synaptic function and activate microglia, which might further enhance neuroinflammation with consecutive loss of neurons.

Not all patients treated with chemotherapy develop CICI. Some people seem to have genetic conditions predisposed to develop malignant tumors and CICI e.g. patients with mutations in DNA repair mechanisms, patients with mutations in the gene for Catechol-O-methyltransferase (COMT), for

brain-derived neurotrophic factor (BNDF) and the apolipoprotein E (ApoE) subgroup of lipoproteins which also predispose these patients to dementia.[32] Probably screening for these genetic variants will become part of the pre-therapeutic screening before starting a cancer therapy in the future. Avoiding and minimizing chemotherapy as much as possible in such patients, by choosing targeted or immune therapies if possible, should be considered.

Of course, limiting all other factors that reduce cognitive performance such as metabolic imbalances, electrolyte disorders, hormonal deficiencies particularly hypothyroidism and hypogonadism caused by cancer treatment and avoiding possible medications with sedative potential (tranquilizers, neuroleptics, antidepressants, anti-epileptics, other sedatives), and pain treatment all help to overcome CICI.

This brief survey shows the great complexity of adverse interactions of chemotherapeutic drugs with the brain. As the brain determines who we are and how we feel, most of the quality of life depends on good functioning of our brain. Every effort must be taken to improve cancer therapy, minimizing adverse events in the future. As this chapter shows, there is still a long way to go and with the increasing appearance of targeted therapies and immune therapies new challenges appear.

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CHAPTER 1.4

NEUROTOXICITY ASSOCIATED WITH CANCER IMMUNOTHERAPIES

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Abstract

Immune evasion has been recognized as a hallmark of cancer for a long time. Fighting cancer using the immune defense mechanisms of the body has been envisioned for many decades but remained an unfulfilled dream as, until recently, most of the tested approaches remained unsuccessful. However, the recent discovery of immune modulating drugs that stimulate the patient's immune system rather than directly targeting cancer cells has revolutionized cancer treatments. Nowadays, immunotherapy is regarded as the fifth pillar of cancer care alongside radiotherapy, surgery,medical and interventional oncology. So far, two main immunotherapy approaches have been proven to be effective and have reached the market: immune checkpoint inhibitors and adoptive cell therapies, including Chimeric Antigen Receptor T- cells (CAR-T cells) and bispecific T-cell engager immunotherapy. These new treatments are however associated with a wide range of specific toxicities. To ensure an optimal management, it is important that neurologists know the specifics of the side effects that involve the central and peripheral nervous system.

Keywords: cancer immunotherapies, neurologic complications, side effects, CAR-T-cell therapy, immune checkpoint inhibitors, adoptive T-cell therapies

Introduction

Immune evasion has been recognized as a hallmark of cancer for a long time.[1] Fighting cancer using the immune defense mechanisms of the body has been envisioned for many decades but remained an unfulfilled dream as until recently most of the tested approaches remained unsuccessful. However, the recent discovery of immune modulating drugs that stimulate the patient's immune system rather than directly targeting cancer cells has revolutionized cancer treatments. Nowadays, immunotherapy is regarded as the fifth pillar of cancer care alongside radiotherapy, surgery and medical and interventional oncology. So far, two main immunotherapy approaches have been proven to be effective and have reached the market: immune checkpoint inhibitors and adoptive cell therapies, including CAR-T cells and bispecific T-cell engager immunotherapy.

Immunotherapy in oncology

Immune checkpoint inhibitors (ICPI)

Immune checkpoints are cell-surface receptors that are involved in immune homeostasis. They are expressed either by T-cells or the target cells and dampen T-cell activation to maintain self-tolerance and prevent autoimmunity.[2] Cancer cells often highjack these inhibitory pathways to gain immune escape capabilities.[3] Immune checkpoint inhibitors (ICPI) are monoclonal antibodies that block these receptors and thus unleash the brakes restraining T-cells from attacking the tumor cells. Antibodies against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death-(ligand)-1 (PD-1/PD-L1) have been the first ICPI to reach the market and are now approved for a growing number of cancer indications[4] (Table 1-4-1). Monoclonal antibodies against CTLA-4 and PD-1/PD-L1 have very different mechanisms of action: CTLA-4 prevents the T-cells from being fully activated.[5] CTLA-4 is a key regulator functioning in a negative feedback loop upon T-cell activation. CTLA-4 is recruited to the plasma membrane and competes with CD28 for the B7 costimulatory signal provided by dendritic cells and antigen-presenting cells (APC) thus dampening T-cell activation and expansion. CTLA-4, an important immune suppressive mechanism also found in regulatory T-cells (Tregs) is largely overexpressed in intratumoral T-cells.[6] Treating tumors with blocking MAbs against CTLA-4 allows this immune regulatory mechanism to be overcome and induces strong immune responses against the tumor.[5]

Unfortunately, even when T-cell activation is achieved in the tumor-draining lymph nodes, tumors still have the capacity to inhibit immune effector T-cells once they enter the tumor. PD-1 is expressed predominantly by activated T-cells and may interact with its ligand PD-L1 that is expressed on the target cells. This interaction induces T-cell exhaustion.[7] Exhausted T-cells lose their cytotoxic capacity, stop proliferating, stop secreting inflammatory cytokines, upregulate checkpoint receptors and ultimately die out.[8] Anti-PD1/PD-L1 antibodies block this interaction within the tumor, thus allowing the expansion of anti-tumor cytotoxic T lymphocytes.

Table 1-4-1: Approved immunotherapies and their indications

Target	Name	Indication
Immune checkpoint inhibitors		
CTLA-4	Ipilimumab (Yervoy®)	Melanoma
PDL-1	Pembrolizumab (Keytruda®) Nivolumab (Optivo®)	Melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer, head & neck carcinoma, renal-cell carcinoma (RCC), Hodgkin lymphoma, cervical carcinoma, primary mediastinal large B cell lymphoma (PMBCL), urothelial carcinoma, hepatocellular carcinoma, gastric cancer, MSI-H or dMMR solid tumor
PD1	Atezolizumab (Tecentriq®) Durvalumab (Imfinzi®) Avelumab (Bavencio®)	Urothelial cancer, NLCLC, Merckel cell carcinoma
CTLA-4 + PDL-1	Ipilimumab + Nivolumab	Metastatic melanoma, RCC, colorectal cancer (MSI-H or dMMR)

Chimeric Antigen Receptor T-cells		
CD19	Tisagenlecleucel (Kymriah®) Axicabtagene ciloleucel (Yescarta®)	Refractory B-cell acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL), non-Hodgkin lymphoma
Bi-specific T-cell Engagers		
CD19-CD3	Blinatumomab (Blincyto®)	Philadelphia chromosome-negative relapsed or refractory B-ALL, minimal residual disease (MRD)-positive B-ALL

ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; DLBCL, diffuse large B-cell lymphoma; dMMR, deficient mismatch repair; MRD, minimal residual disease; MSI-H, microsatellite instability high; NSCLC, non small-cell lung cancer; PD1, programmed cell death 1; PD-L-1, programmed cell death-ligand 1; PMBCL, primary mediastinal large B cell lymphoma; RCC, renal-cell carcinoma.

Adoptive T-cell Therapies (ACT)

ACT consists of re-infusing a patient with their own (autologous) or donor (allogenic) anti-tumor T-cells to attack tumor-specific antigens of the patient's cancer cells. This approach mimics successful T-cell immunization with the expansion and activation of antigen-specific T-cells. In ACT this expansion is however performed *ex vivo* to maximize the response. Tumor infiltrating lymphocytes (TILs) are isolated from a tumor biopsy, then activated and expanded in culture prior to being reinfused into the patient after preparative lymphodepletion. Tumors thus face much larger T-cell numbers. Moreover, preactivated cells are less susceptible to the intratumoral immunosuppressive microenvironment. Such treatment protocols were proven successful, obtaining complete responses in metastatic melanoma patients that were previously refractory to other treatments.[9] Furthermore, adoptive transfer of TILs in metastatic melanoma patients is effective in 30% of patients refractory to anti-PD1 treatment and 25% of patients refractory to CTLA4 inhibition.[10]

An immune attack against tumor cells presupposes the existence of tumor-specific neoantigens. Not surprisingly, the first tumor antigen, MAGEA1 was found in melanoma, which is one of the most mutated cancers.[11] Since then, hundreds of tumor T-cell epitopes have been identified. Interestingly, many of them are epitopes from non-mutated proteins reflecting the tissue of origin of the tumor cells. For example, the melanocyte differentiation antigens Pmel, MART1 and TYRP1 and 2 allow targeting of melanoma cells.[9,12] Other epitopes result from epigenetic changes in the tumor cells. Among these, we find cancer-testis antigens (NY-ESO-1 and many others) normally expressed only in the germline. Cancer-testis antigens are typically found in lung carcinomas, head and neck cancer and melanoma. T-cells targeting NY-ESO-1 are undergoing clinical trials.[13]

In the absence of a high mutational load, ACT can still be used if the antigen specificity is provided by engineering the T-cells. This is done by expressing a high-affinity TCR directed toward a preselected tumor epitope. One can either isolate a TCR from a patient with a strong response to treatment or from T-cells screened *in vitro* for high reactivity. Such TCRs are then cloned and used to transform the patient's lymphocytes. Alternatively, mice can be vaccinated against human cancer epitopes. As the antigen is non-self, this typically results in highly reactive T-cell clones. TCRs are then humanized before being used in human T-cells. Pmel TCRs used in clinical trials were generated in this manner.[13]

A third approach has emerged as patients often lack intratumoral T-cells or too few immunogenic tumor-epitopes are present: The goal is to activate

T-cells and kill target cells in a TCR and co-stimulation independent fashion. Chimeric Antigen Receptor T-cells (CAR-T) are engineered lymphocytes harboring a chimeric transmembrane-receptor consisting of an extracellular scFv-fragment for target recognition linked to T-cell specific intracellular signaling domains. These signaling domains consist of CD3ξ containing the key TCR ITAM motives as well as various costimulatory domains from CD28, 4-1BB or OX-40. Such receptors allow full T-cell activation with a single target-antigen recognition event without requiring MHC-epitope presentation or co-stimulation from an antigen-presenting cell.[14] Until now, two CAR-T based therapies have been approved: Axicabtagene ciloleucel (Yescarta®) for non-Hodgkin lymphoma[15] from Kite pharmaceuticals® and the anti-CD19 CAR-T Tisagenlecleucel (Kymriah®) for refractory B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma (DLBCL) from Novartis®.[16,17] According to clinicaltrials.gov, as of today, over 450 CAR-T trials are ongoing including over ten phase III trials. Few patients have been receiving these novel therapies but as their number grows rapidly, clinicians should be prepared to deal with their potential adverse events.

Bispecific T-cell engagers (BiTEs)

BiTEs are fusion constructs obtained by linking two scFvs fragments with two distinct specificities. One of the scFvs targets the CD3 receptor of T-cells, and the other the desired tumor epitope. This confers tumor-specificity to any T-cell and leads to its activation and degranulation in an MHC-independent manner.[18] Blinatumomab (Blincyto®), a CD19-specific BiTE, is the first and only to be FDA approved since 2014 for Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), and minimal residual disease (MRD)-positive B-cell precursor ALL.[19]

Systemic adverse events

Immune-related adverse events (IrAE) result from T-cell over-activation and non-specific inflammation. These adverse events have been described throughout various organs including colon, lungs, liver, kidneys, thyroid, pituitary gland, skin, muscles, joints and eyes. The physiopathological pathway at their root remains only partially understood. However, as immune checkpoints are key receptors preventing autoimmunity and promoting self-tolerance, it is not surprising that their inhibition results in pro-inflammatory reactions.[20]

Overall, the incidence of irAEs varies between 15–90% depending on the type of immune checkpoint.[21,22] The rate of severe irAEs requiring treatment discontinuation is however much lower and ranges between 0.5 and 13%, depending on the agent evaluated and the clinical trial.[23–29] It remains unclear whether the differences observed in the different trials relate to a differing susceptibility to irAEs based on different cancer types or whether these differences are linked to a difference in standards (and precision) of the follow ups of different clinical trials.

IrAEs can arise at any time but the onset usually occurs within the first twelve weeks after treatment initiation. Interestingly, irAEs have been reported up to six months after treatment interruption.[30,31]

In general, PD-1/PD-L1 inhibitors show a lower incidence of irAEs compared to CTLA-4 inhibitors. This can be explained by different checkpoint receptors being targeted as well as the location at which the inhibition takes place: PD-1/PD-L1 inhibition occurs directly within the tumor, whereas CTLA-4 inhibition takes place in the lymph nodes, thus enabling a broader unspecific T-cell activation. Combined inhibition of both checkpoints (CTLA-4 & PD-1/PD-L1) results in more irAEs with 30-50% of patients developing grade 3-4 side effects in contrast to 10-20% with either monotherapy.[22,23,28,32–43] Interestingly, whereas anti-PD-1/PD-L1 irAEs appear to be dose-independent, risks of severe AE rise from 7 to 25% when ipilimumab dosage increases from 3 mg/kg to 10 mg/kg.

Overall, neurologic side effects linked to ICPI remain rare. The most commonly affected organs are, in order, the skin and gastrointestinal tract followed by the lung and thyroid.[44] This does not account for the 16–24% of patients reporting unspecific symptoms such as fatigue.[30]

Neurologic adverse events of immune checkpoint inhibitors:

Overall, the reported incidence of neurological adverse event (nAE) of any grade is 3.8% with anti-CTLA-4, 6.1% with anti-PD-1/PD-L1 and 12% with the combination of anti-PD-1 and anti-CTLA-4 therapies. The most frequent side effects described are unspecific symptoms such as headache, dysgeusia and dizziness.[45] Peripheral sensory neuropathy also commonly occurs. Severe (grade 3–4) nAEs occur less frequently: 1.9% under anti-CTLA-4 (ipilimumab),[46] 0.2–0.4% under anti-PD-1 (nivolumab or pembrolizumab)[33,47] and 0.1–1% under anti-PD-L1 (atezolizumab, avelumab or durvalumab).[41,48,49]

Little is known in terms of the pathogenesis of central nervous system (CNS) irAEs. Until now, only working hypotheses are available: As described by Yshii et al., these adverse events could arise from 1. ICPI-induced immune reactions resulting from autoantigens that react against the CNS similar to the pathway in classic paraneoplastic syndromes. 2. An increase of unspecific inflammatory reactions against the tumor as well as against healthy CNS tissue. Moreover, 3. ICPIs might recognize their target on normal brain cells (endothelial cells, astrocytes or neurons) and elicit a direct on-target side effect.[50] In support of these mechanisms, Williams et al. described nAE in melanoma patients, where a two-step mechanism takes place: Firstly the increased tolerance to self allows the development of autoantibodies against N-methyl-D-aspartate receptor (NMDAR) which is aberrantly expressed on the melanoma cells leading to the subsequent development of autoimmune encephalitis upon ICPI treatment.[51]

Diagnosis and management of neurological adverse events

When patients with cancer are treated with immune therapies, the development of neurological symptoms must always be suspected, but given other etiologic possibilities, it should remain a diagnosis of exclusion. Ruling out potential differential diagnoses including vascular, toxic, metabolic, epileptic, or infectious causes or the presence of progressive oncologic disease (brain metastasis, leptomeningeal carcinomatosis or spinal cord compression) remains at the center of the diagnostic algorithm.

Moreover, in the event of nAE, rapid diagnosis and early treatment initiation are crucial to limit the magnitude of potential sequelae or even a fatal outcome. Early intervention was proven to reduce both the severity and duration of the symptoms.[52] Although there are no prospective trials to help determine the optimal management plan, handling such patients should rely on multidisciplinary teams, as discontinuation of the oncologic treatment might decrease its efficiency and jeopardize the patient's oncologic outcome.

Given the link between immune activation and nAEs, corticosteroids at immunosuppressive dosage are recommended in the presence of severe symptomatology or in certain specific situations (encephalitis, myasthenia gravis) (Table 1-4-2).[44] Plasmapheresis and other immunosuppressants, either unspecific agents (mycofenolate, methotrexate, cyclophosphamide, rituximab) or more targeted agents (natalizumab, bortezomib, tacrolimus or IL-17 inhibitors) have been considered in refractory cases.[52–54]

Table 1-4-2: Differential diagnosis and workup of common ICPI related neurological adverse events (adapted from[31,44,99])

Work up and management of common neurological complications of immune checkpoint inhibitors				
Diagnosis	**Differential diagnosis**	**Recommended work-up**	**Grade**	**Management**
Peripheral nervous system				
Polyneuropathy				
	metabolic		Grade 1 (mild symptoms, without interference in daily life activities)	Low threshold to withhold immune checkpoint inhibitors for a week or continue treatment. Close monitoring for any progression.
	toxic (previous chemotherapy, vitamin deficits)		CAVE: any cranial nerve involvement must be considered as grade 2	

	exclude leptomeningeal spread in case of cranial nerve involvement		Grade 2 (moderate symptoms with interference in activities of daily life)	Withhold immune checkpoint inhibitor treatment / Close monitoring or steroids (prednisolone / 0.5–1 mg/kg). Pregabalin or duloxetine for pain
			Grade 3 (severe limitation in activities of daily life or life threatening problems (respiratory, other)	Hospitalize patient / withhold ICPI, High-dose steroids (prednisolone 2 mg/kg)
Guillain-Barré Syndrome (progressive symetricascending muscle weakness with decreased reflexes ±facial, respiratory or oculomotor/bulbar muscle involvement ±autonomic nerve dysregulation)				
	spinal cord compression, myelitis	ENMG (acute demyelinating polyneuropathy)		First line: high dose corticosteroids. CAVE: possible initial deterioration

	infection (Lyme, HIV, HSV, HZV)	CSF: normal WBC, elevated proteins		In case of lack of improvement: plasmapheresis or IVIG
	metabolic (acute intermittent porphyria, hypo-, hyperkalemia	Pulmonary function test with measure of vital capacity and max inspiratory/expiratory pressures		Autonomic dysfunction or pulmonary function deterioration determines requirement for management in intensive care
	drug induced (amiodaron, disulfiram, organophosphates)	Anti-GQ1b (positive in Miller Fisher variant)		
	critical care polyneuropathy			
	CIDP, vasculitis			
Myasthenia gravis (fluctuating muscle weakness, including cranial nerves with fatiguability, possible respiratory nerve involvement				
	metabolic myopathy	serum: acetylcholinereceptor & anti musk antibodies		High dose corticosteroids

	toxic induced myasthenic syndrome	Tensilon or ice pack test		Pyridostigmine 30 mg TDS
	Polymyositis	Repetitive nerve stimulation and single fiber EMG		If no improvement: plasmapheresis, IVIG, azathioprine cyclosporine or mycophenolate to be considered
				discontinue ICPI
Myositis (bilateral proximal limb weakness, possible muscle pain, fever, possible bulbar weakness, oculoparesis, bilateral ptosis)				
	steroid myopathy	serum: elevated CK		High-dose corticosteroids
	drugs (statins,…)	ENMG:fibrillations		Monitor patient closely if respiratory muscle weakness
		Consider muscle biopsy: necrotizing myopathy with inflammatory infiltrate		

Central Nervous system				
Encephalitis (Confusion or altered behaviour, headaches, motor or sensory deficits, dysphasia, ±fever)				
	Infection	Brain ±spine MRI	Grade 1 (mild symptoms, no limits on activities of daily life)	Hold ICPI / Initiate diagnostic work-up, consider permanent discontinuation in case of lack of improvement or if worsening
	Metabolic disturbances	Serum: electrolytes, glucose, total proteins, serum electrophoresis, consider viral serologies	Grade ≥2	Exclude viral and bacterial infection (consider concurrent antiviral & antibacterial treatment until infection ruled out)
	brain meatastasis	CSF: WBC (usually <250/mm3 with lymphocytic predominance), normal gram stain, protein, glucose, PCR for HSV and other viruses, cytology		high-dose corticosteroids (0.5-1 mg/kg/d methylprednisolone once infection excluded

	Leptomeningeal dissemination			
	cerebrovascular infarct			
	Intracerebral hemorrhage			
Meningitis (Headache, photophobia, neck stiffness, possible fever, vomiting, normal cognition)				
	Infection	Brain & spine MRI		Exclude bacterial & viral infection
	metabolic disturbances	CSF: WBC (typically <500 mm3), PCR for viral infection, cytology		High-dose corticosteroids
	leptomeningeal dissemination			
	metastasis			

Transverse myelitis (acute or subacute, often bilateral motor or sensory symptoms ±autonomic deficits, sensory level)				
	spinal metastasis	Brain & spine MRI		High-dose corticosteroids
	spinal cord compression	CSF: usually normal		Plasmapheresis or IVIG if non repsonsive to steroids
	Infection	Serum: B12, TSH, HIV, syphilis, ANA, anti-RO & La antibodies, anti aquaporin-4 IgGs		

Toxicities of the central nervous system

Hypophysitis

Hypophysitis can evoke unspecific neurological symptoms in particular headache, fatigue, and weakness. It is one of the most common nAE affecting up to 10% of patients receiving ipilimimab. Interestingly, it has not yet been reported with drugs targeting the PD-1 axis. Typical onset of hypophysitis takes place two to three months after the initiation of treatment.[55] Low serum levels of pituitary hormones establish the diagnosis. In the presence of endocrine modifications, brain MRI should be performed as it may show swelling or abnormal contrast enhancement of the gland as well as allowing the exclusion of other possible diagnoses, such as a metastasis in the pituitary gland for example.

High-dose steroids do not improve the patient's outcome and should not be prescribed. The inflammation almost inevitably results in the destruction of the pituitary gland and long-term pituitary hormone substitution is the only available strategy.[56] Once the patient is substituted, ICPI therapy can be resumed.

Encephalitis

ICPI-induced encephalitis is difficult to diagnose as it is clinically indistinguishable from other causes of encephalitis. The onset can occur anytime from two weeks to many months after initiation of treatment. It is rare, as it occurs in only 0.1–0.25% of ICPI-treated patients, most notably when combined immunotherapy regimens are employed.[57–60]

The clinical presentation may be variable and range from unspecific symptoms to altered mental status with confusion, hallucinations, aphasia, agitation, memory problems, seizures, fever, fatigue, weakness, sleepiness, headache, or stiff neck.[61] A complete workup is required to exclude a broad differential diagnosis including progressive disease (brain metastasis, leptomeningeal dissemination), infectious disease and metabolic encephalopathy. The workup must include a lumbar puncture with viral, bacterial, paraneoplastic panel as well as cytology analyses, MRI, EEG, evaluation of the pituitary hormonal axes, toxic screening, and complete blood tests. The paraneoplastic panel is important as some patients present serum paraneoplastic antibodies such as anti-Hu or anti-NMDA autoantibodies and this finding may help establish the pathogenic role of the ICPI.[62]

Management of encephalitis implies rapid discontinuation of the immunotherapeutic treatment and high-dose corticosteroids with or without

IVIG. Empirically antiviral and broad-spectrum antibiotics and antivirals should be started until an infectious etiology can be formally excluded.

Aseptic meningitis

Aseptic meningitis is a rare nAE, occurring especially in ipilimumab-treated patients. Typical onset is between one to seven weeks after treatment initiation. Symptoms are typical of meningitis with neck stiffness, fever, and headache.[63] Lumbar puncture is key in the workup and the CSF should be sterile with a lymphocytic predominance. Meningeal enhancement is usually present on MRI. Steroid treatment is generally effective.[52,61] Again, broad-spectrum antibiotics should be started immediately until a bacterial etiology is formally excluded.

Multiple sclerosis (MS)

Downregulation of CTLA-4, PD-1, and TIM-3 checkpoints and perturbation of immune homeostasis has been shown to be an integral part of the pathophysiological mechanism causing multiple sclerosis.[64] It is thus not surprising that ICPI can induce *de novo* or relapsed MS. Many forms have been described including optic neuritis, transverse myelitis, and acute tumefactive demyelinating lesions with both anti-CTLA-4 and anti-PD-1 /PD-L1 treatments.[50,65–67] A previous history of MS is found in less than 60% of patients and median time before symptom onset is 29 days. The clinical presentation varies from paresthesia, weakness, vision changes, and altered mental status. Unfortunately, the disease often progresses rapidly and may lead to the patient's death. Administration of IV corticosteroids should allow symptom resolution within eight weeks. Outcomes appear to be similar, regardless of whether the causing agent is an inhibitor of CTLA-4 or PD-1/PD-L1, although symptoms last longer with anti-CTLA-4 treatment.[68]

Toxicities of the peripheral nervous system

Myasthenia gravis (MG)

ICPI (anti-PD1 or anti-CTLA-4) can induce *de novo* cases of MG in patients as well as reactivate previously treated cases of MG (30%) when ICPI is given as monotherapy or in combination.[69] A large cohort of Japanese patients treated with nivolumab showed that the incidence of MG was 0.12%.[70] Clinical manifestations included ptosis, diplopia, muscle

weakness, dyspnea, and dysphagia. Interestingly, AChR antibodies were detected in less than 60% of patients. Symptoms usually begin seven to eleven weeks post-treatment initiation. ICPI-induced MG is difficult to treat and fatal outcomes have been reported. Aggressive treatment with pyridostigmine, steroids, IVIG, plasmapheresis or plasma exchange is warranted. Patients with mild MG typically respond well to immunosuppressive treatment. Patients with severe MG (66% of patients) only partially respond and 25% die despite early and aggressive intervention.[70]

Peripheral neuropathies including Guillain Barré (GBS)

Less than 1% of patients develop ICPI-induced neuropathies and the severity of symptoms is highly variable from one patient to another. Typical symptoms of chronic inflammatory demyelinating polyneuropathy (CIDP) are often observed but ICPI-mediated inflammation may also affect small sensory-type fibers.[45,63,71–74] One study, from Gu et al., reported fourteen cases of acute neuropathy, describing mostly sensorimotor neuropathy predominating in the lower limbs with accompanying hyporeflexia. 50% of patients showed lymphocytosis in the CSF and an axonal pattern on ENMG allowing the distinction with GBS.[75] Most cases are mild and do not interfere with daily activities. In such cases, ICPI treatment should be continued. Otherwise, treatment should be halted, and steroids administered. In all cases, close neurologic monitoring is necessary.

Polyradiculopathies and meningo-radiculoneuritis with facial diplegia, muscle weakness and contrast enhancement of the nerve roots have been described,[63,72,76] as have cases of isolated cranial mononeuropathies.[61,77] Steroids and IVIG have been used with success.

GBS is a rare side effect that, in contrast to other nAEs, has been reported to develop relatively late after treatment initiation (around the third cycle). Symptoms typically include sensory loss, paresis, areflexia, weakness, paresthesia, numbness, and dysphagia. In the CSF, an albuminocytologic dissociation is found and ENMG results show a typical demyelinating polyneuropathy pattern. Supakornnumporn et al. described the outcome of five patients under different treatment regimen, including steroids alone, IVIG alone or in combination with steroids, as well as tacrolimus or corticoids plus plasma exchanges. Regarding outcomes, two patients died, two improved and one remained debilitated.[78]

Inflammatory myopathies

Autoimmune myositis, are the most frequent nAE with anti-PD-1/PD-L1 and occur less frequently with anti-CTLA-4.[71,76,79–85] Orbital myositis and eosinophilic fasciitis have also been reported although they are much rarer.[85–87] Isolated cases of dermatomyositis and polymyositis have also been described, although at a much lower rate than myositis. Typically, symptoms include fatigue, muscle pain, proximal limb weakness, difficulties speaking/swallowing, ptosis or oculomotor weakness. One study from Moreira et al. described nineteen cases of myositis following anti-PD-1 alone or in combination; It must be noted that concomitant myocarditis was observed in 32% of patients and 5% presented an associated myasthenia gravis.[88] In some patients, diaphragm involvement led to respiratory distress. Elevated plasmatic CK can often be found. Electrophysiological investigations may reveal a myopathic pattern. Muscle biopsies may show necrotic myofibers and inflammatory remodeling.[86] Although patients typically respond well to high-dose corticosteroids, ICPI discontinuation is still required. Recovery is very often complete, but patients with sequelae have been described.

Toxicity of adoptive cell therapy (ACT)

In contrast to ICPI AEs, adoptive T-cell and CAR-T cell complications are usually linked to acute, life-threatening symptoms upon T-cell reinfusion called cytokine release syndrome (CRS). However, it is important to realize that nAEs may arise in the frame of the CRS or with distinct timing. Diagnosis of neurologic toxicity of CAR-T-cell therapy is facilitated by the fact that symptoms appear relatively soon (within days, more rarely weeks) after the treatment infusion.

Cytokine release syndrome (CRS)

Patients receiving CAR-T cells are at risk of developing CRS. Clinically, it resembles a septic shock, with high fever, hypotension, tachycardia, respiratory insufficiency, myalgias, vascular leak, coagulopathy (diffuse intravascular coagulopathy; DIC) and oliguria leading to multiple organ failure in severe cases. CRS is systemic and can affect any organ, including the nervous system. Symptoms typically start within hours to days following T-cell infusion and peak around seven to fourteen days post-infusion. CRS represents a clinical challenge as virtually all CAR-T patients elicit some degree of CRS. Severe CRS requiring intensive care support

occurs in up to 27% of CAR-T treated patients.[89] Unfortunately, even when managed according to the guidelines, CRS remains a major cause of fatal outcome in CAR-T treated patients.[90]

The recognition of the first target cells by the engineered T-cells sets off an immunological hyperactivation: Activated T-cells and other immune cells release substantial amounts of cytokines especially IL-2, sIL-2Rα, IFNγ, IL-6, s-IL-6R, and GM-CSF, generating a so-called cytokine storm. The severity of the CRS correlate with serum IL-6 and IL-6R blockade with tocilizumab has been approved as the standard of care to treat CRS following tisagenlecleucel infusion.[91] Siltuximab, a direct IL-6 inhibitor is also effective. Corticosteroids should be avoided when possible as they inhibit T-cell function, induce T-cell apoptosis and diminish the oncologic treatment efficacy.

CAR-T related encephalopathy (CRES)

CRES is the most severe CNS toxicity imputable to CAR-T-cells and represents an important cause of morbidity and mortality. It is a frequent complication, with 40% of patients developing severe, potentially fatal neurologic symptoms.[89,90,92,93] All CD-19 CAR trials have recorded CRES developing patients irrespective of the costimulatory domain used (CD28 or 4-1BB)[91]. Mechanistically, a lot of work remains to be done, but the toxicity appears to be linked to the disruption of the brain-blood barrier[91–93] and results in cerebellar edema[15] caused by massive cytokines release.[91] Apart from the cerebellar edema, this leakage also causes an intravascular coagulation cascade with hemorrhage, infarction, and necrosis.[93] Measuring elevated plasma DIC markers in patients with severe neurological symptoms can provide an estimation of the amount of intravascular coagulation.[91]

CRES and CRS generally occur concomitantly; isolated CRES in the absence of CRS is observed in less than 9% of cases. Both syndromes normally show correlating severities again arguing that CRES is linked to *in vivo* T-cell expansion. It occurs late and in the presence of elevated CAR-T-cells counts.[91,93] A stereotypical progression of symptoms is observed, starting with somnolence, disorientation, confusion, diminished attention, mild aphasia, which then progresses to delirium, hallucinations, global aphasia, myoclonus or tremor. Severe cases can develop generalized seizures and encephalopathy leading to coma and death.[91] Such patients are at risk of developing posterior reversible encephalopathy syndrome (PRES) and acute necrotizing encephalopathy.[93] In comparison to CRS, IL-6R blockade (tocilizumab) is ineffective in CRES. Dexamethasone IV and anti-

convulsive medication (levetiracetam) are the only available treatments.[90,91] Plasmapheresis is being investigated, as it works for thrombotic thrombocytopenic purpura, which shares similar endothelial cell activation mechanisms.[94] Consensus guidelines have been published by the American Society of Bone Marrow Transplantation (Table 1-4-3).[95]

Table 1-4-3: Diagnosis and management of cytotoxin release syndrome (CRS) and CAR T cell-related encephalopathy syndrome (adapted from[90,91,95,100])

Grading and Management of CRS & CRES				
1. Grading of CRS				
	CRS grade 1	**CRS grade 2**	**CRS grade 3**	**CRS grade 4**
Symptoms or signs of CRS				
A) Temperature >38°C	yes	yes	yes	yes
B) Systolic blood pressure <90 mmHg	None	Yes, responds to IV fluids / does not require vasopressors	Requires vasopressor with or without vasopressin	Requires multiple vasopressors (excluding vasopressin)
C) AND/OR Hypoxia	None	Requiring low-flow nasal canula (≤ 6 L/min) or blow-by	Requiring high-flow cannula (>6 L/min), facemask, non rebreather mask or Venturi mask	Requires positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

2. Grading of CRES				
	CRES grade 1	**CRES grade 2**	**CRES grade 3**	**CRES grade 4**
Neurological assessment score (by ICE score)	7-9 (mild impairment)	3-6 (moderate impairment)	0-2 (severe impairment)	0 patient in critical condition and/or unable to perform assessment
Depressed level of consciousness (not attributable to other factors (sedation,…)	spontaneous awakening	awakens to voice	awakens only to tactical stimulus	Patient is unarousable or need for vigourous/repetitive tactical stimulus. Stupor or coma
Raised intracranial pressure	NA	NA	Focal/local edema on neuroimaging	diffuse cerebral edema on neuoimaging; decerebrate or decorticate posturing or cranial nerve VI palsy; or papilledema or Cushing's triad
Seizure	NA	NA	Any clinical seizure that resolves rapidly or non convulsive seizure on EEG that resolves with intervention	Life-threatening generalized seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	NA	NA	NA	Deep focal motor weakness such as hemi or paraparesis

3. Management recommendations for CRS				
Grade 1:				
Fever or organ toxicity	Acetaminophen and hypothermia blanket to treat fever /8 mg/kg IV or siltuximab 11 mg/Kg IV for fever lasting >3 days Ibuprofen as 2nd line option / assess for infection / Hydration with IV fluids /consider tocilizumab			
Grade 2				
Hypotension	500-1000 ml normal saline IV bolus (may be repeated) / Tocilizumab or siltuximab if refractory to fluid boluses / if refractory: start vasopressors, transfer to ICU / consider starting corticosteroids			
Hypoxia	O2 substitution (high flow+/- non invasive positive pressure ventilation / Tocilizumab or siltuximab plus high dose corticosteroids			
Organ toxicity	Symptomatic management / Tocilizumab or siltuximab plus high dose corticosteroids			
Grade 3				
Hypotension	500-1000 ml normal saline IV bolus (may be repeated) / Tocilizumab or siltuximab if refractory to fluid boluses / vasopressors as needed /transfer to ICU, echocardiogram & haemodynamic monitoring / corticosteroids (dexamethasone 10 mg IV q6h, if refractory increase to 20 mg /			
Hypoxia	O2 substitution (high flow+/- non invasive positive pressure ventilation / Tocilizumab or siltuximab plus high dose corticosteroids			
Organ toxicity	Symptomatic management / Tocilizumab or siltuximab plus high dose corticosteroids			
Grade 4				
Hypotension	ICU management: IV fluids,Tocilizumab or siltuximab & methylprednisolone 1 g/d IV, vasopressors and hemodynamic monitoring			
Hypoxia	Mechanical ventilation / Tocilizumab or siltuximab plus high dose corticosteroids and supportive care as described for grade 3 CRS			
Organ toxicity	Symptomatic management of organ toxicity/Tocilizumab or siltuximab plus high dose corticosteroids and supportive care as described for grade 3 CRS			

4. Management recommendations for CRES				
Grade 1				
IV hydration, vigilant supportive care, aspiration precautions				
Withhold oral intake of food, fluids & medicines, assess swallowing				
Avoid all medications that may cause CNS depression				
Agitated patients may be controlled with low dose lorazepam (0.25-0.5 mg IV q8h) or haldoperidol (0.5 mg IV q6h)				
Search for and follow a possible papilledema				
Brain MRI				
Lumbar puncture with measurement of opening pressure				
MRI of spine if focal peripheral neurological deficits				
Daily 30 min EEG until toxicity symptoms resolve, in absence of seizure prophylactic levetiracetam q12h				
Consider Tocilizumab 8mg/kg IV or Siltuximab 11 mg/kg IV if concomitant CRS				

Grade 2				
Consider transferring patient to ICU if CRES associated with ≥ grade 2 CRES				
Supportive care & neurological work-up as indicated for grade 1 CRES				
Tocilizumab 8mg/kg IV or siltuximab 11 mg/kg IV if concurrent CRS				
Dexamethasone 10 mg IV q6h if refractory to anti-IL-6 or for CRES without CRS				
Grade 3				
Transfer to ICU				
Supportive care & neurological work-up as indicated for grade 1 CRES				
Anti IL-6 therapy if associated with concurrent CRS				
Dexamethasone 10 mg IV q6h if CRES symptoms worsen despite anti IL-6 therapy or for CRES without CRS. Taper once CRES is resolved to grade 1				
Follow papilledema				
Consider repeat MRI every 2-3 days if persistent CRES ≥ grade 3				

Grade 4				
ICU monitoring, consider mechanical ventilation for airway protection				
Supportive care & neurological work-up as indicated for grade 1 CRES				
Anti IL-6 therapy and repeat neuroimaging as described for grade 2&3 CRES				
High dose corticosteroids continued until improvement to CRES grade 1 (methylprednisolone IV 1g/day , followed by rapid taper at 250 mg q12h for 2 days, 125 mg q12h for 2 days, 60 mgq12h for 2 days)				
Stage ≥3 papilledema with CSF opening pressure ≥20 mmHg: High dose corticosteroids (methylprednisolone IV 1g/d) / elevate head end of patient's bed to 30° / Hyperventilation to achieve a partial pressure of arterial carbon dioxide ($PaCO_2$) of 28-30 mmHg, but maintained for no longer than 24h / hyperosmolar therapy wit mannitol or hypertonic saline / consider neurosurgery consultation for Ommaya reservoir/drain / consider anesthetics for burst-suppression pattern on EEG / metabolic profiling & daily imaging of brain to prevent rebound cerebral edema, renal failure, electrolyte abnormalities, hypovolemia & hypotension				
Comments: ICE evaluation chart: 1 point for each of the following points: orientation to year, month, city, hospital (4 pts), name 3 objects (3 pts), ability to follow simple command (show me 2 fingers: 1pt), write a standard sentence (1 pt), count backwards from 100 in tens (1pt)				

Autoimmunity induced by autologous T-cells may occur but is rare. Tumor isolated lymphocytes targets are usually tumor-specific neoantigens with limited cross-reactivity to normal tissue epitopes. However, cross-reactivity and off-tumor immune attack can occur with engineered TCRs. One example is a TCR cloned from murine T-cells targeting the tumor-specific antigen MAGE-A3 which cross-reacted with an epitope of MAGE-A12 expressed in the brain. Infusion of these engineered T-cells resulted in severe and irreversible neurotoxicity with obtundation and seizures.[96,97]

Toxicity of bispecific T-cell engager immunotherapy (BiTEs)

BiTEs can be considered to be at the frontier between ICPI and ACT, being an antibody-based, infused drug but directly conferring a novel T-cell specificity. Blinatumomab elicits systemic AEs that resemble CAR-T cell toxicity with typical development of fever, headache and neutropenia as well as a cytokine release syndrome. However, this therapy is also known to induce neurologic adverse events in up to half of all treated patients. These events include tremor, seizures, confusion, febrile delirium, (leuco)-encephalopathy and cerebellar ataxia. Up to 30% of patients experience ≥ grade 3 symptoms.[19,98] These nAEs typically occur at the onset of treatment (median onset at 9 days) and are generally reversible and manageable with high-dose dexamethasone (3x 8mg/day over 4 days) and interruption of the blinatumomab infusion. Premedication with dexamethasone 20mg IV 1h prior to blinatumomab infusion is recommended to minimize the risk of nAE development. Patients that experience grade 4 symptoms or seizures should be permanently discontinued from treatment. Otherwise, blinatumomab can be resumed once symptoms have resolved to grade 1 or have disappeared. Although not entirely understood, it is believed that blinatumomab nAEs are due to transitory neuroinflammation in the CNS due to endothelial adherence of the BiTE activated T-cells.[19]

Conclusion

Although immunotherapy is revolutionizing cancer care, it is associated with new and specific side effects that treating physicians must be aware of. Immunotoxicity and autoimmunity are frequent complications of checkpoint inhibitors and autologous T-cells. Among the vast range of immune-related adverse events, neurological AEs are rare but present an unfavorable evolution if not managed adequately. The timing of symptom onset is highly variable rendering patient monitoring and diagnosis difficult. Preventing or reducing the severity and duration of neurologic symptoms

remains a key challenge. Current consensus guidelines remain based on empirical data, however. Prospective clinical trials remain a key priority.

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Chapter 1.5

Central Nervous System Toxicities of Targeted Therapies and Hormone Therapy

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Abstract

Central nervous system (CNS) complications of anticancer drugs are an important source of morbidity and mortality in patients with cancer. CNS toxicities of targeted therapies and hormonotherapy treatments have been reported. Some of these toxicities are reversible after interruption of the treatment, others are irreversible.

Several subtypes of targeted agents are now available and associated with a risk of CNS toxicity such as therapeutic antibodies, epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, tyrosine-kinase inhibitors, BRAF inhibitors, and mitogen-activated protein kinase (MEK) inhibitors.

Therapeutic antibodies (bevacizumab, rituximab and blinatumomab) may cause immunosuppression and are associated with a risk of CNS toxicity. CNS toxicities from hormonal therapies (tamoxifen, aromatase inhibitors, enzalutamide) have also been reported.

The main CNS toxicities from these agents are headaches, seizures, encephalopathy, posterior reversible encephalopathy syndrome, progressive multifocal leukoencephalopathy and cerebrovascular events.

Neurocognitive impairment is also described as a more tardive complication.

The most frequent CNS complication, encephalopathy, can occur as an acute or chronic encephalopathy and may cause unspecific symptoms, focal neurological deficits, seizures or hallucinations, associated with MRI findings typically including difuse white matter hyperintensities. Posterior reversible leukoencephalopathy syndrome (PRES), a clinicoradiologic syndrome characterized by reversible cortical dysfunction preferentially involving the occipital lobes with imaging findings of reversible subcortical vasogenic edema, has been reported with several targeted therapies including therapeutic antibodies, antiangiogenic agents and hormonal therapy.

Progressive multifocal leukoencephalopathy (PML), an infectious demyelinating disease of the CNS caused by reactivation of the polyomavirus John Cunningham virus, results from profound cellular immunosuppression and toxic effects on oligodendrocytes related to antibodies (such as rituximab, alemtuzumab, brentuximab vedotin, bevacizumab and cetuximab). Patients who develop PML develop visual complaints and visual field defects often in a homonymous heminaopsia pattern due to the involvement of the posterior visual pathways within the parietal–occipital lobes. This disease is associated with a poor prognosis and can result in severe neurological deficits. It is associated with a high mortality rate.

The onset of seizures has been reported with EGFR inhibitors, Imatinib and hormonotherapy agents. Cerebrovascular events such as ischemic strokes, intracranial hemorrhages, and arterial thromboembolic events have been described with antiangiogenic agents and tamoxifen use. Other CNS toxicity reported with these therapies includes cerebellar syndrome (trastuzumab and rituximab), cognitive impairment (bevacizumab, hormonal therapies), and headaches (bevacizumab, imatinib, rituximab, trastuzumab and BRAF inhibitors).

Keywords: Neurological syndromes; Targeted therapies; CNS toxicities; PNS toxicities

Introduction

Central nervous system (CNS) complications of anticancer drugs are an important source of morbidity and mortality in patients with cancer. The mechanisms of neurological sequelae from systemic therapies are not completely understood. Neurologic complications can result from the direct or indirect effects of cancer therapy.

Some neurologic complications occur during treatment. However, others such as cognitive impairment only become apparent months to years after the completion of therapy.

These complications can result in a limitation of potential therapies by precipitating dose reductions and premature cessation of treatment. Early recognition of these complications is an important outcome for patient management and to prevent permanent neurologic damage, particularly because cerebral tissue repair is limited.

Several targeted agents and hormonotherapy are associated with syndromes affecting the CNS.

Monoclonal antibodies (MABs) and small molecules have been developed as targeted agents and have the ability to selectively impair or inhibit specific pathways involved in the process of malignant transformation. These drugs interfere with a specific molecular target (typically a protein) involved in tumor growth and progression. These targets include growth factor receptors, signaling molecules, cell-cycle proteins, modulators of apoptosis, and molecules involved in invasion and angiogenesis, which are essential for development and homeostasis in normal tissues. The two main types of targeted agents are kinase inhibitors and monoclonal antibodies. However, several subtypes of targeted agents are now available: MABs, EGFR inhibitors, VEGF inhibitors, TKIS, BCR-ABL and Bispecific antibodies (BABs).

Small-molecule kinase inhibitors are a group of anticancer drugs that affect the intracellular signal pathways that are dysfunctional in cancer cells. Small-molecule kinase inhibitors are adenosine triphosphate (ATP) mimetics or analogs that can target the extracellular or intracellular components of a cell surface receptor as well as intracellular protein kinases.

Some of the kinase inhibitors target a single protein while others target multiple proteins.

Several CNS toxicities of targeted therapies have been described.

In this chapter we present the most important CNS toxicity complications from current targeted therapies and hormonotherapy agents and their potential mechanisms of toxicity.

Central Nervous System (CNS) Complications

Most frequently CNS complications of anticancer drugs occur as encephalopathy. Encephalopathy can cause unspecific symptoms (such as fatigue, coma, agitation), focal neurological deficits (such as paresis, apraxia), seizures and hallucinations. Encephalopathy can occur as acute

encephalopathy (confused state, insomnia, agitation), or chronic encephalopathy (cognitive dysfunction consistent with subcortical dementia, incontinence, gait disturbance).[1]

MRI findings typically include difuse white matter hyperintensities.[1]

Neurologic Syndromes

Acute encephalopathy

Acute encephalopathy can be focal (involving only a part of the brain) or general (the whole brain is involved). A well-described example of a focal presentation of acute encephalopathy is reversible encephalopathy syndrome (PRES).[1]

Regarding MRI findings in patients with acute encephalopathy, the MRI might be unremarkable at the initial presentation. In addition to MRI, an important assessment to make a diagnosis is cerebrospinal fluid analysis to detect infectious and autoimmune differential diagnoses, such as progressive multifocal leukoencephalopathy (PML) or encephalitis whose initial presentation can be similar.[1]

Typical clinical signs of acute encephalopathy are a sudden change in alertness and attention, confusion, epileptic seizures and hallucinations.[1]

Targeted treatments might induce acute encephalopathy by several—direct and indirect—mechanisms such as direct neurotoxicity, sodium disturbance and metabolic changes.[1]

Blinatumomab and high-dose tamoxifen might cause acute encephalopathy.[1]

Chronic encephalopathy

Chronic encephalopathy from cancer therapy is typically seen after whole-brain irradiation and high-dose methotrexate-based chemotherapy but has also been associated with targeted agents including sunitinib and sorafenib and with biological agents such as blinatumomab, rituximab and alemtuzumab.[1]

Symptoms of difuse progressive leukoencephalopathy are indistinguishable from radiation-induced leukoencephalopathy.[1] Several pathomechanisms are involved including severe cytokine release syndrome, microvascular pathologies, and direct inflammatory damage to oligodendroglial cells.

Progressive leukoencephalopathy might occur as a consequence of a cellular immune response against a CNS antigen, despite it not being the primary target of cellular immune response.[1]

MRI findings on chronic encephalopathy typically include diffuse white matter hyperintensities and cerebral atrophy resulting in enlarged ventricles.[1]

Posterior reversible leukoencephalopathy syndrome (PRES)

Posterior reversible leukoencephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome, is a clinicoradiologic syndrome characterized by reversible cortical dysfunction preferentially involving the occipital lobes in conjunction with imaging findings of reversible subcortical edema.[2] This syndrome is characterized by acute or subacute onset of confusion, headache, seizures and visual changes.[3] PRES has a predilection in the posterior lobes but can also occur in the frontal or temporal lobes. It is typically bilateral at onset and might cause seizures, headache, apraxia, or visual field deficits.[1]

The pathogenesis involves cerebral blood flow autoregulation and endothelial dysfunction resulting in vasogenic edema. The pathomechanism is related to blood–brain barrier disruption due to endothelial injury by abrupt blood pressure changes, resulting in typical vasogenic edema, which mainly involves the bilateral parietal–occipital lobes of the brain. The susceptibility of the posterior regions of the brain might be because of the reduced sympathetic innervation and ability to counter-regulate (auto-regulate) blood pressure fluctuations.[1]

Reversible posterior leukoencephalopathy is a syndrome of headache, seizures and visual loss, often associated with an abrupt increase in blood pressure. It is not the absolute blood pressure that predisposes patients to develop PRES but the change in blood pressure from baseline; patients can present with modest diastolic increase.

On an MRI, the lesions are not necessarily confined to the posterior regions of the brain and can affect both white and gray matter. Magnetic resonance imaging findings of increased T2 and fluid-attenuated inversion recovery signal predominantly involving the posterior regions of the cerebral hemispheres.

Patients typically present with acute neurological symptoms such as encephalopathy, seizures, headaches, and vision deficits. The clinical manifestations of PRES most often include the acute onset of generalized seizures, headache, delirium and cortical blindness. Focal neurological

deficits are also possible. Visual abnormalities may range from blurred vision to cortical blindness.

MRI findings are characterized by symmetric hyperintense T2 signal involving bilateral occipital and parietal lobes in a subcortical distribution. Brain MRI typically demonstrates focal regions of symmetric hemispheric edema that are visible on T2-weighted or fluid-attenuated inversion recovery sequences (hyperintensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images involving the posterior circulation areas, especially the parietal and occipital lobes).[1,2,4] The parietal and occipital lobes are most commonly affected, followed by the frontal lobes, the inferior temporal-occipital junction, and the cerebellum.

Several anticancer drugs are reported to cause reversible posterior leukoencephalopathy, such as rituximab, tamoxifen, trastuzumab, and the antiangiogenic drugs sorafenib, sunitinib, axitinib and bevacizumab.[2,3,5] Symptoms and imaging findings are often reversible with removal of the offending agent and supportive care (including blood pressure management). The mainstay of treatment for PRES is supportive and directed at symptom management (i.e. anti-seizure medication, anti-hypertensive medication and correction of electrolyte abnormalities). PRES is a reversible condition that warrants either a dose reduction or withholding of the causative agent, which will result in a complete recovery for most patients. This syndrome is usually reversible within two weeks with the treatment of concurrent hypertension and removal of the causative agent.[6,7]

Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is an infectious demyelinating disease of the CNS caused by reactivation of the polyomavirus John Cunningham virus (JC virus) associated with significant morbidity and mortality.[8] This affection has a poor prognostic and results in CNS demyelinisation secondary to oligodendrocytes lytic infection from JC virus.

PML is a result of profound cellular—mainly CD4 or CD8 T-cell—immunosuppression and toxic effects on oligodendrocytes related to antibodies such as rituximab, alemtuzumab, brentuximab vedotin bevacizumab and cetuximab.[1,9]

The pathophysiology of this syndrome is not fully understood but infiltrates of cytotoxic T cells have been implicated.[10] Patients who develop PML develop visual complaints and visual field defects often in a homonymous hemianopsia pattern due to the involvement of the posterior

visual pathways within the parietal–occipital lobes. In suspected PML diagnostic assessments should include MRI and cerebrospinal fluid analyses. Countermeasures include discontinuation of the treatment, plasmapheresis, and steroids. Patients might survive the infection when immune reconstitution inflammatory syndrome occurs. Patients treated for PML might develop neurological deficits, and brain MRI with white matter lesions and contrast enhancement that do not indicate worsening of PML but signify immune reconstitution inflammatory syndrome. The outcome of PML is determined not only by the infection but also by the underlying disease and possibly by the ability to generate an antiviral immune response. PML can result in severe neurological deficits and is associated with a high mortality rate.

Although the reconstitution of the immune system is important for controlling the JC virus, CNS inflammation due to immune reconstitution inflammatory syndrome can result in death or permanent neurological disability; therefore, the syndrome needs to be recognized early and treated with steroids, plasmapheresis, or tocilizumab. The re-institution of normal immune system function is critical to suppress infection.[1] The outcome with PML varies depending on the underlying disease and speed with which an effective immune reconstitution is achieved.[11]

Cerebellar syndrome

Cerebellar syndrome is characterized by cerebellar signs onset including ataxia, dizziness and eye movement disorders. Functional impairment of cerebellar cells and effects on the vestibular nerve have been reported with several targeted agents such as trastuzumab and rituximab.[1,12,13] In cases of cerebellar syndrome in patients receiving such treatment, the drug should be halted when first symptoms are reported. The differential diagnosis of treatment-associated cerebellar syndromes includes paraneoplastic cerebellar degeneration, a paraneoplastic syndrome frequently associated with non-small-cell lung cancers.[1]

Seizures

Seizures are common neurologic complications in cancer patients. They can occur as a result of structural abnormalities of the brain (brain metastasis), cerebrovascular disease, reversible posterior leukoencephalopathy syndrome (PRES), and radiation toxicity. Seizures can also occur as a result of the metabolic impact of the cancer or cancer treatment (mainly sodium disturbance).

EGFR (Epidermal growth factor receptor) inhibitors are associated with the onset of seizures because of electrolyte depletion, especially in patients with CNS involvement. Epileptic fits have also been associated with anti-BCR-ABL therapies (Imatinib), although the exact mechanism remains elusive.[1]

Moreover, in patients with metastatic castration-resistant prostate cancer, patients receiving enzalutamide treatment after chemotherapy displayed higher incidences of epileptic fits than the placebo group.[1] The main targeted agents associated with the onset of seizures are letrozole, cetuximab, panitumumab, gefitinib, erlotinib, imatinib, blinatumomab and enzalutamide.[1,4]

A cautious approach to treatment would thus be warranted in patients with a known predisposition to seizures.

Cerebrovascular events

Certain cancer drugs are more frequently associated with ischemic strokes, intracranial hemorrhages and arterial thromboembolic events. This list includes bevacizumab, sunitinib, sorafenib and imatinib. Several antiangiogenesis agents developed to target VEGF/VEGFR, including bevacizumab, sunitinib, and sorafenib, are associated with hemorrhagic events as well as arterial thromboembolism. Hemorrhage and arterial thromboembolism (including ischemic strokes) are known toxicities of this class of agents.

A rare but severe neurological complication of VEGF inhibitors (bevacizumab) is brain hemorrhage (<1% of patients), which has been reported especially for patients with cancer and brain involvement or on anticoagulation.[1] A meta-analysis of twenty randomized trials of bevacizumab based therapy demonstrated a significantly increased relative risk of ischemic strokes of 1.46 compared with controls.[14] Similarly, patients receiving sorafenib or sunitinib had a threefold increased risk of arterial ischemic strokes compared with controls.[15]

Cessation of therapy is recommended in patients who develop an arterial thromboembolic event.

Regarding ischemic stroke, distinct pathomechanisms need to be considered in the context of anticancer treatments. One pathomechanism for all anticancer treatments is a tumor-associated (paraneoplastic) and potentially drug-aggravated coagulation disorder. Another is related to arterial hypertension and, although rare, the inflammation of larger vessels associated with checkpoint inhibition is a potential causative factor. The assessment is primarily non-specific for the underlying pathomechanism,

and treatment might include both systemic thrombolysis and also local intra-arterial thrombectomy according to international guidelines.[1] Because of the potential cause, and also to avoid bleeding complications, the anticancer therapy needs to be halted or permanently discontinued. Tamoxifen and anti-VEGF agents such as Bevacizumab are associated with an increased risk of cerebral stroke.[16]

Cognitive impairment

Antiangiogenic agents might cause cognitive impairment. A long-term neurological complication of the VEGF antibody bevacizumab is cognitive impairment, which is considered to be caused by reduced synaptic plasticity in the hippocampus, especially after long-term bevacizumab treatment.[17] VEGF is expressed by CA1 pyramidal neurons in the hippocampus, and VEGF reduction impairs learning and memory. Supportive treatments to improve cognitive status have not shown a clear benefit. Therefore, regular cognitive testing is necessary to detect cognitive decline and to determine whether bevacizumab treatment should be stopped. However, whether cognitive impairment is reversible after bevacizumab discontinuation is not clear.[1]

Cognitive dysfunction may be associated with anticancer therapies. Several anticancer drugs such as hormonal therapies (tamoxifen, antiaromatases) can lead to impairments in memory, processing speed, and executive function. In some patients, symptoms of neurotoxic effects may present years after completion of treatment.[1]

Headache

Headache is a common symptom and is associated with several anticancer treatments. Targeted therapies associated with headaches are antiangiogenic agents (bevacizumab), imatinib, rituximab and trastuzumab and BRAF inhibitors.[1,18]

Targeted Therapies

Monoclonal antibodies

Bevacizumab

Bevacizumab is a humanized monoclonal antibody against VEGF, approved for the treatment of renal, colorectal, lung, and cervical cancer,

as well as recurrent glioblastoma. Neurological adverse events associated with bevacizumab are mainly headaches, cerebrovascular events (ischemic stroke and hemorrhagic stroke), and posterior reversible leukoencephalopathy syndrome.[19]

In a meta-analysis, bevacizumab was found to be associated with a threefold higher risk of cerebral stroke and brain hemorrhage.[20] A rare but severe neurological complication of VEGF inhibitors such as bevacizumab is brain hemorrhage (<1% of patients), which has been reported especially for patients with cancer and brain involvement or on anticoagulation. Although the risk is considered negligible, cases of intratumoral hemorrhage associated with bevacizumab use have been described. In two large randomized, placebo-controlled, phase 3 trials in patients with newly diagnosed glioblastoma that compared bevacizumab plus standard first-line therapy (consisting of chemoradiation and adjuvant temozolomide) with standard therapy alone, the risk of cerebral hemorrhage was slightly higher in the bevacizumab group than in the placebo group (3.3% vs 2.0% in one study), but this did not reach statistical significance.[21,22]

In addition, similar to other anti-VEGF agents, bevacizumab increases the risk of ischemic strokes.[15] A meta-analysis of randomized trials, including more than 10,000 patients treated for different cancers with chemotherapy with or without bevacizumab, analyzed the risk for vascular adverse events, revealed an incidence of all-grade arterial thromboembolic complications in bevacizumab-treated patients of 3.3% (relative risk 2.08) with a frequency of severe events (grade ≥3) of 2.0%.[23]

Moreover, antiangiogenic agents such as bevacizumab might cause cognitive impairment.

Most VEGF-targeting agents, including sunitinib and sorafenib, cause hypertension and thus predispose to PRES.[5,24] PRES has been reported with bevacizumab.[25]

Cases of optic neuropathy have also been described. Sherman et al. reported six patients who developed optic neuropathy while taking bevacizumab in addition to fractionated radiation therapy and temozolomide for glioblastoma.[26]

Brentuximab vedotin

Brentuximab vedotin is a conjugated monoclonal antibody against the cell surface protein CD30, used for the treatment of patients with relapsed or refractory Hodgkin's lymphoma and systemic anaplastic large-cell lymphoma. There are few cases of PML associated with brentuximab vedotin,[27] which is thought to be mediated by the removal of CD30+ T

cells and B cells contributing to the control of latent CNS JC virus infections.[28,29]

Rituximab

Rituximab is a chimeric IgG1 monoclonal antibody directed against cluster of differentiation CD 20, approved for treatment of non-Hodgkin lymphoma. Neurological adverse events are uncommon but may include headaches, dizziness, and paresthesias.[1] Moreover, rituximab can induce long-lasting cellular immunosuppression, predisposing patients to opportunistic CNS infections, such as PML secondary to JC virus reactivation.[19,30] Rituximab has been associated with the development of PML in a few patients.[30]

Trastuzumab

Trastuzumab is a humanized IgG1 monoclonal antibody directed against the epidermal growth factor receptor 2 (HER2). It is used alone or in combination with chemotherapy to treat patients with breast or gastric cancer overexpressing human epidermal growth factor receptor-2. In patients treated with trastuzumab, CNS manifestation is the most prominent neurological complication. Patients may experience headaches, dizziness, or insomnia. Cases of cerebellar syndrome have been reported with trastuzumab use.[1,12] The pathophysiology of trastuzumab toxicity might be mainly a result of antibody-dependent cellular cytotoxicity due to the activation of natural killer cells, expressing the Fcγ receptor, which can be bound by the Fc domain of trastuzumab.[1,31,32]

Alemtuzumab

Alemtuzumab is a humanized IgG1 mAb that targets a variety of immune cells including B cells, T cells, and macrophages that express the cluster of differentiation (CD) 52 antigen.

Alemtuzumab neutralizes the CD52 receptor and is approved for chronic lymphocytic leukemia. Neurotoxicity is rare, but nonspecific symptoms such as headaches, myalgias, dizziness, and paresthesias can occur.[33] Headaches, dizziness and PML (secondary to JC virus reactivation) have been reported with alemtuzumab only rarely.[19]

PML has been reported to occur in the setting of alemtuzumab therapy.[34]

No specific ocular toxicities have been associated with alemtuzumab.[35]

Bispecific antibody

Blinatumomab

Blinatumomab is an anti-CD19/CD3 bispecific T-cell engager approved for the treatment of relapsed or refractory B-precursor acute lymphoblastic leukemia. Blinatumomab is associated with neurotoxicity. CNS adverse events associated with blinatumomab use are dizziness, confusion and headaches.[19] Headaches can affect approximately one-third of patients. Seizures and aphasia have also been reported but are not common (2%–4%).[36,37]

A phase 2 trial in patients who received blinatumomab for acute B lymphoblastic leukemia has shown that neurological toxic effects occur in up to 50% of patients, most commonly paresthesia, tremor, dizziness, and confusion; 13% of the events were classified as severe or life-threatening (grade 3 or 4 toxicity).[36] Symptoms included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders.[36,38] Although the exact pathomechanism of blinatumomab-induced encephalopathy is not known, it is believed that blinatumomab-activated T cells might cross the blood–brain barrier and bind to CD19-positive B cells, which in turn release cytokines that disrupt the blood–brain barrier. The pathophysiology of these neurotoxic effects is still unclear.

Blinatumomab-related adverse events are usually reversible and can usually be resolved with discontinuation of the drug. Restarting blinatumomab use after the resolution of neurological symptoms should be done with caution: in an acute lymphoblastic leukemia cohort with blinatumomab-related CNS symptoms, two of six patients had recurrent CNS events after re-initiation of treatment.[39]

Tyrosine-kinase inhibitors (TKI)

TKIs are a class of small-molecule drugs that inhibit the intracellular binding of adenosine triphosphate (ATP) to the tyrosine domain of cognate receptors of growth factors. This interrupts the intracellular cascade of phosphorylation in several pathways. Small molecules, such as TKIs, are less specific than therapeutic MABs, and some of them can inhibit multiple targets simultaneously, including cell receptors or signal transduction pathway proteins. Similarly, the most common neurological adverse events with receptor tyrosine-kinase inhibitors—caused by inhibition of multiple pathways, such as the VEGFR, platelet-derived

growth factor receptor, and c-KIT, with differential affinity—are headaches, arterial cerebrovascular events, and posterior reversible leukoencephalopathy syndrome.[1,31,32] Neurological adverse events are related to hypertension induced by tyrosine-kinase inhibitors, which are probably caused by inhibition of the VEGF signaling pathway. MABs mostly bind to the extracellular domain of EGFR or VEGF, while most of the available TKIs bind to the intracellular domain of these receptors and inhibit the subsequent activation of their signaling cascade.

Sunitinib and sorafenib are both multikinase inhibitors that target the vascular endothelial growth factor (VEGF) receptor among other receptor families. Both are approved for advanced renal cell carcinoma; sunitinib is additionally indicated in GIST and sorafenib for unresectable hepatocellula carcinoma.

Sunitinib

Sunitinib is a multi-targeted TKI that can be administrated orally. It targets VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor-α receptor (PDGFR-α), PDGFR-β, stem-cell receptor (KIT). Sunitinib is approved for advanced renal cell carcinoma and in Gastrointestinal Stroma Tumor (GIST). In addition to hypertensive encephalopathy, sunitinib has been associated with hallucinations, confusion, and extrapyramidal symptoms in patients aged over seventy years with pre-existing arteriosclerotic leukoencephalopathy.[40] Rare cases of PRES and ischemic stroke have been reported with sunitinib in the literature, similar to other anti-VEGF agents.[19]

Sorafenib

Sorafenib is a multikinase inhibitor that targets growth signaling and angiogenesis by blocking VEGF-2-receptor (VEGFR-2), VEGF-3-receptor (VEGFR-3), PDGF-β-receptor (PDGFR-β), Raf, c-KIT protein (c-KIT), and FMS-like tyrosine kinase 3 (Flt-3). Sorafenib is approved for advanced renal cell carcinoma and unresectable hepatocellular. As with the other antiangiogenesis agents, cases of PRES and ischemic stroke have been reported with sorafenib rarely.[19]

Epidermal growth factor receptor inhibitors (EGFR inhibitors)

EGFR is a transmembrane protein that plays a key role in signal transduction pathways regulating cellular proliferation, survival, and differentiation.

EGFR inhibitors include monoclonal antibodies (MABs) which bind to the extracellular domain of EGFR such as cetuximab and panitumumab (commonly used in advanced colorectal cancer), and EGFR TKIs (erlotinib, gefitinib, mainly used in metastatic lung cancer) that are oral tyrosine-kinase inhibitors which bind to the intracellular domain of EGFR and inhibit the activation of the TK activity of the receptor.[31,41]

In addition to fatigue as an unwanted effect for all inhibitors and headaches mainly with cetuximab, EGFR inhibition is associated with electrolyte depletion, which might predispose individuals to seizures, especially in patients with CNS involvement.[4]

Cetuximab is a chimeric IgG1 mAb that is an EGFR inhibitor. Exceptional cases of aseptic meningitis have been reported with cetuximab.[42]

EGFR TKIs are classified in first-generation, second-generation and third-generation molecules.

Gefitinib and erlotinib are two small-molecule, first-generation, reversible EGFR TKIs that have been used as a first-line treatment of advanced non-small-cell lung cancer (NSCLC) in chemotherapy-naive patients, or as second- or later-line treatment after failure of chemotherapy. Afatinib, is a second-generation, irreversible, EGFR-TKI, approved for treating advanced NSCLC. Few data about CNS toxicity are available for these drugs.

Osimertinib is an oral, third-generation, irreversible EGFR-TKI that selectively inhibits both EGFR-TKI sensitizing and EGFR T790M resistance mutations. Osimertinib is approved for the treatment of patients with metastatic T790M-positive NSCLC who have disease progression during or after EGFR-TKI therapy. Preclinical data support the ability of osimertinib to cross the blood–brain barrier and penetrate the CNS.[43] Lorlatinib is an oral, reversible, ATP-competitive macrocyclic TKI of ALK and ROS1. This potent and highly selective third-generation inhibitor was designed to penetrate the blood–brain barrier and to overcome known ALK resistance mutations. Lorlatinib is associated with cognitive and mood effects. Cognitive, speech and mood effects are generally transient and reversible.[44]

Imatinib

Imatinib is an oral tyrosine-kinase inhibitor that inhibits the constitutively active fusion product of the BCr-ABL translocation in Philadelphia-chromosome-positive leukemia as well as c-KIT in gastrointestinal stromal tumors. Imatinib is approved for the treatment of gastrointestinal stromal tumors and chronic myelogenous leukemia refractory to interferon therapy. Neurologic side effects are usually mild and may include headache and fatigue.[31]

Intracranial bleeding is a rare complication of imatinib therapy.[4] Imatinib is associated with the onset of subdural hematomas.[19] Spontaneous subdural hematomas in the absence of concurrent trauma or anticoagulation are seen in 2% to 7% of patients receiving imatinib.[45,46]

BRAF inhibitors

BRAF inhibitors such as dabrafenib and vemurafenib are anticancer drugs used as first-line therapy in patients suffering from metastatic melanoma associated with BRAF mutation. Vemurafenib is a powerful inhibitor of mutated BRAF. Dabrafenib is a reversible, ATP-competitive inhibitor that selectively inhibits BRAF kinase.[47]

Headache is a common adverse event associated with BRAF inhibitors, affecting 32% of melanoma patients in one trial of dabrafenib and 23% of patients in a trial of vemurafenib.[48] Headaches are more frequent with combined anti-BRAF–anti-MEK treatments than with BRAF inhibition alone.[18]

A study of patients with brain metastasis from melanoma treated with vemurafenib demonstrated clinically meaningful response rates of melanoma brain metastasis to vemurafenib with a good clinical tolerance and without significant CNS toxicity [47].

Mitogen-activated protein kinase kinase inhibitors (MEK inhibitors)

Trametinib and cobimetinib are mitogen-activated protein kinase kinase inhibitors (MEK inhibitors), used in metastatic melanoma treatment in association with BRAF inhibitors.

Trametinib has been associated with an increase in overall survival in patients with BRAF-mutated metastatic melanoma, compared with chemotherapy. Intracranial hemorrhage has been reported with the use of trametinib and dabrafenib.[49]

Hormonal therapies

Hormonal treatments are commonly used in the care of breast and prostate cancer patients. Women with estrogen receptor/progesterone receptor-positive breast cancer are frequently recommended treatment with tamoxifen (TAM) or with an aromatase inhibitor. However, estrogen blockade associated with these agents may adversely impact cognitive function.

Tamoxifen

Tamoxifen is a nonsteroidal estrogen receptor antagonist that is mainly used for the treatment of estrogen receptor-positive breast cancer. CNS neurotoxicity is relatively infrequent with tamoxifen. Headache is one of the most common side effects, especially in patients with a history of migraine. Visual system dysfunction is also described, with damage to the retina or optic nerves.[50] Retinal injury is more common and presents with reduced visual acuity and central scotoma. Visual complaints, including decreased central vision, are reported in less than 5% of patients. Retinal changes on ophthalmologic examination include small, refractile deposits in the region surrounding the macula with macular edema. This complication is more common in patients receiving high-dose therapy or those with large cumulative doses.[50,51] Discontinuation of tamoxifen usually results in clinical improvement, although retinal deposits may persist.

Tamoxifen has also been associated with increased risk of arterial and venous thrombosis.[52] A meta-analysis in women receiving tamoxifen has reported a risk elevation of ischemic stroke of 82% in comparison with the control group.[53]

Tamoxifen therapy is also associated with cognitive impairment and emotional difficulties.

Rare cases of cerebellar syndromes, PRES and decreased vision because of macular edema, are described in the literature.[54]

Aromatase inhibitors

Anastrozole and letrozole are nonsteroidal, selective inhibitors of aromatase. The most common side effects of these drugs are lethargy and somnolence that may affect up to 10% of patients.[55] Cerebral thrombembolic risk is less important with aromatase inhibitors than with tamoxifen (thromboembolic risk is inferior at 2% with letrozole).[56]

Anastrozole is associated with headache in 13% of patients. Dizziness, anxiodepressive trouble and irritability can occur with letrozole.[57]

Hormonotherapy and prostate cancer

In prostate cancer, luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide and goserelin are the most commonly utilized hormonal therapies. These treatments are associated with a neurocognitive impact. Cognitive decline has been demonstrated in up to 50% of men treated with an LHRH agonist.[58] The adverse cognitive effects most often reported are alterations in spatial processing and visual memory. Androgen-deprivation therapy, which results in low testosterone concentrations, can cause major depression and other toxic events of the CNS.[59] Depressive syndromes with cyproterone actetate (Androcur®) have been described. Other neuropsychiatric troubles are uncommon. Regarding more recent agents, the androgen receptor signaling inhibitor enzalutamide results in a higher incidence of epileptic fits in patients with metastatic castration-resistant prostate cancer after chemotherapy than in the placebo.[1]

Discussion / Conclusion

Neurologic complications from cancer drug therapies impact quality of life and remain an important source of dose-limiting toxicity. The mechanisms of CNS toxicity from these agents are quite variable and can result from direct damage to neural tissues (e.g. vascular injury and ischemia) as well as from systemic causes (e.g. electrolyte disturbances, hepatotoxicity). CNS complications have been described in patients receiving targeted therapies and hormonotherapy treatments. Some of the complications are reversible after interruption of the treatment, others are irreversible.

The main CNS toxicities from these agents are headaches, encephalopathy, posterior reversible encephalopathy (PRES), progressive multifocal leukoencephalopathy (PML) and cerebrovascular events, especially in patients treated with anti-angiogenesis agents. Neurocognitive impairment is also described as a more tardive complication.

Therapeutic antibodies such as bevacizumab, rituximab and blinatumomab may cause immunosuppression and are associated with a non-negligible risk of CNS toxicity. They have to be managed with precautions.

A better knowledge of these toxicities and their initial symptoms is necessary to better manage their complications and interrupt treatment as soon as the first symptoms appear.

Table 1-5-1: Main CNS complications associated with targeted therapies and hormonotherapy.

CNS complications	Symptoms	Agents	Main Pathomechanism
Acute encephalopathy	Confusion, reduced alertness, hallucinations	Blinatumomab, tamoxifen (high dose)	Cytokines release direct neurotoxicity
Chronic encephalopathy	Reduced executive function, reduced processing speed, and reduced memory	Rituximab, alemtuzumab, brentuximab, sunitinib, sorafenib	Progressive diffuse leukoencephalopathy
Epilepsy	Seizures	EGFR inhibitors (cetuximab, panitumumab, gefitinib, erlotinib), imatinib, enzalutamide, blinatumomab, letrozole	Electrolyte disturbance
Progressive multifocal leukoencephalopathy (PML)	Personality change, confusion, deficits	Rituximab, alemtuzumab, brentuximab vedotin, bevacizumab, cetuximab	Immunosuppression, reactivation of JC virus
Posterior reversible leukoencephalopathy syndrome (PRES)	Headache, confusion, visual changes, (cortical blindness), seizures	Bevacizumab, rituximab, sorafenib, sunitinib, axitinib, tamoxifen, trastuzumab	Autoregulatation cerebral blood pressure failure

Ischemic stroke	Sudden focal neurological deficit	Bevacizumab, sunitinib, sorafenib, tamoxifen	Vessel inflammation, coagulation disorder, arterial hypertension
Brain hemorrhage	/	Bevacizumab, imatinib sunitinib, sorafenib	Coagulation disorder, arterial hypertension

The decision to discontinue or continue the treatments needs to be discussed with the prescribing oncologist and depends on the severity of the adverse events. However, in some instances it may be possible to treat the symptoms either with supportive therapy or more directed therapy without discontinuing the treatment.

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CHAPTER 1.6

SUPPORTIVE TREATMENT IN CANCER AND BRAIN TOXICITY

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Abstract

Besides antineoplastic treatments, the management of brain tumors requires supportive treatments, such as antiepileptic drugs (AEDs) in patients with seizures, corticosteroids as anti-edema therapy and antithrombotic drugs for venous thromboembolism.

Seizures represent an important problem for brain tumor patients. There are several antiepileptic drugs, belonging to the first, second and third generations, which exert side effects on the central nervous system (CNS). First generation antiepileptic drugs cause more frequent and severe adverse events and are less tolerated. As a consequence, in patients taking first generation AEDs retention rate is lower and second and third generation AEDs are preferred.

Corticosteroids are frequently used to treat peritumoral edema which may cause headaches, nausea, vomiting, papilledema (symptoms and signs of intracranial hypertension). Corticosteroid treatment may lead to cognitive, behavioral and psychiatric adverse effects: the frequency of side effects depends on several factors, such as sex, age, type of steroid, duration and dose of treatment.

Finally, thromboembolic events are very frequent among brain tumor patients, affecting up to 30%; the treatment of choice is anticoagulation, mainly with low molecular weight heparin (LMWH) rather than warfarin or direct oral anticoagulants (DOACs). The placement of an Inferior Vena Cava (IVC) filter is preferable in patients at high risk of intratumor hemorrhage (brain metastasis from melanoma, choriocarcinoma, renal cell

carcinoma and thyroid carcinoma, low platelets count, previous CNS bleeding, recent bleeding or active bleeding, etc.).

Keywords: Antiepileptic drugs, seizures, dizziness, diplopia, visual field defect, ataxia, somnolence, psychiatric disorders, cognitive deficit, corticosteroids, behavioral side effects, antithrombotic treatment, low molecular weight heparin (LMWH), direct oral anticoagulant (DOACs), venous thromboembolism, inferior vena cava (IVC) filter, intracranial hemorrhage

1. Introduction

Supportive treatments include all drugs, apart from those with an antitumoral activity, which are used in cancer management to improve clinical symptoms or treat tumor complications (for example AEDs for seizures, corticosteroids as anti-edema therapy and anticoagulants for venous thromboembolism).

Seizures are very common among patients with brain tumors: DNETs and gangliogliomas show the highest seizure rate (90–100%), followed by low-grade gliomas (75%), meningiomas (29–60%), glioblastomas (29–49%), brain metastasis (20–35%) and primary CNS lymphomas (10%).[1-2]

Cochrane guidelines suggest starting antiepileptic treatment only after at least one seizure and not as prophylactic treatment. Indeed, prophylactic treatment with AEDs was not effective in preventing seizure onset according to some studies.[3]

In patients with brain tumors, headache, nausea, vomiting and papilledema are a consequence of raised intracranial pressure: to relieve these symptoms, anti-edema therapy is recommended, mainly with osmotic agents (mannitol) and corticosteroids. Patients treated with mannitol may experience, as side effects on the CNS, headache, dizziness and convulsions.

Steroids have several side effects on glycidic and lipid metabolism, bone mineral density, blood pressure, muscle proximal trophism and strength. Conversely, adverse events on the CNS, which are quite frequent and can be divided into psychic and psychological, cognitive and behavioral, are less known.

Another frequent complication of brain tumors is the development of deep venous thrombosis and, as a consequence, pulmonary embolism, due to an intrinsic thrombophilia. About 30% of patients with glioblastoma may develop venous thromboembolism during the disease course. Because of the high mortality derived from pulmonary embolism, guidelines suggest

treating this critical condition with antithrombotic treatment, despite the high risk of intratumor hemorrhage.[4]

In this chapter we will focus on supportive treatment in cancer and its toxicity.

2. Antiepileptic drugs and side effects

Seizures are very common among patients with brain tumors, with a prevalence ranging from 10–15% of patients with primary CNS lymphoma to 90–100% of patients with ganglioglioma or DNET (which are the most epileptogenic CNS tumors). Moreover, epilepsy in patients with brain tumors is usually refractory to antiepileptic treatments (resistant to two or more AEDs used at full doses) and often requires pharmacological polytherapy.

The association of two or more antiepileptic drugs leads to more frequent side effects; moreover, some first generation AEDs are inhibitors or inducers of the cytochromes P450 system and might interfere with antineoplastic agents, thus reducing their clearance and increasing toxicity.

Studies indicate that drug tolerability is a significant limiting factor in maintenance treatment, and drug retention rates are often influenced by the side effect profile. For these reasons, the choice of the most suitable antiepileptic drug for a patient is complex and driven by several factors.

First of all, there are mainly three categories of antiepileptic drugs, with different abilities to interact with the CYP450 system and with other drugs:

- First generation (including phenobarbital, phenytoin, carbamazepine, primidone, ethosuximide and valproate): high induction of CitP450 system, except for valproate, which is an inhibitor;
- Second generation (including felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide): intermediate properties;
- Third generation (eslicarbazepine, brivaracetam, perampanel): low or absent (lacosamide) interaction with CYP450 system and drug-drug interactions.

Antiepileptic drugs can also be grouped depending on their mechanism of action:

- Sodium channel blockers (carbamazepine, phenytoin, lamotrigine, oxcarbazepine, zonisamide, lacosamide, eslicarbazepine, felbamate, topiramate, valproate). Lacosamide and eslicarbazepine enhance a slow inactivation of voltage-gated sodium channels and eslicarbazepine has a much lower affinity for voltage-gated sodium channels (VGSC) in the resting state compared with carbamazepine and oxcarbazepine;
- Calcium-channel blockers (ethosuximide, zonisamide, topiramate, eslicarbazepine);
- GABA-mediated chloride currents enhancers (clonazepam, gabapentin, tiagabine, vigabatrin, topiramate, valproate, phenobarbital);
- Glutamate-mediated currents blockers (perampanel, felbamate, lamotrigine, topiramate);
- Blockers of synaptic vesicle glycoprotein 2A (SV2A) (levetiracetam, brivaracetam).

2.1 Adverse events on the CNS

The main adverse events of AEDS on the CNS can be grouped into:

- affecting the brainstem and vestibulo-cerebellar system (dizziness, vertigo, ataxia, nystagmus, diplopia),
- affecting the visual system,
- affecting the extrapyramidal system (chorea and dystonia, parkinsonism, tremor),
- affecting vigilance (somnolence) and cognition (psychiatric and psychological side effects, anxiety, depression, fatigue, psychosis, suicidal thoughts, irritability, aggression).[5]

Drug-related side effects are generally classified into three types:

- Type A: dose-dependent, usually occurring at toxic doses and directly related to the pharmacological effect of the drug.
- Type B: subject-dependent or non-dose-dependent or idiosyncratic, occurring at low drug doses and disappearing after treatment discontinuation.
- Type C: caused by a cumulative effect from long-term therapy with the recommended daily dose, usually persisting after drug discontinuation.

Most side effects on the CNS are dose-related (type A) rather than idiosyncratic (type B) or cumulative (type C); conversely, those affecting the visual system are often type C.

Table 1-6-1: AEDs and frequency of CNS side effects

AED name	Dose range	Uncommon-rare (lower than 1%)	Common (1 to 10%)	Very common (10% or more)
Phenytoin	Starting dose: 10-20 mg/kg; maintenance: 300 mg/day	Babinski sign positive, hemiplegia, hypotonia, convulsions, hypokinesia and hyperkinesia, paralysis, aphasia, myoclonus, meningoencephalitis, subdural hematoma, brain edema, visual field defects, confusion, psychosis, emotional lability, amnesia, tics	Headache, incoordination, extrapyramidal syndrome, tremor, vertigo, tinnitus, taste loss, reflexes decreased or increased, slurred speech and dysarthria, paresthesia and hyporeflexia, blurred vision, diplopia, visual impairment, agitation, depression	Ataxia (18%), nystagmus (59%), somnolence (27%), dizziness (31%)
Valproate	Starting dose 10-15 mg/kg; maintenance: 20-30 mg/kg	Ataxia, lethargy, cognitive deficits, dementia, encephalopathy	Abnormal gait, amnesia, convulsion, dysarthria, extrapyramidal disorders, hypertonia, hypokinesia, attention deficits, memory impairment, nystagmus, paresthesia, increased reflexes, tardive dyskinesia, agitation, anxiety, confusion, depression, emotional lability, hallucinations	Dizziness, headache, somnolence, tremor, blurred vision

Phenobarbital	100-300 mg/day	Ataxia, delirium, tics	Somnolence, amnesia, memory impairment, attention deficit, aggression, agitation, nystagmus, dizziness	-
Carbamazepine	Starting dose 200-400 mg/day; titration up to 800-1200 mg/day; maximum dose 1600-2000 mg/day	Asterixis, dystonia, tics, dyskinesias, choreoathetosis, dysarthria and slurred speech, paresthesia, visual hallucinations, myoclonus	Headache, tremor, behavioral changes, confusion, seizures	Dizziness (44%), somnolence (32%), ataxia (15%), diplopia and blurred vision, nystagmus
Oxcarbazepine	Starting dose 600 m/day; maintenance 600-2400 mg/day	-	Amnesia, convulsions aggravated, gait disturbances and dysmetria, hypoesthesia, impaired concentration, speech disorder, involuntary muscle contractions, confusion, agitation, apathy, depression, emotional lability	Ataxia, dizziness, headache, nystagmus, somnolence, tremor, diplopia
Pregabalin	150-600 mg/day	Myoclonus, dyskinesia, intention tremor, nystagmus, hyporeflexia, hyperesthesia, ageusia, convulsions, hypokinesia and hyperkinesia, dysarthria, dystonia, encephalopathy, cognitive disorders, agitation, apathy, hallucinations, delirium, depression, retinal infarct	Ataxia, vertigo, incoordination, tremor, headache, speech disorder, twitching, confusion, amnesia, irritability, disorientation, attention deficits, anxiety	Dizziness (up to 37%), somnolence (up to 25%)

Gabapentin	900-3600 mg/day	Choreoathetosis, dyskinesia, dystonia, visual field defect, hallucinations, myoclonus	Abnormal gait, incoordination, tremor, dysarthria, hyperkinesia, seizures, paresthesia, vertigo, reflexes alterations, diplopia, nystagmus, amnesia, depression, confusion, anxiety, nervousness	Somnolence (21%), dizziness (17%), ataxia (13%)
Ethosuximide	500-1500 mg/day	Aggression, depression, suicide ideation, psychiatric disorders, attention deficits	Headache, ataxia, dizziness, somnolence	-
Felbamate	Starting dose 600-1200 mg/day; maximum dose 3600 mg/day	Hallucinations, suicide attempt	Tremor, abnormal gait, ataxia, paresthesia, diplopia, anxiety, nervousness, agitation, emotional lability, nystagmus, dyskinesia	Headache (36.8%), somnolence (19.3%), dizziness (18.4%), insomnia (17.5%)
Topiramate	Starting dose 25 mg/day, slow titration up to 100-200 mg/day; maximum dose 500 mg/day	Visual field defect, aphasia, hypokinesia, dyskinesia, cerebellar syndrome, dysesthesia, hypogeusia, dystonia, apraxia, hyposmia, hyperesthesia, suicidal ideation, hallucinations, hypomania	Attention deficits, cognitive disorder, convulsions, coordination abnormal, tremor, nystagmus, balance disorders, dysarthria, sedation, diplopia and blurred vision	Paresthesia, somnolence (15%), dizziness, depression, memory loss (10%)

Lamotrigine	Starting dose 25 mg/day, titration up to 100-200 mg/day	Aphasia, akathisia, dysarthria, dyskinesias, hyperkinesias, hypertonia, myoclonus, choreoathetosis, dystonia, hemiplegia, extrapyramidal syndrome, hypotonia, hypokinesia, hyperesthesias, muscle spasms, paralysis, apathy, hallucinations, memory deficits, psychosis, suicidal ideation, delirium, visual field defects, tics	Seizure exacerbation, insomnia, incoordination, tremor, speech disorders, amnesia, vertigo, hypoesthesia, paresthesia, confusion, depression, anxiety, irritability, disturbances in concentration, nystagmus	Dizziness (38%), headache (29%), ataxia (22%), somnolence (14%), diplopia (28%), blurred vision (16%)
Zonisamide	300-500 mg/day	Convulsions, neuroleptic malignant syndrome, aggression, suicidal ideation, hallucinations, mania	Paresthesia, tremor, difficulty concentrating, memory deficits, mental slowing, insomnia, psychotic disorders, anxiety, nystagmus, diplopia	Somnolence (17%), dizziness (13%), headache (10%), ataxia, agitation, irritability, depression
Primidone	500-1500 mg/day	Diplopia, nystagmus, hyperirritability, psychosis, personality changes, headache	Visual disturbances, ataxia, nystagmus, vertigo	Coordination and balance disorders, dizziness

Tiagabine	Starting dose 5-10 mg/day; maintenance 30-50 mg/day	Status epilepticus, psychosis, hallucinations, dyskinesias	Ataxia, paresthesia, abnormal gait, nystagmus, speech disorders, diplopia, difficulty with concentration/attention, insomnia, confusion, memory loss, depressed mood, aggression, agitation	Dizziness (27%), somnolence (18%), nervousness (10%), tremor, blurred vision, visual field defects
Vigabatrin	2-3 g/day	Retinal disorders, optic neuritis and optic atrophy, ataxia, encephalopathy, hypomania, mania, psychotic disorders, hallucinations, suicide attempt, myoclonus	Speech disorders, paresthesia, dystonia, dyskinesia, hypertonia, hyperreflexia, hyporeflexia, hyperesthesia and hypoesthesia, dysarthria, status epilepticus, aggression, nervousness, irritability, disturbances in attention	Visual field defects (30% or more), nystagmus (up to 19%), blurred vision (up to 16%), diplopia (up to 16%), headache (up to 33%), somnolence (up to 26%), dizziness (up to 26%), tremor (up to 16%), memory impairment (up to 16%) abnormal coordination (up to 16%), agitation in children

Levetiracetam	Starting dose 1000 mg/day; maintenance 1000-3000 mg/day	Choreoathetosis, dyskinesia	Dizziness, ataxia, vertigo, paresthesia, coordination difficulties, depression, nervousness, amnesia, anxiety, irritability, hypersomnia, insomnia, diplopia, blurred vision	Headache (14%), somnolence (14%), non-psychotic behavioral symptoms (up to 38%), psychotic symptoms (up to 17%)
Brivaracetam	50-200 mg/day	Suicidal ideation, psychotic disorders, aggression, agitation	Convulsion, depression, anxiety, insomnia, irritability	Somnolence (up to 27%), dizziness and disturbances in gait and coordination (up to 16%)
Eslicarbazepine	Starting dose 400 mg/day; maintenance 800-1600 mg/day	Coordination abnormal, hypersomnia, sedation, aphasia, dysesthesia, dystonia, convulsions, cerebellar syndrome, nystagmus, paresthesia, nervousness, agitation, irritability, attention deficit, confusion, psychotic disorders	Vertigo, ataxia, tremor, dysarthria, memory impairment, blurred vision, visual impairment, depression, insomnia	Dizziness (up to 28%), somnolence (up to 18%), headache (up to 15%), diplopia (up to 11%)

Lacosamide	Starting dose 100 mg/day; maintenance 400 mg/day in add-on therapy and 600 mg/day in monotherapy	Aggression, agitation, suicide attempt, hallucinations	Somnolence, tremor, nystagmus, memory impairment, coordination abnormal, cognitive disorders, dysarthria, paresthesia, disturbances in attention, depression, insomnia	Dizziness (up to 60%), headache (up to 13%), ataxia (up to 15%), diplopia (up to 16%), blurred vision (up to 16%)
Perampanel	Starting dose 2 mg/day, maintenance 4-12 mg/day	Homicidal ideation, suicidal ideation	Ataxia, dysarthria, hypoestesia, abnormal coordination, memory impairment, paresthesia, anxiety, hypersomnia, euphoria, confusion, blurred vision, diplopia	Dizziness/vertigo (47%), somnolence (18%), gait disturbances (13%), headache (13%), irritability (12%), hostility and aggression-related reactions (20%)

2.2 Vestibulo-cerebellar and brainstem toxicity

2.2.1 Dizziness and ataxia

Concerning the vestibulo-cerebellar system, dizziness and ataxia are the most common side effects of all AEDs, both older (phenytoin, carbamazepine, phenobarbital, primidone), and newer (second and third generation: gabapentin, lamotrigine, topiramate, oxcarbazepine, esclicarbazepine, zonisamide, lacosamide, levetiracetam, brivaracetam and perampanel).

Ataxia is reported in a high percentage of patients (54% according to some series), becoming even more frequent among people aged over 70 years.

Ataxia and dizziness are usually dose-dependent (especially with carbamazepine and phenytoin) and in only a few patients may be idiosyncratic reactions to AEDs. Patients with previous gait disturbances receiving a pharmacological polytherapy are more susceptible to these adverse effects. In addition, patients with cerebellar atrophy seen on MRI were found to be more sensitive to the effects of carbamazepine[6]. In carbamazepine-treated patients, dizziness is described in up to 44% of patients and ataxia in 15% of patients. During treatment with phenytoin, patients may experience dizziness in 31% and ataxia in 18% of cases. Ataxia in phenytoin-treated patients may appear insidiously and worsen progressively: it is usually reversible and dose-related but in some patients it can persist after drug withdrawal. Some hypotheses have been advanced to explain the persistence of ataxia, including Purkinje cells and astrocytes degeneration and cerebellar atrophy. In addition, phenytoin-induced chronic ataxia and cerebellar atrophy may predispose to carbamazepine toxicity. Furthermore, ataxia may be an early sign of phenytoin intoxication (see below).

Patients treated with valproate often develop dizziness, while ataxia is less frequent.

Phenobarbital is significantly associated with truncal ataxia and primidone with dizziness.

Among newer AEDs, dizziness and ataxia are often the most frequent side effects. Ataxia and dizziness are the most frequent side effects of lamotrigine, but lamotrigine seems to be the least likely drug among the newer AEDs to cause treatment discontinuation because of these adverse events.

In some studies comparing new and old generations of antiepileptic drugs, the frequency of lamotrigine-ataxia was significantly lower than in patients treated with carbamazepine or phenytoin.

Gabapentin and pregabalin have been related to the development of ataxia and dizziness (up to 20% of patients in gabapentin and 37% in pregabalin), dizziness being the most frequent adverse event.

Studies using tiagabine revealed dizziness and incoordination as the most frequent symptoms in up to 27% of patients.

Dizziness is also described among patients treated with topiramate.

In patients taking oxcarbazepine and eslicarbazepine, dizziness is the most common adverse event, more often mild and transient.

Zonisamide is significantly associated with ataxia and dizziness occurring in the titration phase.

Dizziness and ataxia are described in 10% of patients taking levetiracetam, and dizziness represents the most common adverse events leading to treatment discontinuation.

Dizziness is the second most common adverse event (following somnolence) described in patients treated with brivaracetam (up to 16% of patients) and similarly, in patients treated with levetiracetam it is the main cause of treatment discontinuation.

In perampanel treated patients, dizziness is the most frequent reported adverse event: there is a relationship with the dose, ranging from 10% at 2 mg per day to 42.7% at 12 mg per day. Ataxia and balance disorders were reported in a lower percentage of patients (up to 8%) and at higher dosage (over 8 mg per day).

Finally, dizziness and ataxia are the most frequent adverse events in patients treated with lacosamide and are dose-dependent: dizziness may be present at a low dosage of 200 mg per day, while ataxia may appear after titration up to 400-600 mg per day.

In conclusion, comparing the old with the newer antiepileptic drugs, dizziness is less frequent with newer AEDs and it is usually mild or transient as compared to old AEDs, in particular in the cases of levetiracetam, oxcarbazepine and lamotrigine.

2.2.2 Ocular movements

Pathways regulating ocular movements and located in the brainstem and cerebellum are very sensitive to the effects of antiepileptic drugs.

Several studies documented ocular motility dysfunctions with AEDs. These side effects vary from asymptomatic or subclinical (which can be detected by quantitative and qualitative measurements) to severe subjective and objective manifestations (diplopia, oscillopsia, nystagmus, oculomotor apraxia, gaze palsy, vergence problems, external ophthalmoplegia and

oculogyric crisis). They are mainly type A or dose-related adverse events, as they usually occur with high doses or drug intoxication[7].

Ocular motility dysfunction induced by AEDs is believed to be a consequence of ion-channel blockade activity (by sodium channel blockers) or stimulation of GABAergic system (by drugs enhancing GABAergic transmission). In fact, voltage-gated sodium channels are present in presynaptic and postsynaptic membranes of the neocortex and cerebellum and GABA is the main inhibitory neurotransmitter in the synapses of the vestibulo-oculomotor pathway and Purkinje cells of the cerebellum.

Nystagmus has been described during the administration of almost all AEDs, in particular with phenytoin, carbamazepine, phenobarbital, lamotrigine, oxcarbazepine, vigabatrin and felbamate (even at non-toxic dosage), producing diplopia and oscillopsia.

Diplopia may be a complaint of patients treated with carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine, topiramate, vigabatrin, zonisamide, tiagabine, lacosamide, levetiracetam, perampanel and phenytoin.

Phenytoin may cause gaze-evoked, downbeat or periodic alternating nystagmus, partial or total gaze palsy, convergence spasm and external ophthalmoplegia. These adverse effects occur at higher phenytoin concentrations and disappear with dose reduction or drug withdrawal.

Phenobarbital may lead to up-beating, gaze-evoked vertical or horizontal nystagmus, partial or total gaze palsy, impaired vergence and internuclear ophthalmoplegia, hours to days after assumption of high or toxic doses of the drug. Recovery occurs after dose reduction or drug withdrawal.

Carbamazepine has been associated with lateral gaze-evoked and downbeat nystagmus, ocular skew deviation, partial or total gaze palsy, complete external ophthalmoplegia and oculogyric crisis, both with high/toxic and lower doses: with dose reduction or drug withdrawal ocular manifestations disappeared.

Nystagmus was more frequent among patients with higher carbamazepine concentration in monotherapy and with lower carbamazepine concentration in add-on therapy to phenobarbital, suggesting that the threshold at which side effects appear is reduced in the presence of phenobarbital. Also, some authors advanced the hypothesis that carbamazepine-10,11-epoxide (an active metabolite of carbamazepine) may contribute significantly to toxic adverse events due to carbamazepine. Among patients experiencing adverse events at lower carbamazepine levels, moderate or severe cerebellar atrophy was reported, probably increasing susceptibility for cerebellar adverse effects for carbamazepine.

Ophthalmological signs (ranging from horizontal nystagmus to complete external ophthalmoplegia) may be the first sign of acute phenytoin (>30 mcg/ml) or carbamazepine (>40 mcg/ml) intoxication, whereas ataxia appears at higher doses. In high-dose phenytoin treatment nystagmus and ataxia are a stable condition (because of the long half-life of phenytoin), while carbamazepine usually determines intermittent symptoms, which are strictly related to fluctuations of carbamazepine serum levels. This is a possible explanation of why controlled-release carbamazepine is better tolerated than a conventional formulation. Moreover, some studies suggest a mechanism of adaptation of the patient to these common adverse events.

Lamotrigine may cause diplopia and rotary nystagmus, mainly at toxic doses. Impaired pursuit and gaze-holding were reported in patients treated with pregabalin. During therapy with felbamate, nystagmus is mainly gaze-evoked and downbeat. In lacosamide-treated patients, nystagmus and diplopia may appear at doses over 400 mg per day. Diplopia and blurred vision may also occur in patients treated with eslicarbazepine and are usually of mild or moderate severity.

Modifications induced by antiepileptic therapy and subclinical changes may be quantified by testing saccades and smooth-pursuit movements: in some studies, carbamazepine was shown to reduce the peak velocity of saccades and smooth pursuit, while phenytoin reduced only smooth pursuit and oxcarbazepine only peak velocity of saccades. These parameters were unchanged during treatment with lamotrigine.

In conclusion, the most toxic AEDs on vestibulo-cerebellar and brainstem functions are phenytoin and carbamazepine, while among the first generation of antiepileptic drugs, valproate is considered to be less active on vestibulo-cerebellar structures. However, side effects may be also observed quite frequently with the newer antiepileptic drugs.

2.3 Visual system toxicity

Visual disturbances are a common side effect of many antiepileptic drugs: in particular, some anticonvulsants—such as vigabatrin and sodium channel blockers—are associated with specific visual problems related to mechanistic properties of the drug that alter GABAergic and glutamatergic neurotransmission and ion-dependent conductance of retinal signals. As a consequence, antiepileptic drugs active on the GABAergic system or blocking voltage-gated sodium channels (VGSCs) are the most frequently associated with visual disturbances.[8]

Visual adverse events are generally classified into type A (dose-dependent), type B (subject-dependent or idiosyncratic) and type C

(cumulative effect from long-term therapy with the recommended daily dose). Most of the side effects on the visual system are type C (see below).

Vigabatrin binds irreversibly to GABA transaminase and therefore enhances GABAergic neurotransmission.

Vigabatrin-associated visual field loss is characterized by bilateral concentric nasal constriction with temporal and central sparing. According to some studies, vigabatrin-associated visual field loss affects approximately 30-60% of adults and 34-54% of children receiving the drug at normal therapeutic levels. Men seem to be more susceptible than women. Adults and older children are at greater risk compared to infants and younger children, probably due to lower retinal plasticity. According to some studies, children treated for epilepsy due to structural lesions in the occipital lobes or with occipital electroencephalogram alterations are at greater risk. Cumulative exposure to vigabatrin in terms of total dose and duration of treatment is actually the most important factor implied in the onset of visual field deficit: for this reason, vigabatrin-associated visual field loss is probably a type C adverse drug reaction.

The natural history of vigabatrin-associated visual field loss is unknown: symptoms may occur early, six weeks after starting therapy, or within two to three years of treatment. Nevertheless, the majority of these patients are asymptomatic.

The defect in the visual field is permanent, persisting after the withdrawal of vigabatrin: only a few cases of visual field improvement following cessation of vigabatrin have been described in children. On the other hand, in patients who continued to take vigabatrin despite the visual defect no evidence of progression of the deficit was found on repeated testing.

Treatment with vigabatrin, by blocking the activity of GABA transaminase, leads to high levels of GABA in the retina resulting in improper depolarization of the retinal bipolar cells and induction of a potentially cytotoxic calcium influx at this level. As a consequence, vigabatrin may produce a reduction in retinal cell function and organization, cone photoreceptor damage, retinal gliosis, altered expression of proteins in Muller cells and rod bipolar cells and movement of photoreceptor nuclei toward the retinal pigment epithelium. In some studies, more severe visual field constriction has been reported in patients treated with vigabatrin in association with carbamazepine and sodium valproate as compared to patients treated with vigabatrin alone. Indeed, valproate influences the GABAergic system and the association may potentiate GABAergic transmission, thus resulting in more severe side effects. Some predisposing factors have been hypothesized, such as some genetic polymorphisms or

altered ocular hemodynamics with decreased retinal and pulsatile ocular blood flow.

Another side effect described in patients treated with vigabatrin is altered color perception and acquired short wavelength defects. Toxic injury to the medium wavelength sensitive cones and long wavelength sensitive cones is less common. Monotherapy with vigabatrin may produce this effect by enhancing GABAergic inhibition at the retinal level rather than a direct neurotoxic effect. In addition, vigabatrin monotherapy may lead to impaired contrast sensitivity in up to 50% of patients.

Altered color perception and contrast sensitivity suggest that not only might the peripheral retina be damaged but also central areas with the degeneration of cones.

Because of the frequent visual side effects during treatment with vigabatrin, visual field testing is required at the start of treatment and at regular time intervals. If visual field defects are noted, the therapeutic dosage of vigabatrin should be reduced in order to determine if field defects improve or stabilize.

Retinal toxic adverse effects are frequent among other types of AEDs and include color vision deficiency (particularly in the blue/yellow axis), reduced contrast sensitivity, visual field defects, retinal nerve fiber layer loss and vision loss. They occur not only with high or toxic doses of AEDs but also with chronic long-term use of drugs in their therapeutic concentration (type C side effects). Retinal toxic adverse effects are described in patients treated with topiramate (blurred vision), tiagabine (visual fields deficits and altered color vision similar to vigabatrin), valproate (impairment of chromatic and achromatic discrimination, blurred vision), carbamazepine (mainly color vision disturbances and blurred vision), gabapentin (visual field defects), lamotrigine (blurring of vision, bilateral visual field constriction, reduction in contrast sensitivity), lacosamide (blurred vision at dosage over 400 mg per day), oxcarbazepine (blurred vision), eslicarbazepine (blurred vision), perampanel (blurred vision) and phenytoin (color vision deficiency, blurred vision).

The exact mechanism of color vision deficiencies in the absence of visual field defects or impaired contrast sensitivity is unknown. In a similar way to visual field defects, AEDs may also alter retinal membrane conductance by blocking voltage-gated channels present on retinal cell layers or by enhancing GABAergic transmission.

Further ocular side effects may include retinal stroke and optic neuropathy. Retinal stroke was observed in pregabalin-treated patients. Optic neuropathy was reported in long-term monotherapy with carbamazepine, valproate and vigabatrin. Its severity varies from subclinical

to symptomatic reduction of visual acuity. Chronic use of carbamazepine or valproate, even in therapeutic doses, may lead to prolonged latency and reduced amplitude of P100 wave of VEPs, suggesting both demyelinating and axonal optic nerve dysfunction. Conversely, in vigabatrin-treated patients, pallor of the optic disc and reduced P100 amplitude in VEPs suggest the prevalence of axonal damage and degeneration. In addition, carbamazepine may exert its effect by blocking voltage-dependent sodium channels present in ganglion cells and optic nerve fibers, while valproate exerts its effect by perturbating GABAergic system. Optic neuropathy seems to be a type C adverse drug reaction, occurring after long-term therapy.

2.4 Motor system toxicity

The most frequent side effect affecting the extrapyramidal system is tremor, which is mainly seen in patients treated with valproate, less frequently with lamotrigine, pregabalin, tiagabine, gabapentin, phenytoin, felbamate, topiramate, vigabatrin, lacosamide and eslicarbazepine.[6]

Interestingly, many AEDs have been successfully used in the treatment of tremor, such as phenobarbital, felbamate and primidone in essential tremor and carbamazepine in cerebellar tremor.

According to some case reports, valproate may cause a reversible parkinsonian syndrome, sometimes associated with dementia and brain pseudoatrophy. This syndrome may appear within a few days or in an insidious manner after some years: valproate discontinuation leads to the disappearance of symptoms.

Tremor induced by valproate is characterized by low-amplitude and high frequency, resembling the essential or adrenergic tremor. Tremor is observed at a dosage greater than 750 mg/day, but there is no close correlation to plasma levels. Propranolol, amantadine and acetazolamide may be used to treat this condition when it becomes disabling. Add-on of lamotrigine, carbamazepine and phenytoin to valproate may worsen this adverse effect.

Tremor is one of the five most frequent adverse effects of tiagabine and it is strictly related to drug concentration (being observed at high doses > 36 mg/day).

Tremor is also described in patients treated with lacosamide at the maximum dosage (600 mg per day).

Dyskinesias, chorea, athetosis and dystonia are described in a small group of patients and in some case reports. More than two-thirds of cases have been associated with the use of phenytoin (choreoathetosis is the most

represented): in more than 50% of these patients, the phenytoin level was in the toxic range and phenytoin therapy was associated with other AEDs, especially valproate, which is an inhibitor of the cytochrome p450 system and may increase phenytoin concentrations. Given the paucity of data, the causal relationship between AEDs and dyskinesias has not been completely established: even if a dose-response relationship exists, the appearance of these side effects is unpredictable and host-dependent, and they may be classified as type B adverse events (idiosyncratic). Rare cases of dyskinesias are described in patients treated with carbamazepine, valproate, ethosuximide, gabapentin, pregabalin, felbamate, lamotrigine, tiagabine, vigabatrin, topiramate and levetiracetam. Since each drug, when administered alone, did not cause dyskinesias, an additive or synergistic effect has been postulated when drugs are co-administered in polytherapy or as an add-on to phenytoin. Also, some predisposing causes have been proposed, such as pre-existing basal ganglia damage or mental retardation, and myoclonic epilepsy. To explain the relationship between dyskinesias and AEDs, it has been hypothesized that dysfunction of dopaminergic system is induced by AEDs, in addition to potentiation of GABAergic effects and/or inhibition of excitatory neurotransmission.

Tics have been described in patients treated with carbamazepine and lamotrigine and exceptional cases were reported with phenobarbital and phenytoin. The mechanism could be an increase of dopaminergic activity at the basal ganglia level: carbamazepine has been demonstrated to increase dopamine and its metabolites in the striatum and hippocampus, while lamotrigine does not seem to have an activity on dopamine receptors and may act by enhancing glutamatergic transmission.

Myoclonus is an involuntary jerky muscle contraction (positive myoclonus) or a brief lapse of muscle activity (negative myoclonus) and can be epileptic (when epileptic discharges are recorded on EEG) or non-epileptic. All of these types of myoclonus may be induced by AEDs. The main implicated AEDs in the development of epileptic and non-epileptic myoclonus are phenytoin and carbamazepine. Furthermore, they may worsen myoclonic jerks in several epileptic syndromes, especially carbamazepine in juvenile myoclonic epilepsy and in benign rolandic epilepsy.

In patients treated with valproate, negative myoclonus (probably non-epileptic according to neurophysiological evaluation) may appear as a consequence of hyperammonemia and toxic encephalopathy (despite normal serum levels of valproate).

Among the newer generation of antiepileptic drugs, vigabatrin, gabapentin, pregabalin and lamotrigine may induce myoclonic jerks or

worsen seizures in myoclonic epilepsy. Vigabatrin and lamotrigine have been associated with epileptic myoclonus (with paroxysmal EEG discharges recorded), while gabapentin and pregabalin seem to be related to non-epileptic myoclonus (some studies showed no EEG correlation).

2.5 Psychiatric and psychological adverse events

Some patients may present behavioral and psychiatric side effects during treatment with AEDs. The most frequent is irritability, followed by depression and behavioral change. Other rare side effects are psychosis, anxiety, suicidal thoughts and aggression.

The greater percentage of these adverse events is described in patients treated with levetiracetam (up to 38% of patients), followed by zonisamide (17.8%), perampanel (12%) and tiagabine (10%), while the use of carbamazepine, clobazam, gabapentin, lamotrigine, oxcarbazepine, phenytoin, and valproate is significantly associated with a lower rate of psychiatric and behavioral side effects.[9]

In perampanel treated patients, irritability is dose-dependent, reaching 11.8% of patients at a dose of 12 mg per day; other possible side effects are depression, aggressive behavior and suicidal ideation.

Psychosis occurs in about 3% of patients treated with levetiracetam and about 1.5% of patients treated with zonisamide. Less frequently these side effects may be severe with physical violence, requiring AED discontinuation in about 2% of patients and psychiatric emergency treatment.

Among patients treated with brivaracetam, which is a more selective inhibitor of SV2A with respect to levetiracetam, behavioral and psychiatric side effects are less common than in levetiracetam-treated patients, leading to treatment discontinuation in 1.7% of patients.

A previous psychiatric condition is the strongest predictor of AED-related psychiatric/behavioral side effects, also when psychiatric symptoms are controlled at the start of AED treatment. Other predictors are a history of febrile convulsions and of status epilepticus. No differences between partial epilepsy and primary generalized epilepsy were found, as well as between temporal lobe epilepsy and extratemporal epilepsy. In addition, freedom from seizures was not a significant predictor of psychiatric/behavioral side effects as well as the titration schedule of levetiracetam. Biological vulnerability has been hypothesized.

2.6 AEDs affecting cognition and vigilance

Somnolence and sedation are described as possible side effects in almost all antiepileptic drugs, being frequent in patients treated with gabapentin, levetiracetam, brivaracetam, oxcarbazepine, pregabalin, topiramate, zonisamide, phenytoin, phenobarbital, valproate, carbamazepine, eslicarbazepine and perampanel. In patients treated with perampanel sedation is dose-related, reaching 17.6% of patients at 12 mg per day. Among the newer antiepileptic drugs, lacosamide, even at high doses, does not substantially affect vigilance and alertness.

All available antiepileptic drugs may potentially exert detrimental effects on cognitive function, altering executive abilities and therefore compromising patient well-being. These effects vary depending on both patient characteristics and drug-related variables. Certain individuals seem to be more vulnerable to cognitive adverse effects with particular AEDs.[10] Also, AED dosage, titration rate and combination of different antiepileptic drugs may be linked to the incidence of cognitive adverse effects (CAEs). Furthermore, some studies have reported that temporal lobe epilepsy may be a risk factor for CAEs.

On the other hand some AEDs, such as lacosamide, levetiracetam and lamotrigine (see below), may have the advantage of improving cognitive performance in a direct way by improving alertness or cognitive capacity (besides a possible improvement linked to seizure reduction).

Among the older AEDs, a number of cognitive effects have been linked to carbamazepine. The main adverse events are poor verbal fluency, deterioration in processing speed, attention, memory and arithmetic skills; drug discontinuation significantly improves cognitive performances. In some studies it has been suggested that carbamazepine has a worse cognitive profile than levetiracetam and lamotrigine.

Phenytoin has been implicated in the decline in concentration, memory, visuomotor functions and mental speed with a possible relationship with drug concentration. These are potentially reversible after drug withdrawal. When compared to carbamazepine, phenytoin seems to produce similar cognitive side effects.

Phenobarbital may affect cognitive functions in children, more frequently than carbamazepine and valproate: in fact, children treated with phenobarbital show a lower IQ and discontinuation of the drug may improve total IQ. Also, lowering of processing speed and impaired attention have been attributed to phenobarbital use, without a clear relationship with drug concentration.

Primidone, when compared to carbamazepine, may more frequently affect attention and concentration; memory difficulties may improve after drug discontinuation as observed in phenobarbital treatment.

A large number of studies on patients treated with valproate show a modest detrimental impact on cognitive functions; thus, valproate may be preferable to carbamazepine, phenobarbital, phenytoin, primidone and topiramate.

Ethosuximide has been associated with a favorable profile in terms of cognitive functions; furthermore, a possible role in improvement in cognitive performance has been reported.

Cognitive problems were also described during treatment with newer AEDs, such as zonisamide and topiramate.

Among patients treated with zonisamide, cognitive problems have been reported in about 25-35% of patients (mainly memory loss, attentional problems and verbal fluency alteration), and are related to drug concentration. After one year of treatment, a high percentage of patient's complaints of cognitive deficits were the main reason for treatment discontinuation in 6% of patients.

A large proportion of patients treated with topiramate have reported cognitive problems (about 44%). The main adverse effects were memory impairment (both short-term and working memory), impaired concentration, psychomotor slowing, language and comprehension problems, poor verbal fluency and wordfinding deficits, reduced IQ score and cognitive speed, and abnormal thinking. Also, EEG alterations may be seen in frontal regions. Furthermore, some studies have reported that patients with temporal lobe epilepsy, past psychiatric history and pre-existing cognitive difficulties may be more vulnerable to topiramate-cognitive effects. In conclusion, topiramate may exert more frequent negative effects on cognition as compared with other AEDs (valproate, oxcarbazepine, lamotrigine, levetiracetam).

In patients treated with vigabatrin, clobazam, gabapentin, lamotrigine, oxcarbazepine, lacosamide and levetiracetam no adverse effects on cognitive functions have been described. In patients taking pregabalin and oxcarbazepine, cognitive problems and deterioration in visual and verbal episodic memory, have been described in a low percentage of patients (4%).

According to some series, lamotrigine, lacosamide and levetiracetam seem to have an additional positive effect on cognitive functions, even when compared to other antiepileptic drugs.

In lamotrigine-treated patients, this improvement in cognitive functions may be related to EEG changes.

Levetiracetam may have the potential to improve visual short-term memory, working memory, motor functions, psychomotor speed and concentration.

No adverse events related to cognition were significantly associated with lacosamide treatment. Conversely, a positive impact of lacosamide on cognition has been suggested in comparison to lamotrigine and superior to topiramate and carbamazepine (with an increase in Epitrack score, which is a tool for assessment of cognitive side effects in antiepileptic drug use).[11]

To summarize, among older antiepileptic drugs, phenobarbital and primidone show the greatest cognitive toxic potential, while ethosuximide may have the best cognitive profile.

With regard to newer drugs, topiramate shows the worst detrimental influences on cognition, followed by zonisamide. The agents least likely to interfere with cognitive processes are lamotrigine, lacosamide and levetiracetam, with a possible positive impact on cognitive functions instead.

2.7 Other side effects

2.7.1 Headache

Almost all antiepileptic drugs may cause headaches.

Headache is frequent in patients treated with sodium valproate, oxcarbazepine, felbamate, lamotrigine, zonisamide, vigabatrin, levetiracetam, lacosamide, eslicarbazepine and perampanel.

Headache is also a side effect, though less frequent, of phenytoin, carbamazepine, ethosuximide, pregabalin and primidone.

Among patients treated with topiramate, tiagabine, gabapentin, phenobarbital and brivaracetam, headache is not reported as a side effect.

2.7.2 Sensory deficits

The main adverse sensory effects are paresthesias, followed by hypoesthesia.

Paresthesias are very frequent in topiramate-treated patients, but are less frequent with phenytoin, carbamazepine, valproate, gabapentin, felbamate, lamotrigine, zonisamide, vigabatrin, levetiracetam, eslicarbazepine, perampanel and lacosamide.

Hypoesthesia is reported in patients treated with oxcarbazepine, lamotrigine, vigabatrin and perampanel, while hyperesthesia is reported with vigabatrin, lamotrigine, topiramate and pregabalin.

3. Corticosteroid-related CNS side effects

Glucocorticoids are a class of steroid hormones released from the cortex of adrenal glands under the control of the hypothalamic-pituitary-adrenal axis. They regulate stress response, growth, metabolism, development and immune function by binding to glucocorticoid receptors (GR) and regulate hydro-saline balance by binding with lower affinity to mineralocorticoid receptors (MR). Endogenous glucocorticoids also control the feeling of hunger, the sleep-wake cycle, learning and memory processes by binding to specific receptors located in the entire CNS, especially in the prefrontal cortex, hippocampus and basolateral amygdala, which role is regulation of various neurotransmission, including serotonin and dopamine. In particular glucocorticoids, by exerting their effect at hippocampal level, provide processing of emotional information and memory. Furthermore, some studies report a correlation between high doses of endogenous glucocorticoids and hippocampal atrophy resulting in cognitive dysfunction. How this damage occurs is not clear: it may be mediated by an increase in excitatory amino acids and serotonin, or may be attributable to glucocorticoids rendering hippocampal neurons more vulnerable to other insults, such as ischemia, through impaired neuronal glucose uptake.[12]

The damage to the hippocampus adversely affects its ability to provide negative feedback on glucocorticoid levels to the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased levels of these hormones and hence more damage.

Corticosteroids (CS), similar to endogenous glucocorticoids, bind to MR and GR and trigger the transcription of anti-inflammatory genes such as NF-kB, AP-1, STAT, c-Jun, Fos, leading to the inhibition of cytokines and pro-inflammatory proteins production.

About 20% of patients receiving high doses of corticosteroids develop psychiatric disorders including depression, mania and psychosis requiring pharmacological treatment, and about 75% complain of psychiatric symptoms reversible after therapy discontinuation. Other patients may present cognitive deficits or behavioral effects.

Symptoms induced by corticosteroids may arise in the first phases of treatment, during or even at the end of therapy; in most cases (86%) they occur within the first five days of treatment.

There are approximately 550 polymorphisms identified for the gene of GR, and this may explain individual responses and sensitivity to treatment with corticosteroids.

3.1 Behavioral effects

Chronic intake of corticosteroids may lead to an increase in appetite and body weight in 70% of patients. Weight gain does not correlate with the cumulative dose of steroids.

Sleep disorders, such as restlessness and insomnia, were observed in 73% of cases, strongly related to the increase in daily dose.

Some patients treated with oral prednisolone develop a sense of well-being called "steroid euphoria," characterized by reduced anxiety and depression.

3.2 Psychic effects

The corticosteroids-related psychic effects occur in quantitatively and qualitatively distinct forms, ranging from an initial slight increase in the overall sense of well-being (independent of improvement in their underlying disease activity) or low-grade mood changes (euphoria, grandiosity, emotional lability, depressed mood) up to severe psychiatric disorders and suicidal thoughts.

The frequency of psychiatric adverse events among several studies varied from 1.3% to 62% of adults. They were found to be mild to moderate in one-third of cases and severe in 5-10% of cases.

Incidence of depression in patients treated with corticosteroids is described from 2-4% to 40.5% of patients according to different series; also, mania, psychosis and delirium are very frequent with an incidence of 27.8%, 13.9% and 10.1%, respectively.

Compared with the unexposed population, the risk of suicide or suicide attempt increased five to sevenfold in people treated with corticosteroids.[13] Emotional lability, irritability, auditory hallucinations and paranoia are other common symptoms.

Rarely, altered consciousness and disorientation may be observed.

It has been hypothesized that psychic symptoms may be caused by a decrease in corticotrophin, norepinephrine and beta-endorphin levels in the cerebrospinal fluid, or by an increase in the release of glutamate that induces neuronal cytotoxicity.

Psychiatric symptoms appear in 89% of patients in the first six weeks, in 62% within two weeks and in 39% in the first week, with an average time of 11.5 days.

These adverse events are time and dose-dependent: adult studies suggest a presumable threshold dose of ≥ 20 mg/day of prednisone or equivalent for development of psychiatric side effects and patients receiving more than 40

mg/day appeared to be at greater risk. A multicentric prospective case series recorded acute psychiatric reactions in 1.3% of patients receiving ≤ 40 mg oral prednisolone/day, 4.6% of patients receiving 41-80 mg and 18.4% of patients receiving ≥ 80 mg per day. However, data from this and other adult case series suggest that it is not a straightforward dose-response effect because there was no predictable relationship between the timing, severity or duration of psychiatric side effects and the timing, dosage and duration of CS treatment.

Notably, the duration of treatment may influence qualitative aspects of psychiatric side effects: for example mania and hypomania have been reported in pulse intravenous medium/high doses of corticosteroids with depression reported less frequently, while long-term therapies have been associated with depressive disorders.

Other possible risk factors are sex (some studies suggest that women are more prone to these side effects, particularly depression), pre-existing psychiatric problems, previous lifetime GC exposure and age. 73% of the pediatric population receiving steroids may develop hyperactivity, irritability, insomnia, a deficit in attention and memory, especially those under ten years old, meaning that children are more susceptible to the adverse effects of corticosteroids.[14] Women are more likely to develop depressive mood, while men are more prone to developing mania, delirium, confusion, or disorientation. Patients' susceptibility to psychiatric adverse events may also be influenced by polymorphisms of the GRs.

Psychiatric adverse events usually display rapid resolution after corticosteroids reduction or discontinuation, and frequently restart after dose increase or re-administration. Sometimes, switching to alternative corticosteroids was found to be helpful, because some types of corticosteroids may cause more frequent side effects than others. For example, in a Medical Research Council randomized controlled trial of 1600 children and adolescents with ALL, "behavioral toxicity" was reported in 6% of patients in the dexamethasone group compared with 1% in the prednisolone group. In addition, most patients on dexamethasone with severe side effects were switched to prednisolone with no significant recurrence of behavioral problems. There is therefore some evidence that dexamethasone may be associated with more frequent and more severe psychiatric adverse events than prednisolone or prednisone, probably related to pharmacokinetic differences. It is debated whether the alternate-day schedule of corticosteroids administration might reduce the incidence and severity of psychiatric side effects.

Because of "psychological dependency" on corticosteroids due to their euphoric effects, psychiatric adverse events may also be seen during

tapering or after cessation of CS treatment. According to some reviews, a significant proportion of the reported suicidal behavior associated with CS treatment in adults occurs during withdrawal.

3.3 Cognitive effects

Corticosteroids-related cognitive effects are described both in acute and chronic therapy.

Whereas acutely administered glucocorticoids enhance memory consolidation, at the same time they impair the retrieval of previously acquired information.

After prolonged treatment with high doses of corticosteroids, cognitive deficits, lowering in mental speed and efficiency, a deficit in concentration and poor memory are often observed, in particular, declarative memory and working memory are affected. Human adult studies showed that "working memory" (a frontal lobe function) is more sensitive than declarative memory (a hippocampal function) to exogenous administration of CS, suggesting that other areas of the brain apart from the hippocampus are also involved in corticosteroids-cognitive adverse events.[15]

Cognitive effects of corticosteroids appear to be occasional and may be related to hippocampal and brain atrophy due to reduced blood flow in areas of the brain responsible for cognitive functions. In addition, a correlation was found between prolonged exposure to moderate/high doses of corticosteroids and hippocampal and amygdala atrophy. Some studies reported a decreased activity on single-photon emission computed tomography in left frontal and parietal lobes.

Otherwise, corticosteroids in low doses seemed not to affect adult cognitive functions in both short and long-term courses, and prednisone in low chronic doses did not induce negative effects on hippocampal volume.

Memory impairment was reported in 71% of patients and marked distractibility in 79% of patients. There is evidence that initial cognitive deficits remain relatively stable over time and also after treatment discontinuation, especially among children, while in adulthood alterations were found to be largely reversible within three to eleven months after treatment discontinuation.

In some cases, dementia or delirium may also appear.

3.4 Treatment

First, a preventive approach may be achieved by the use of corticosteroids doses as low as possible, particularly in pediatric patients,

and by tapering long-term therapy as gradually as possible, especially in high dose use.[16]

Generally, steroid discontinuation or dose reduction leads to the disappearance of symptoms in between two weeks and several months. If symptoms worsen rather than improve on reduction or cessation, this suggests that a withdrawal reaction has been triggered. Reintroduction of low-dose CS may be effective.

However, some patients require pharmacological therapy, such as mood-stabilizing drugs (lithium, lamotrigine, gabapentin or valproic acid), carbamazepine (by inducing steroids metabolism and reducing the neurotoxic effects), atypical antipsychotics (olanzapine, risperidone, quetiapine), phenothiazines (promethazine, chlorpromazine) and antidepressants (fluoxetine, venlafaxine). Atypical antipsychotics were found to induce fewer dystonic reactions or other extrapyramidal adverse effects than typical ones. There is evidence that tricyclic antidepressants can actually worsen symptoms. Lamotrigine leads to a significant improvement in declarative memory impairment.

The administration of memantine, a low-affinity antagonist of N-methyl-D-aspartate-type receptors, may provide improvement in declarative memory, but not in mood.

Some antiepileptic drugs have been tested: both levetiracetam and phenytoin showed no effect on declarative memory and cognition, while phenytoin is effective in preventing corticosteroid-induced hypomania.

Electroconvulsive therapy has proved useful in adult and pediatric patients with severe psychoses refractive to medical treatment.

In some cases, lithium and lamotrigine have been used prophylactically.

4. Anticoagulation therapy in venous thromboembolism

Patients with malignancy are at high risk of developing venous thromboembolism (VTE: deep venous thrombosis and pulmonary embolism) and thrombotic events are the second cause of death in cancer patients.

In cerebral tumors, deep venous thrombosis and pulmonary embolism are described in up to 30% of patients. The high frequency of this complication may be explained by the intrinsic propensity of glioblastoma to induce a hypercoagulable state and by the presence of concomitant neurological deficits (such as leg paresis).

The risk of VTE is very high in the postoperative period following craniotomy and during intensive chemotherapy but persists throughout the clinical course.

Other risk factors include age ≥ 60, obesity, glioblastoma histology, absence of the isocitrate dehydrogenase type 1 (IDH1) mutation, large tumor size, subtotal resection, use of steroids, presence of leg paresis, presence of thrombocytopenia or other coagulopathies, vitamin K deficiency and A or AB blood type. Further biological factors have been hypothesized, such as tumor expression of vascular endothelial growth factor and metalloproteinases, leading to aberrant vascularization and vascular permeability.

The choice of the best treatment in patients with primary and metastatic brain tumors with venous thromboembolism is complicated by the fact that antithrombotic agents may precipitate hemorrhage into the tumor with neurological worsening. The rate of symptomatic bleeding into high-grade gliomas in the absence of antithrombotic therapy is approximately 1-3%. Spontaneous bleeding into low-grade tumors is uncommon, except for pituitary adenomas, which are quite prone to spontaneous intratumor hemorrhage.

Among secondary brain tumors, metastasis from melanoma, choriocarcinoma, hepatocellular carcinoma, thyroid carcinoma and renal cell carcinoma have particularly high propensities for spontaneous hemorrhage: up to 37% of patients with brain metastasis from melanoma or renal cell cancer show spontaneous intratumor hemorrhage in the absence of anticoagulation therapy and only 19% in patients with non-small cell lung cancer.[17]

The management of VTE requires a balance between the effectiveness of the treatment, the mortality of untreated pulmonary embolism (about 30% according to some series), the risk of intracranial hemorrhage and, as a consequence, mortality related to intracranial hemorrhage (ICH) (about 0.9%). As the mortality rate related to VTE is much higher than mortality related to ICH, the risk-benefit balance is in favor of antithrombotic treatment.

The incidence of intracranial hemorrhage in cerebral tumors treated with antithrombotic treatment ranges from 1.9 to 23%, and the overall incidence of fatal ICH is less than 1%. The rate of intracranial bleeding differs according to tumor type: in gliomas the rate of intracranial bleeding is much higher, involving about 12-16% of patients, representing a sevenfold higher risk of ICH compared to those who did not receive antithrombotic treatment, while among brain metastasis the risk is not apparently increased by anticoagulation. Interestingly, the survival rate of glioma patients, who developed ICH, was similar to those who did not. The median time between the initiation of anticoagulation and bleeding was twenty-seven days, and

the platelet count at the time of bleeding ranged between 113000 and 338000/µl.[18]

Historically, patients with primary or metastatic brain tumors and venous thromboembolism were often managed with the placement of inferior vena cava (IVC) filters rather than anticoagulation because of the risk of intratumor hemorrhage.

The efficacy of IVC filters for the prevention of recurrent pulmonary embolism in patients with cerebral tumors is not well established: in the general population, the rate of recurrent pulmonary embolism is low (< 5% in most series). However, some studies show that IVC filters may lead to more complications than anticoagulation in patients with cerebral tumors.[19]

According to an old series of forty-two patients with IVC filter, 12% had recurrent pulmonary embolism and 57% developed IVC or filter thrombosis, recurrent deep venous thrombosis (DVT), or post-thrombotic syndrome.[17]

For these reasons, anticoagulation is now generally preferred, while IVC filter placement may be the treatment of choice in patients at high risk of spontaneous bleeding, such as in some types of brain metastasis (melanoma, thyroid carcinoma, renal cell carcinoma, choriocarcinoma), patients with prior intratumor hemorrhage, patients with severe bleeding diathesis (platelet count < 50000/µl), recent bleeding or active bleeding. However, selected patients may be reasonable candidates for anticoagulation such as those who underwent complete surgical resection or otherwise effectively treated brain metastases.

The drug of choice for anticoagulation therapy is low molecular weight heparin (LMWH) rather than warfarin, because of the increased effectiveness in preventing recurrent thromboembolism, the lack of interaction with other drugs and the advantage of not monitoring the level of anticoagulation.

There are no randomized trials that have compared LMWH with warfarin specifically in patients with brain tumors: in a series of 673 cancer patients with VTE, thirty-four patients with primary cerebral tumors were included and in addition a considerable number of patients with brain metastasis. LMWH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding. The incidence of ICH was 0.36% in patients treated with LMWH and 0.92% in patients treated with vitamin K oral antagonists (VKA).[20] The majority of available data were derived from six-month follow-ups, while we are not able to estimate the risk for over six months of treatment.

In a series of eighty-one gliomas (mainly glioblastomas), the cumulative incidence of major hemorrhage after the start of enoxaparin was 17.03% at

one year (greater than a threefold increased risk with respect to patients who were not treated with LMWH), while it was lower (14.36%) when enoxaparin was initiated after glioma-directed therapy.[21]

In a case-control study including 364 patients with cancer-associated VTE (half of whom had a primary or metastatic brain tumor) treated with LMWH with a median follow-up of 6.7 months, the incidence of major bleeding was similar in patients with and without brain tumors (8.6% versus 5% patient-years)[22].

Studies on warfarin in patients with brain tumors also indicate that the risk of tumor-associated ICH may not be significantly increased in patients with primary or metastatic brain tumors if the degree of anticoagulation with warfarin is carefully monitored.

The safety profile of direct oral anticoagulants (DOACs), is not yet well established in patients with brain tumors. Edoxaban, a direct factor Xa inhibitor, was compared with LMWH (dalteparin) in 1050 patients with active cancer and VTE, of which seventy-four patients had a primary or metastatic brain tumor. The trial showed a nonsignificant reduction in the rate of recurrent thrombosis in the edoxaban group but a higher rate of major bleeding. However, the rate of serious bleeding such as ICH was equal between the two groups[23]. In another study, 172 patients with cerebral tumors and VTE were assigned to DOAC therapy (rivaroxaban and apixaban) or to LMWH therapy (mainly enoxaparin). Both in primary brain tumors and in brain metastases, DOACs did not increase the rate of ICH with respect to LMWH. In particular, among primary brain tumors there were no major ICH events in the DOAC group and eight in the LMWH group. Of those who developed ICH, 28% developed midline shift and 11% of patients developed cerebral herniation. Post-ICH 30-days mortality rate was 0% in the DOAC group and 39% in the LMWH group[24]. Among brain metastasis, the 12-month cumulative incidence of ICH was 27.8% in the DOAC group and 52.9% in the LMWH group. While these data support the use of DOACs in patients with cancer, the experience in patients with brain tumors remains quite limited, with some unsolved problems such as the absence of specific antidotes for some of the DOACs and of routine coagulation tests to determine the degree of anticoagulation.

The performance of PANWARDS risk score (previously developed to predict the development of ICH among patients receiving warfarin or rivaroxaban for atrial fibrillation) was evaluated in the same study, showing a sensitivity of 100% and a specificity of 40% in predicting the risk of ICH hemorrhage in antithrombotic treatments in patients with cerebral tumors. The score includes eight variables, which are platelet count, albumin, no

congestive heart failure, warfarin, age, race, diastolic blood pressure, and stroke.[21]

The duration of anticoagulation treatment depends on the continued presence of predisposing factors: an indefinite duration is recommended for patients with primary brain tumors or active systemic malignancy. In patients who are no longer considered at risk for recurrent VTE (grossly resected meningiomas, primary central nervous system (CNS) lymphoma with complete response, systemic malignancy with durable response to chemotherapy) anticoagulation duration is recommended for three to six months and it should be individualized based on an assessment of the risk of recurrence, risk of bleeding, patient values and preference.

Primary prophylaxis with anticoagulants is not generally recommended in patients with brain tumors except in the perioperative period when incidence of VTE is higher (approximately 10 to 15%). The use of pneumatic compression stockings combined with LMWH or unfractionated subcutaneous heparin started 24 hours after surgery is effective and relatively safe. These measures are generally continued until the patient resumes ambulation.

In the PRODIGE trial, the role of LMWH (dalteparin) as primary prophylaxis has been explored: 186 patients were randomly assigned to six months of treatment with dalteparin or a placebo. At six months the dalteparin group had lower clinically evident VTE in comparison to the placebo group, but this difference was not statistically significant. Furthermore, ICHs were more common in the dalteparin group.[25]

A small phase II trial involving forty patients with malignant gliomas treated with prophylactic LMWH (tinzaparin) for a median of about five months reported symptomatic intracranial hemorrhage in one patient and deep vein thrombosis in one patient.[26]

5. Discussion

Patients treated with antiepileptic drugs experience several side effects, and those affecting vigilance and vestibulo-cerebellar function are the most represented.

In general, older AEDs show a worse tolerability profile than newer AEDs.

Of the older AEDs, phenytoin and carbamazepine are the most toxic on the vestibulo-cerebellar system, causing ataxia, dizziness and nystagmus in a high percentage of patients.

Among newer AEDs, oxcarbazepine, eslicarbazepine, lacosamide, pregabalin and perampanel often affect the vestibulo-cerebellar system.

Somnolence is a common side effect in almost all antiepileptic drugs, especially with older AEDs rather than newer. In the last group, pregabalin and vigabatrin affect vigilance in a high percentage of patients. Somnolence is less frequent in patients treated with lacosamide than other newer AEDs.

The main motor symptom described during antiepileptic therapy is tremor, which is due to valproate treatment in most cases, followed by tiagabine and vigabatrin.

Other extrapyramidal symptoms, such as dyskinesias, choreoathetosis, dystonia, hypokinesias and hyperkinesias, are less frequent and may be observed among patients treated with older AEDs (mainly phenytoin) and newer AEDs (such as gabapentin and vigabatrin).

Visual field defects are the main side effect of treatment with vigabatrin; other GABAergic drugs, such as tiagabine, may also cause visual field deficits.

Blurred vision is a common symptom in patients treated with oxcarbazepine, lamotrigine, eslicarbazepine, lacosamide, perampanel, topiramate, valproate, carbamazepine and phenytoin.

Levetiracetam can lead to very frequent psychiatric disorders (non-psychotic behavioral symptoms in up to 38% of patients, psychotic symptoms in 17%); brivaracetam, which has the same mechanism of action as levetiracetam but inhibits more selectively protein SV2A, shows no significant psychiatric side effects, with a frequency similar to placebo. Agitation and irritability are also seen quite commonly in patients treated with perampanel, tiagabine and zonisamide, while depression is a common symptom in patients treated with zonisamide and topiramate.

All available antiepileptic drugs may exert detrimental effects on cognitive function. Memory impairment is very common in patients treated with phenobarbital, primidone, zonisamide and topiramate; it is also described, though less frequently, in almost all remaining antiepileptic drugs.

Concerning CNS side effects of corticosteroids, both behavioral effects (up to 73% of patients), and cognitive deficits (up to 71%) show high frequency rates.

The frequency of psychiatric side effects varies among studies, ranging from 1.3% to 62% of patients according to some series.

Corticosteroid-related side effects depend on several factors, such as age, dose and duration of treatment; in some studies, prednisolone seemed to be tolerated better than dexamethasone, leading to less frequent adverse events. In most cases, steroid discontinuation leads to the disappearance of symptoms; in a low percentage of patients symptoms may worsen after

discontinuation with improvement after reintroduction of low doses of steroids.

In some patients, psychiatric symptoms are severe and require pharmacological treatment with mood-stabilizing drugs, antipsychotics and antidepressants.

The mainstay of treatment of venous thromboembolism in patients with cerebral neoplasms is LMWH, which is preferred to warfarin and DOACs for its efficacy in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding. Nevertheless, there are some promising studies on DOACs and risk of ICH during antithrombotic treatment in cerebral tumors.

In neoplasms at high risk of intratumor bleeding (previous bleeding, recent bleeding, brain metastasis from renal cell carcinoma, melanoma, choriocarcinoma, thyroid carcinoma, severe hemorrhagic diathesis), the use of IVC filters may be an alternative treatment, although related to frequent side effects (recurrent pulmonary embolism and deep venous thrombosis, IVC filter thrombosis, post-thrombotic syndrome).

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CHAPTER 1.7

RADIOTHERAPY AND SPINAL TOXICITY

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Abstract

Radiation myelopathy (RM) is the most devastating late effect that can occur after radiotherapy (RT). Fortunately, this side effect is exceptional. The clinical presentation of RM is aspecific, typically occurring between six and twenty-four months after RT, and RM remains a diagnosis of exclusion. Magnetic resonance imaging (MRI) is the most commonly used imaging tool for diagnosis. Mechanisms of RM are poorly understood, with vascular changes and parenchymal cell loss. Radiation oncologists (RO) must be extremely cautious about the spinal cord dose, and particularly in stereotactic RT or reirradiation. The low incidence of this late side effect complicates the prediction of its occurrence. Conventionally, a maximum dose of 50 Gy is tolerated in normofractionated RT (1.8 to 2 Gy-fractions). Repeat RT treatments lead the RO to consider cumulative doses above this recommendation to offer individualized reirradiation. Some factors increase the risk of RM and must be considered, such as the administration of concomitant radiosensibilizing or neurotoxic chemotherapy. The development of predictive algorithms to predict the risk of RM is promising. However, a comprehensive informed consent regarding risks must be obtained, and the RT prescription should be cautious, and regard the *ALARA* principle (*As Low As Reasonably Achievable*). As the advent of immunotherapy has improved patient

survival, the concept of oligometastatic cancer is increased in daily practice, and stereotactic treatments and reirradiations will be increasingly frequent indications. Predicting the risk of RM is therefore a major issue in the following years and remains a daily challenge for ROs.

Keywords: radiation myelopathy, bone metastases, palliative radiotherapy, reirradiation, spinal toxicity.

Introduction

The radiation oncologist (RO) has only one nightmare: radiation myelopathy (RM). This side effect is devastating and can occur following any radiation therapy (RT) that affects the spinal cord. Fortunately, this side effect remains exceptional[1] because the RO is very cautious before each RT to prevent its occurrence. A treatment cannot start without careful attention to the benefit/risk ratio of RT, represented by the analysis of dose-volume histograms (DVH). The architecture and function of the spinal cord, described as a serial organ-at-risk (OAR), mean that a side effect can occur with a single-point damage (maximum dose = Dmax). In this sense, Dmax is the most important value on DVHs to estimate the risk of spinal toxicity and RM. Several irradiations can affect the spinal cord: irradiation of vertebral bone metastases or other irradiations, such as irradiation of lung or esophageal cancers, head and neck cancers, or pancreatic cancers. Conventionally, the Dmax recommended for the spinal cord is 45 to 50 Gy, for a conventional RT (1.8 to 2 Gy-fractions), for a total of 25 fractions ("normofractionated" RT). Therefore, RM is exceptional after normofractionated RT, but the difficulty is predicting and preventing the risk of RM after reirradiation or severe hypofractionated treatments such as stereotactic irradiation. These reirradiations or stereotactic treatments are increasingly being used since the advent of the concept of oligometastatic cancer[2], and the development of systemic treatments such as immunotherapy[3], that have led to an improvement in overall survival or progression-free survival. This review discusses the pathobiology, diagnosis, prevention and treatment of RM, and offers a

[1] Suppli et al., "Diabetes Increases the Risk of Serious Adverse Events after Re-Irradiation of the Spine."
[2] Otake and Goto, "Stereotactic Radiotherapy for Oligometastasis"; Palma, Louie, and Rodrigues, "New Strategies in Stereotactic Radiotherapy for Oligometastases."
[3] Formenti and Demaria, "Combining Radiotherapy and Cancer Immunotherapy"; Velcheti and Schalper, "Basic Overview of Current Immunotherapy Approaches in Cancer."

practical guideline to predict the risk of RM associated with reirradiations and stereotactic treatments.

Pathobiology of radiation myelopathy (RM)

The pathobiology of RM is still poorly understood. Two classical radiobiological models have been in conflict for many years: glial theory and vascular theory. Several histological changes appear over time after irradiation of the spinal cord, allowing early and late histological changes to be described. These changes mainly affect the white matter of the posterior spinal cord, with a grey matter injury excluding any RM[4]. Usual radiobiological models often involved parenchymal cell loss and vascular changes, but other mechanisms are being investigated. Histologically, many changes are observed in late RM: reaction gliosis, demyelination and necrosis of white matter, and vascular changes in both white matter and grey matter[5]. Necrosis and demyelination frequently occur without vascular modification, while vascular modifications often occur later and with lower doses of irradiation and are more inconsistent and variable over time[6]. In this sense, the theoretical opposition between vascular and glial changes is currently perceived not as an opposition but a probable continuum and dynamic process of glial, vascular and intercellular changes (cytokines)[7]. However, one study showed that selective irradiation of the vascularization without affecting the glial cells still resulted in white matter necrosis[8].

A study identified genes expressed early after irradiation of the central nervous system (brain)[9] in rodents. These genes overexpressed after RT are involved in signal transduction, cell survival, cell proliferation, cell metabolism and protein synthesis. As with any high-dose stereotactic RT, an increase in reactive oxygen species was observed after radiosurgery[10].

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[4] Schultheiss et al., "Radiation Response of the Central Nervous System."
[5] Schultheiss, Stephens, and Maor, "Analysis of the Histopathology of Radiation Myelopathy."
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[7] Tofilon and Fike, "The Radioresponse of the Central Nervous System."
[8] Coderre et al., "Late Effects of Radiation on the Central Nervous System."
[9] Mahmoud-Ahmed, Atkinson, and Wong, "Early Gene Expression Profile in Mouse Brain after Exposure to Ionizing Radiation."
[10] Limoli et al., "Using Superoxide Dismutase/Catalase Mimetics to Manipulate the Redox Environment of Neural Precursor Cells."

The earliest cellular change observed after spinal cord irradiation is the early rupture of the blood-spinal cord barrier (BSCB), as observed after brain irradiation, with apoptosis of endothelial cells[11]. The other early cellular change is the apoptosis of oligodendroglial cells (oligodendrocytes and their cellular progenitors), associated with demyelination, which is the hallmark of late RM (mediated by p53). The apoptosis of glial cells decreases after this early phase, then increases between four to five months after irradiation but cannot be associated with this late apoptosis and late demyelination[12]. This late demyelination is associated with the rupture of the BSCB, but the mechanisms involved are still poorly understood. A change in the architecture of the cell junctions is discussed. Hypoxia (mediated by the Vascular Endothelial Growth Factor (VEGF)) may also be associated with the rupture of the BSCB[13]. Indeed, irradiated with the same dose, non-paralyzed mice have a higher VEGF level than paralyzed mice.

Finally, neural stem cells can also be involved with preserving spinal cord function after high-dose irradiation[14], but the involvement of these stem cells is still poorly understood.

Diagnosis of radiation myelopathy (RM)

RM is a diagnosis of exclusion. The clinical symptoms and imaging tools are not specific. The diagnosis of RM is rarely involved before the delayed phase, whereas clinical symptoms may appear in the first few months after RT. One of the early non-specific clinical symptoms is the L'hermitte syndrome, which is typically characterized by paresthesiae in the back and extremities upon neck flexion. These symptoms are followed by complete recovery after a few months and are not predictive of late RM. Late RM is progressive. Late RM can occur beyond the sixth month after RT, mostly in the first two years after irradiation, but can occur

[11] Li et al., Endothelial Apoptosis Initiates Acute Blood-Brain Barrier Disruption after Ionizing Radiation."

[12] van der Maazen et al., "Repair Capacity of Adult Rat Glial Progenitor Cells Determined by an in Vitro Clonogenic Assay after in Vitro or in Vivo Fractionated Irradiation"; Atkinson, Li, and Wong, "Changes in Oligodendrocytes and Myelin Gene Expression after Radiation in the Rodent Spinal Cord."

[13] Nordal and Wong, "Molecular Targets in Radiation-Induced Blood-Brain Barrier Disruption"; Nordal et al., "Hypoxia and Hypoxia-Inducible Factor-1 Target Genes in Central Nervous System Radiation Injury."

[14] Lu and Wong, Time-Dependent Neurosphere-Forming Ability of Adult Rat Spinal Cord after Irradiation."

beyond the first two years after irradiation. Late RM is typically irreversible, which characterizes its devastating character. The symptoms of late RM range from minor neurologic deficits to a full-blown Brown-Séquard syndrome, with associated spastic hemiplegia, homolateral sensitivity and contralateral thermo-algic sensitivity disorders. However, late RM could be characterized by sensory disorders followed by motor and sphincter disorders. Therefore, symptoms remain non-specific, and late RM should be considered as a diagnosis of exclusion. Other myelopathies should be excluded, such as cancer progression, infection, degenerative or deficiency pathologies.

In order to improve the diagnosis of myelopathy, several imaging tools are necessary. A spinal tomography can be performed. In late RM, few changes are found in the cerebrospinal fluid (CSF). Changes in CSF in late RM could be characterized by a moderate proteinorachy and a lymphocytosis. Magnetic Resonance Imaging (MRI) can help diagnosis. MRI changes in late RM are T1 hypointensity, T2 hyperintensity, T1 contrast enhancement after injection[15], medullary atrophy[16], changes in perfusion or cells diffusion[17] and increased medullary diameter (early medullary edema). Finally, Positron Emission Tomography (PET) findings consist of increased 18-Fluoro-Deoxy-Glucose uptake, with focal increased metabolic activity at the injury site.

Tolerance of the spinal cord

Normofractionated RT

According to a normofractionated RT (fraction of 1.8 to 2 Gy), the dose tolerated by the spinal cord (considered without risk of late RM) is 45 Gy. The risk of late RM is considered as almost zero with 50 Gy normofractionated RT (risk $\leq$ 0.5%), about 5% for a 59.3 Gy normofractionated RT, and about 50% for a 70 Gy normofractionated RT[18]. The main aim of the RO is to optimize the risk-benefit balance of a treatment, in order to improve local control and overall survival without toxicities. The development of static or rotational IMRT (intensity

[15] Melki et al., "MRI in Chronic Progressive Radiation Myelopathy."
[16] Maranzano et al., "Radiation-Induced Myelopathy in Long-Term Surviving Metastatic Spinal Cord Compression Patients after Hypofractionated Radiotherapy."
[17] Keřkovský et al., "Diffusion Tensor Imaging in Radiation-Induced Myelopathy."
[18] Emami et al., "Tolerance of Normal Tissue to Therapeutic Irradiation"; Schultheiss, "The Radiation Dose-Response of the Human Spinal Cord."

modulated RT) allows excellent dose gradients. Moreover, IGRT (image-guided RT) ensures the reproducibility and accuracy of daily treatment, which is essential for IMRT, because of high dose gradients.

The occurrence of vertebral metastases in the context of metastatic cancer is common. The management of these vertebral metastases is based on surgery and RT, because of the BSCB, which limits access to CSF for systemic treatments. Common RT fractionations are 30 Gy in ten fractions over two weeks, and 20 Gy in five fractions over one week. In order to evaluate the late RM risk of hypofractionated RT (>2.2 Gy-fraction), several parameters must be considered.

The assessment of the biological equivalent dose (BED) allows estimation of the risk of spinal toxicity, derived from the application of the linear/quadratic model:

$$BED = D \times [1+d/(\alpha/\beta)]$$

D = total dose; d = fraction dose; spinal cord α/β = 2

The α/β value for the spinal cord is 2, underlying the risk of late toxicity. For the lumbar spinal cord, some authors consider that this α/β value is closer to a value of 4[19]. Because of the devastating irreversibility of late RM and spinal toxicities, caution prevails and α/β value = 2 is considered by the authors. In this sense, a BED of 100 Gy is commonly tolerated, with an estimated 0.1% risk of RM for a BED of 99.32 Gy[20]. Table 1 summarizes common RT fractionation for vertebral metastases and corresponding BED.

Number of fractions	Fraction dose	Total dose	BED (α/β = 2)
15	2.5	37.5	84.37
10	3	30	75
5	4	20	60
4	5	20	70
1	8	8	Non available

Table 1-7-1: Common fractionation for vertebral metastases and corresponding BED

[19] van der Kogel, "Radiation-Induced Damage in the Central Nervous System."
[20] Woolley et al., "Changes in the Retreatment Radiation Tolerance of the Spinal Cord with Time after the Initial Treatment."

Reirradiation

Reirradiations increase the risk of late RM. In addition to the maximum dose tolerated by the spinal cord (45 to 50 Gy, BED 100 Gy), other factors must be considered to predict the risk of late RM. Historically, a delay of more than six months between the first irradiation and the reirradiation was considered essential to estimate the risk of late RM, without any evidence-based medicine. A recovery factor is described and estimated at 50%, mostly one year after the first irradiation. For example, 30 Gy in ten fractions, corresponding to a BED of 75 Gy in the first months, would only correspond to a BED of 37.5 Gy one year after RT. This model of spinal cord recovery is uncertain and should be used with caution. An innovative model has recently been proposed by Woolley et al.[21].The latest version of this model is available online free of charge (Graphical User Interface, updates available at http://thomaswoolley. co.uk/codes). Woolley et al. integrate a time factor ("elapsed time", the time between two irradiations, which may correspond to spinal cord recovery, expressed in years) to estimate dose and fractionation of reirradiation. Another factor is considered by Woolley et al.: a "conservative factor", such as neurotoxic chemotherapy, previous spinal cord surgery (suspected spinal cord injury), comorbidities and age (range from 0 to 20%). This model was developed from data from primates (rhesus monkey), rodents and humans[22], and did not correlate with prospective clinical data. In this sense, even if the model seems promising, it must be used with great caution and each patient should be informed of the risks and benefits of reirradiation.

Simplified Woolley model:
$$\mathbf{BED_{x\%} = (BED\ init/BED\ ret) \times 100\ (x\ t\ x\ C)}$$
$$\mathbf{BED\ ret = (BED\ init \times 100) / BED_{x\%}\ (x\ t\ x\ C)}$$

$BED_{x\%}$ = BED of late RM risk of x%
BED init = BED of first course RT (initial)
BED ret = reirradiation BED (retreatment)
t = time factor (elapsed factor)
C = Conservative factor (chemotherapy, age, previous spinal cord surgery)

[21] Woolley et al.
[22] Ang et al., Extent and Kinetics of Recovery of Occult Spinal Cord Injury"; Jones and Hopewell, "Alternative models for estimating the radiotherapy retreatment dose for the spinal cord"; Woolley et al., "Changes in the Retreatment Radiation Tolerance of the Spinal Cord with Time after the Initial Treatment."

From the model proposed by Woolley, we propose a common clinical scenario of "real life": A metastatic prostate cancer 65-year-old patient, without previous spinal cord surgery, with a vertebral metastasis (T8) already irradiated one year ago (20 Gy in five fractions), presenting a radiological progression, contraindicated for surgical management. Using the Woolley model, with a maximum of 0.1% risk of late RM ($BED_{0.1\%}$ = 99.32 Gy), which T8 reirradiation could be considered?

BED ret = (60 x 100) / 99.32 (x t x C)
For 5 fractions: d = 4.89 Gy ; D = 24.45 Gy ; BED ret = 68.3145
For 10 fractions: d = 3.23 Gy ; D = 32.3 Gy ; BED ret = 72.00525

The analysis of this example using the Woolley model leads us to the conclusion that the theoretical dose of 50 Gy spinal cord tolerance (BED 100 Gy) is not available for reirradiation, considering the time factor between the two irradiations. This corresponds with the trend of current practices of ROs. Another example of reirradiation is discussed in Figure 1-7-1. In a recent publication[23], seven German ROs were challenged with a clinical scenario of a third spinal cord irradiation. The clinical scenario is described: A 51-year-old patient, without major comorbidities, presents a fourth local progression of T5 vertebral metastasis of a clear cell renal cell carcinoma, treated three years ago by a first palliative course of RT (30 Gy in ten fractions), treated two years ago by a second palliative course of RT (30 Gy in ten fractions), and treated six months ago by a palliative spinal cord surgery. The seven ROs of this study were challenged regarding a third course of RT—five ROs would offer a third course of RT, and only two ROs did not consider a third course of RT. Of the five that considered third courses of RT, four considered severe hypofractionated RT (≥5 Gy-fraction, because of the radioresistance of clear cell renal cell carcinomas), and one RO offered normofractionated RT (twenty fractions of 2 Gy). Despite a BED already delivered of 150 Gy according to the usual linear quadratic model (first course: BED 75 Gy, second course: BED 75 Gy), more than half of the radiotherapists challenged considered a third course of RT, expecting a higher clinical benefit compared to the risk of late RM. Indeed, they have probably considered that a progression of the vertebral metastasis without a third course of RT would lead to irreversible spinal cord injury. Another argument for reirradiation is the availability of innovative RT planning, such as intensity modulated RT (IMRT) and image-guided RT (IGRT). Stereotactic treatments also provide strong dose

[23] Nieder et al., "Repeat Reirradiation of the Spinal Cord."

gradients between the tumor and the organs at risk (OAR), to improve local control and overall survival without toxicities, increasing the dose in the tumor, and decreasing the dose to the OAR. For stereotactic reirradiations, a higher level of caution must be provided because of the fraction dose above 6 Gy, exceeding the limit of the linear/quadratic model. Therefore, we do not recommend exceeding a dose fraction of 6 Gy for a second course of RT, in order to estimate the risk of late RM according to the quadratic linear model. Finally, it does not seem appropriate to consider radiosurgery for the reirradiation of the spinal cord, as this exceeds the limits of the linear/quadratic model.

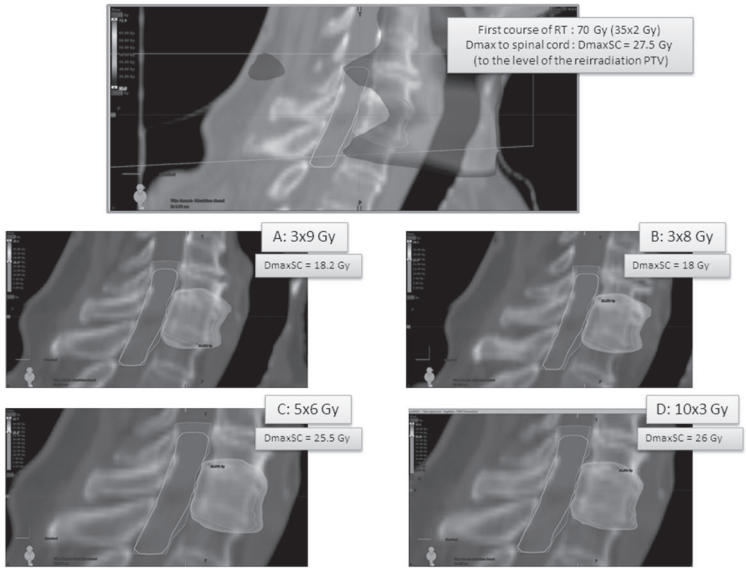

Figure 1-7-1: Isolated C7 spinal metastasis of head and neck squamous cell cancer.
First irradiation 1 year before reirradiation: 70 Gy, 35 fractions of 2 Gy; spinal cord maximal dose in the C7 level = 27.5 Gy.
Four fractionations are discussed for a second course of RT: 3x9 Gy; 3x8 Gy; 5x6 Gy; 10x3 Gy.
According to the Woolley model, we prefer the fractionation D. In light of the Woolley model, we should also discuss other fractionations: 3x7 Gy; 5x5 Gy.
For this treatment, we recommend a stereotactic protocol, using a volumetric modulated arc therapy.

Contributing factors of radiation-induced myelopathy

Many factors influence spinal toxicity and increase the risk of RM. The administration of concomitant chemotherapy is the risk factor most associated with RM, mostly neurotoxic and/or radiosensitizing chemotherapy such as Taxanes, Cisplatin[24], Gemcitabine[25] and Anthracyclines. It is therefore essential to avoid any systemic treatment with reirradiation, especially if this treatment is neurotoxic or radiosensitizing. For children, the administration of chemotherapy in high doses, often very radiosensitizing such as Busulfan, should lead to a higher degree of caution. Some cases of early RM have been described in children for considered non-toxic doses to the spinal cord (<45 Gy)[26].

Other factors promoting RM are discussed. Spinal surgery, mostly if it is recent, is considered as a risk factor for RM. Because of a lack of evidence-based medicine, spinal surgery as a risk factor of RM remains controversial[27]. The level of spinal cord injury is also controversial. Some authors consider that the lumbar spinal cord and the cauda equina are more radioresistant than the cervical spinal cord, with a lower risk of late side effects such as RM, because of an α/β value estimated at 4[28]. A recent retrospective analysis[29] has demonstrated that cardiovascular risk factors are associated with the risk of late RM. Diabetes seems to be closely related and associated with RM (estimated HR=8, multivariate analysis). Other cardiovascular risk factors such as smoking, obesity or high blood pressure should not be underestimated. In this retrospective analysis, a field overlap >6.2 cm increases the risk of RM in univariate and multivariate analysis (HR=3), leading to consider other DVH values. The authors recommend caution for an overlap higher than 6 cm.

Finally, individual radiosensitivity factors should be considered before reirradiation. Some syndromes are associated with increased or dangerous radiosensitivity, such as Ataxia-Telangiectasia syndrome, Progeria (Hutchinson-Gilford syndrome), Huntington's chorea, or Xeroderma

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[24] Bloss et al., "Radiation Myelitis."
[25] Barstis and Black, "Myelopathy after Radiation Therapy and Chemotherapy with Capecitabine and Gemcitabine."
[26] Goldwein, "Radiation Myelopathy"; Raney et al., "Ascending Myelitis after Intensive Chemotherapy and Radiation Therapy in Children with Cranial Parameningeal Sarcoma."
[27] Schultheiss, "The Radiation Dose-Response of the Human Spinal Cord."
[28] Schultheiss et al., "Radiation Response of the Central Nervous System."
[29] Suppli et al., "Diabetes Increases the Risk of Serious Adverse Events after Re-Irradiation of the Spine."

Pigmentosum. Individual radiosensitivity functional assays [30] will be developed in the coming years and could decrease the occurrence of side effects and toxicities such as late RM, improving patient selection.

Prevention and treatment of radiation-induced myelopathy

The functional prognosis of RM remains very poor because most cases of RM are late and irreversible. No treatment provides an improvement once the neurologic deficit is diagnosed. Despite the lack of evidence-based medicine (no randomized trials), corticosteroids are most commonly used. Current hopes are based on the development of treatments able to limit the progression of RM in the early stages. They are based on the physiopathology, mostly on the vascular network (targeting neuroinflammation and hypoxia) and glial cells.

In order to decrease hypoxia, several treatments have been studied. The most promising one seems to be Bevacizumab [31]. Other treatments allowing a reduction of hypoxia have been tried, such as injection of erythropoietin (EPO) [32], hyperbaric oxygen [33] (controversial because hyperbaric oxygen increased the risk of medullar reoxygenation injury). Other treatments investigated decrease hypoxia or the permeability of BSCB (fluoxetine, melatonin, heparin[34] and corticosteroids)[35].

The transplantation of stem cells is discussed to treat RM[36]. Many studies have reported promising results. The cells that have been transplanted are embryonic stem cells[37] (with a risk of induced cancers),

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[30] Ferlazzo, Bourguignon, and Foray, "Functional Assays for Individual Radiosensitivity."

[31] Chamberlain, Eaton, and Fink, "Radiation-Induced Myelopathy"; Levin et al., "Randomized Double-Blind Placebo-Controlled Trial of Bevacizumab Therapy for Radiation Necrosis of the Central Nervous System."

[32] Goldman and Nedergaard, "Erythropoietin Strikes a New Cord."

[33] Sminia et al., "Prophylactic Hyperbaric Oxygen Treatment and Rat Spinal Cord Re-Irradiation."

[34] Liu, Yim, and Wozniak, "Anticoagulation Therapy for Radiation-Induced Myelopathy."

[35] Haddadi et al., "Radioprotective Effect of Melatonin on the Cervical Spinal Cord in Irradiated Rats"; Lee et al., "Fluoxetine Inhibits Matrix Metalloprotease Activation and Prevents Disruption of Blood-Spinal Cord Barrier after Spinal Cord Injury."

[36] Nandoe Tewarie et al., "Stem Cell-Based Therapies for Spinal Cord Injury."

[37] Hess, "Risk of Tumorigenesis in First-in-Human Trials of Embryonic Stem Cell Neural Derivatives"; Kerr et al., "Efficient Differentiation of Human Embryonic

neural stem cells[38], olfactory ensheathing cells[39] and mesenchymal cells[40]. Data from these different studies show that clinical results are associated with early transplantation of stem cells.

Many other therapeutic studies are ongoing. Recently, authors have shown the benefit of prophylactic treatment with Ramipril, an angiotensin converting enzyme (ACE) inhibitor[41].

Discussion

RM remains exceptional. However, as RM is irreversible and devastating, any spinal RT such as reirradiation or SBRT must lead to the greatest caution.

The pathobiology of RM remains poorly described. While two hypotheses seem to be preferred, preclinical studies should progress in order to improve prevention and treatment. The improving knowledge of RM incidence, thanks to several retrospective studies, allows us to develop algorithms to predict the risk of late RM. The proliferation of retrospective studies is essential to obtain some "big data" in order to improve these algorithms. The development of these algorithms will allow larger clinical reirradiation trials to be designed, such as randomized trials. In this sense, the promising algorithm developed by Woolley needs to be evaluated in a phase II or III clinical trial.

Caution should be taken before prescribing spinal reirradiation. The risk/benefit ratio must be well analysed, and the patient must be informed of the risks of such irradiation. All risk factors must be considered. The prescription of concomitant chemotherapy should be avoided. Moreover, at least one week is recommended between any medullary reirradiation and neurotoxic or highly radiosensitizing chemotherapy. Overlap must be

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Stem Cells into Oligodendrocyte Progenitors for Application in a Rat Contusion Model of Spinal Cord Injury."

[38] Yan et al., "Extensive Neuronal Differentiation of Human Neural Stem Cell Grafts in Adult Rat Spinal Cord."

[39] Richter and Roskams, "Olfactory Ensheathing Cell Transplantation Following Spinal Cord Injury"; López-Vales et al., "Acute and Delayed Transplantation of Olfactory Ensheathing Cells Promote Partial Recovery after Complete Transection of the Spinal Cord."

[40] Yoon et al., "Complete Spinal Cord Injury Treatment Using Autologous Bone Marrow Cell Transplantation and Bone Marrow Stimulation with Granulocyte Macrophage-Colony Stimulating Factor."

[41] Clausi et al., "Mitigation of Radiation Myelopathy and Reduction of Microglial Infiltration by Ramipril, ACE Inhibitor."

reduced to a minimum. Finally, the dose must be adapted to the cardiovascular risk, mostly in diabetic patients.

The irreversibility of late RM limits curative treatments. However, there are many promising prophylactic treatments evaluated and that should be considered to reduce the incidence of this serious late toxicity. Treatments decreasing hypoxia and the permeability of BSCB in combination with corticosteroid therapy should be evaluated prospectively in clinical trials. Finally, stem cell transplantation is still experimental, and cannot be considered in clinical trials in humans.

Conclusion

The irreversibility of RM is the RO's worst nightmare. Improving the knowledge of its pathobiology and increasing retrospective and prospective studies are essential to prevent the risk of this toxicity and to improve prescription of spinal reirradiation or stereotactic radiotherapy. The development of predictive algorithms (such as the one proposed by Woolley) to estimate the risk of late RM is promising and may lead to clinical trials, highlighting the impact of applied mathematics on biology and medicine in the twenty-first century.

CHAPTER 1.8

CANCER IMMUNOTHERAPY AND SPINAL TOXICITY

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Abstract

The frequency of spinal cord involvement in cancer immunotherapy toxicities is currently unknown as literature on this topic only exists in the form of case reports. Cases of myelitis have been reported for immune checkpoint-inhibitors and the tyrosine kinase-inhibitor ibrutinib. It remains a diagnosis of exclusion and requires an extensive diagnostic workup including magnetic resonance imaging (MRI) and a number of laboratory tests and cerebrospinal fluid analyses as a broad spectrum of differential diagnoses have to be ruled out. Treatment should be initiated early with corticosteroids as the drug of first choice.

Keywords: transverse myelitis, immunotherapy, side effects, early start of steroids

Introduction

Neurologic toxicity has been reported for various cancer immunotherapies and comprises a broad spectrum of neurologic manifestations, including myelitis. In daily clinical practice, immunotherapy-related neurotoxicity is most relevant for currently evolving cancer immunotherapy-concepts with immune checkpoint-inhibitors and CAR- (chimeric antigen receptor) T cells. Immune checkpoint-inhibitor-related neurologic adverse events were

originally reported with 1% incidence.[1] More recent analyses, however, suggest that the overall incidence of neurological adverse events of any grade is 3.8% in patients receiving anti-CTLA-4, 6.1% in patients receiving anti-PD-1/PD-L1 and 12% in patients receiving a combination of both antibody treatments.[2] In various recent clinical trials on CAR-T cell treatment neurotoxicity represented the second highest adverse event after cytokine release syndrome with up to 28-50% of patients who will develop neurologic complications undergoing CAR-T therapy.[3,4]

The frequency of spinal cord involvement in cancer immunotherapy toxicities, however, is currently unknown and literature on this topic only exists anecdotally in the form of case reports. Cases of myelitis have so far been reported for immune checkpoint-inhibitors and the tyrosine kinase-inhibitor ibrutinib. Despite the high neurotoxicity rate associated with CAR-T cells no specific spinal cord toxicity cases have been published so far. Whether reported cases of encephalitis in the context of immune checkpoint-inhibitor or CAR-T cell treatments were also associated with spinal cord manifestations in the form of encephalomyelitis has not been specified in the literature. In addition, severe relapses of preexisting multiple sclerosis in patients undergoing cancer immunotherapy reported in the literature[5] could also have involved the spinal cord.

When a patient undergoing cancer immunotherapy develops spinal cord symptoms one should keep in mind that neurologic—and especially spinal—toxicity remains a diagnosis of exclusion. Therefore, investigating potential differential diagnoses, including vascular, toxic, metabolic, paraneoplastic, and infectious causes or the presence of progressive oncologic disease (leptomeningeal carcinomatosis, intramedullary metastases or spinal cord compression) has to be ruled out.

The following chapter summarizes current knowledge on cancer immunotherapy-related spinal toxicity based on case reports from literature reviews and institutional experience and gives an overview of the clinical spectrum, diagnostic procedures, pathophysiology and therapeutic approaches.

The clinical spectrum of spinal cord toxicity: cases reported in the literature and institutional experience

Up to now three cases of transverse myelitis (TM) following cancer immunotherapy have been reported in the literature[6–9] and here we report an additional institutional case resembling neuromyelitis optica in a patient being treated with nivolumab and ipilimumab for metastatic melanoma. In two of the three cases the patients developed TM following ipilimumab

monotherapy and one patient developed spinal toxicity after ibrutinib therapy for progressive chronic lymphatic leukemia (CLL).

The first case describes a 62-year-old patient[6] who developed a diffuse inflammatory process after the third infusion of ipilimumab given for metastatic uveal melanoma. The adverse events included uveitis, dermatitis, colitis, and renal failure. Neurologically the patient presented with lower extremity weakness and paresthesias, as well as intermittent urinary retention and fecal incontinence. MRI showed a focal T2 signal abnormality at T9-10. CSF (cerebrospinal fluid) revealed slightly elevated protein, normal glucose and CSF-pleocytosis with predominantly lymphocytoid cells. After differential diagnoses have been ruled out (Table 1-8-1), TM induced by immunotherapy was suspected and ipilimumab was withheld. A course of high-dose intravenous methylprednisolone was given. The patient's symptoms improved throughout a two-week hospitalization. Two weeks after discharge, the patient had a gradual improvement in strength in their lower extremities, but the underlying melanoma progressed.

The second case of spinal cord toxicity during ipilimumab monotherapy[7] reports a 58-year-old man with ulcerated nodular melanoma of the left leg who developed metastatic disease of the vertebral body (T7) with subsequent cord compression. He underwent emergency spinal decompression and postoperatively received radiotherapy. Afterwards he was put on ipilimumab therapy. After the second ipilimumab infusion the patient presented to the emergency department complaining of a one-week history of unsteadiness, weakness of the left leg, constipation and bladder dysfunction. MRI revealed an abnormal T2 hyperintense signal within the spinal cord extending from T7 to L1, consistent with extensive edema without evidence of metastatic disease or cord compression. A PET/CT confirmed a continued complete spinal radiological remission. CSF revealed mildly elevated protein levels and normal glucose levels, with minimal numbers of lymphocytes and no malignant cells. The patient received pulsed weekly intravenous methylprednisone for four weeks with tapering prednisone between dosing. Additionally, he received five days of intravenous immunoglobulins and completed an intensive physiotherapy regimen. There was little clinical improvement; however, repeat imaging with spinal MRI at two weeks and four weeks following admission confirmed a reduction in the T2 signal along the spinal cord. Upon discharge, the patient required a walking frame and a urinary catheter. Unfortunately, he was readmitted eight weeks later with deterioration in muscular strength in the lower limbs and PET/CT indicated disease progression.

The third case reports a 46-year-old male patient who was treated with the tyrosine kinase-inhibitor ibrutinib as a third line treatment for progressive CLL.[8] Ibrutinib was started and well tolerated, resulting in an immediate and complete resolution of B-symptoms and regression of lymphadenopathy. After one month, he developed paresthesias, starting in the left foot and spreading within hours to the right leg, the pelvic floor, and the genital area, accompanied by bladder dysfunction. MRI showed signal enhancements of the spinal cord at the thoracolumbar transition and at height T7. CSF analysis was within normal limits and as other differential diagnoses were ruled out a diagnosis of autoimmune myelitis was rendered. Treatment with 1 g intravenous methylprednisolone over five consecutive days was administered leading to a prompt and continuing neurological improvement while ibrutinib was continued. Ibrutinib was given over a total period of two years without a neurologic relapse or the occurrence of other autoimmune symptoms.

The fourth case, recently observed at our institution, represents a 47-year-old male patient who was diagnosed with a metastatic melanoma on his back with rapid metastatic spread requiring axillary lymph node dissection. First, he was put on interferon therapy (which was stopped due to liver toxicity) and afterwards on nivolumab therapy for eight months followed by ipilimumab. After the third ipilimumab infusion the patient developed pain in his right knee, which was diagnosed as immune-mediated synovitis. Additionally, he developed a right-sided facial palsy. MRI showed enhancement of the cranial nerves. CSF analysis revealed slightly elevated protein (76 mg/dl), normal glucose, and mild pleocytosis (20/µl), with lymphocytic activation. In three consecutive lumbar punctures no malignant cells were present. The imaging findings were interpreted to be immune-mediated and the patient was put on Methylprednisolon 80 mg orally per day with tapering doses. Following steroid treatment the facial palsy recovered completely. Two months later he developed weakness and paresthesias in both legs, as well as intermittent urinary retention and fecal incontinence. Additionally, the patient reported blurred vision at this time point and an optic neuritis was diagnosed. MRI showed an extensive T2 hyperintense edema and contrast enhancement of the entire spinal cord, suggestive of an immune-mediated longitudinal extensive myelitis (Figure 1 A and B). A repeated CSF-study showed an increasing pleocytosis (110 leukocytes/µl, predominantly lymphocytes); again, no malignant cells were detectable and oligoclonal bands were negative. Anti-Aquaporin-4 (anti-AQP-4) antibodies were undetectable. The patient was put on high-dose (1 g) intravenous methylprednisolone for five consecutive days and consequently his neurologic

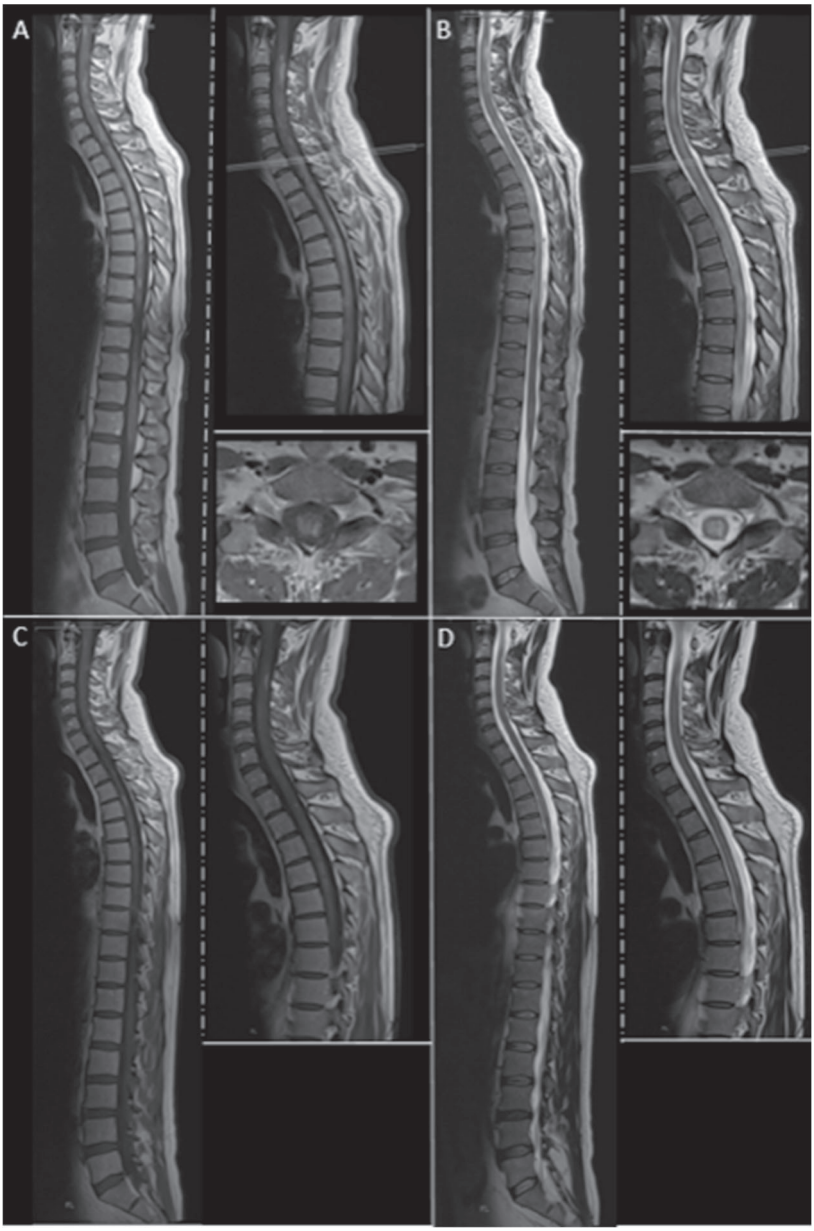

Figure 1:

A. T1 contrast-enhanced spinal MRI shows diffuse contrast enhancement involving the entire spinal cord, punctum maximum from T1-T7 (box shows magnified images of the thoracic spine).

B. T2 weighted images show corresponding T2 hyperintense images thorough the spinal cord, punctum maximum T1-T7.

C. follow-up imaging after high-dose methylprednisolone over five consecutive days. T1 contrast-enhanced spinal MRI shows clear regression of contrast enhancement of all lesions.

D. T2 weighted images also indicate a marked response to corticosteroid treatment.

condition, including vision and spinal symptoms, MR-follow-up study (Figure 1 C and D) as well as CSF findings (protein 35 mg/dl, 9 cells/µl) markedly improved within two weeks. Next, treatment with rituximab will be initiated to reduce the risk of further neurologic relapses.

Pathophysiology

Immune-related adverse events occur when T-cell activation exceeds its normal range and induces inflammation.[2] The pathophysiological pathway remains only partially understood but immune checkpoints play an important role in immune homeostasis, preventing autoimmunity and promoting self-tolerance.[10]

Two out of three immunotherapy-related spinal adverse events reported in the literature so far and in agreement with our institutional case have been observed following treatment with immune checkpoint-inhibitors for metastatic melanoma. Melanoma is an immunogenic cancer that can mount an immune response in the host as melanocytes and Schwann cells are derived from the neural crest and share some similar antigens.[6] An immune response against melanocyte antigens, called molecular mimicry, could therefore also attack similar antigens of the Schwann cells as a result of cross-reaction.[6] Some studies showed that IL-6 levels were markedly elevated in the spinal fluid of transverse myelitis patients. IL-6 is secreted by astrocytes and microglia and binds to oligodendroglia and axons. High levels of IL-6 can cause indirect damage by inducing nitric oxide synthetase in microglia.[11] Some monoclonal antibody-based immunotherapies have been found to increase levels of IL-6, but no studies have yet focused on the association between IL-6 and immune checkpoint-inhibitors. It is known that melanoma cells also induce elevated IL-6 levels.[12] In all cases, however, the onset and improvement of symptoms correlated with the initiation and

discontinuation of immune checkpoint-inhibitors, respectively. Thus, melanoma was unlikely to be the single driving factor inducing TM in these patients.[13]

The tyrosine kinase-inhibitor ibrutinib has been shown to ameliorate CLL-associated autoimmune phenomena but may in turn trigger other inflammatory processes[13,14] inducing pro-inflammatory response of Th1 cells.[15] Neurologic symptoms during ibrutinib treatment have been reported in the elderly population including polyneuropathy, muscle spasms and headache.[16]

Neurologic adverse events such as pauci-symptomatic meningitis may be underdiagnosed in many patients presenting with headaches during the course of immunotherapy.[17] Six patients included in the EORTC 18071 study treated with ipilimumab for stage III melanoma presented with lymphocytic meningitis, frequently associated with flu-like symptoms.[18]

Diagnostics

Rapid diagnosis and treatment initiation are crucial as severe neurologic sequelae can result from spinal neurotoxicity. A thorough and periodic neurologic examination should be part of the follow-up in patients treated with cancer immunotherapy. Spinal MRI, usually complemented by cerebral MRI, is usually the initial study in patients presenting with signs/symptoms of spinal involvement. T2-weighted imaging as well as T1-weighted images with and without contrast constitute the cornerstone of radiodiagnostics (with thin axial cuts through the region of suspected abnormality). Depending on symptom presentation (e.g. stinging belt-like burning pain suggestive of spinal ischemia) imaging studies may require further sequences as, for instance, diffusion-weighted images. According to the literature the finding of involvement of nerve roots, usually in a smooth, non-nodular fashion, with sparing of the surface of the cord should raise suspicion of an autoimmune, inflammatory process[17] as meningoradiculitis is a major differential diagnosis of TM. A summary[1] of the most common neurologic adverse events from twenty-seven cases was reported recently. Meningoradiculitis occurred in six cases and imaging showed typical cranial and/or spinal nerve enhancement in four to six cases.[8] Laboratory analysis of blood should include a differential blood count (eosinophilia may be present if triggered by immunotherapy) and bacterial cultures and a full viral screen. For all PCR and antibody testing please see Table 1-8-1. CSF-studies in patients with spinal toxicity following immunotherapy may show mildly elevated protein, normal glucose levels and slightly elevated leukocytes with a lymphocytic

predominance. Cytology and immunocytological studies are mandatory to rule out neoplastic meningitis. In order to increase the sensitivity of tumor cell detection in the CSF repeated lumbar punctures may be necessary. Nerve conductive studies and EMG may assist in the diagnosis of sensory symptoms or weakness.

Differential diagnoses

The first step is to exclude CNS progression of cancer, seizure activity, and infectious, vascular or metabolic causes of neurologic symptoms. Table 1 summarizes the diagnostic procedures and important differential diagnoses that have to be ruled out prior to suspecting immune-related spinal toxicity.

Differential diagnoses	Clinics, comments	Laboratory analysis	CSF analysis	MRI
Tumor recurrence	Leptomeningeal metastatic spread (frequency of leptometastatic spread of tumors e.g. melanoma in stage IV patients is 22–46%[22]) spinal cord compression by vertebral body metastasis		Elevated protein malignant cells, decreased glucose	Spinal MRI (T1 weighted with and without contrast, T2 weighted sequences)
Infectious meningoencephalitis	Fever, nuchal rigidity, headache, pain	Fungal/bacterial cultures full viral screen for HIV hepatitis B and C virus HSV 1 and 2 (Ab, PCR) VZV, CMV, EBV (Ab, PCR) Enterovirus (Ab) West Nile virus (Ab) Lyme serology JC virus (Ab, PCR) If anamnestic hints occur, test for toxocarosis Trichinosis, cysticercoses,	Fungal/bacterial cultures herpes simplex virus 1 and 2 antibody, PCR HHV 6 PCR VZV antibody, PCR CMV PCR EBV PCR Enterovirus cryptococcal (Ag) West Nile virus (Ab) tuberculosis (culture, PCR) JC virus (Ab, PCR)	Spinal +/- cerebral MRI (T1 weighted with and without contrast, T2 weighted sequences, DWI)

		schistosomosis		
Paraneoplastic syndromes	Confusion, epileptic seizures, memory deficits CAVE: melanoma may be associated with paraneoplastic neurologic syndromes per se	Anti-Ri, -Hu, -Yo if anamnestic hints occur: Purkinje cell Ab (PCA)2, PCA-Tr, ANNA-3, AGNA-1 IgG, amphiphysin IgG, VGKC, calcium channel Abs, GAD65 Ab, NMDA, AMPA, GABA B receptor Abs and acetylcholine receptor Abs.[6]	Anti-Ri, -Hu, -Yo	Spinal +/- cerebral MRI (T1 weighted with and without contrast, T2 weighted sequences)
Myelopathy	Gastrointestinal complaints, polyneuropathy, memory deficits	Serum and urine electrophoresis Serum Vit B12 Vitamin E Copper Folate		Spinal MRI (T1 weighted with and without contrast, T2 weighted sequences)
Radiation myelitis	Talk to radiooncologist and compare radiation field to MRI lesion			

Other immunotherapy-related adverse events	CIDP as a complication of ipilimumab therapy in patients with metastatic melanoma[6,23] (CAVE, melanoma per se can also induce CIDP) GBS has been reported with efalizumab[24] and infliximab[25,26] Multifocal polyradiculoneuropathy (reported during ipilimumab treatment of melanoma.[27]) De novo or relapsed multiple sclerosis, including optic neuritis and acute tumefactive demyelinating lesions have been described under ipilimumab treatment.[5,28–30]	Aquaporin antibodies		Spinal MRI (T1 weighted with and without contrast, T2 weighted sequences)

Table 1: CSF (cerebro- spinal fluid), Ab (antibody), PCR (polymerase chain reaction, HSV (herpes simplex virus), HHV 6 (human herpesvirus 6), VZV (varicella zoster virus), CMV (cytomegalovirus), EBV (Epstein-Barr virus), Ag (antigen), PCA (Purkinje cell Ab), AGNA-1 (anti-glial/neuronal nuclear Ab), VGKC (voltage-gated potassium channel), GAD (glutamic acid decarboxylase), NMDA (N-methyl-d-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, GABA (gamma-aminobutyric acid), CIDP (chronic demyelinating polyneuropathy), GBS (Guillain Barre syndrome).

Treatment

From the experience with this limited number of cases, no specific recommendations can be drawn to treat cancer immunotherapy-related spinal toxicity. Currently, treatment recommendations should follow general guidelines to manage such immunotherapy-related neurotoxicity.[19]

In the case of significant neurologic toxicity associated with immune checkpoint-inhibitors treatment should be discontinued. In all studies, immunotherapy was stopped after spinal toxicity had occurred. The restart of ibrutinib was shown to be safe in the case reported. Steroids are the drug of first choice with the dosage depending on the severity of the neurologic presentation, usually starting with a corticosteroid equivalent of methylprednisolone 1 to 4 mg/kg. Symptom control may require the escalation of corticosteroid therapy to pulse-dose methylprednisolone 1 g daily for three to five consecutive days. All patients presenting with spinal toxicity clearly benefited from steroids. Additional treatment options include IVIGs, plasma exchange, and particularly for patients presenting with longitudinal extensive myelitis, rituximab may be considered, as anti-CD20 treatment proved to be particularly beneficial in neuromyelitis optica.[20,21]

Summary

Given the very limited experience with spinal toxicity of cancer immunotherapy with only three cases reported in the literature and one case observed at our institution, conclusions can only be drawn with great caution. The spectrum of cancer immunotherapy-related spinal cord toxicity may range from mild transverse myelitis to longitudinal extensive myelitis. Interestingly, in two of the four cases more than one immunotherapy-related adverse event occurred apart from spinal toxicity, including other neurologic side effects such as cranial neuritis in the first case and non-neurologic manifestations such as uveitis, dermatitis, colitis, and synovitis in our institutional case. All patients benefited from steroid treatment. Whether cancer immunotherapy treatment can be reinitiated after control of spinal cord toxicity cannot be answered at present. The patient who developed mild transverse myelitis after ibrutinib showed no neurological worsening after the restart of the drug. There is a broad spectrum of differential diagnoses that has to be ruled out and treatment decisions should be discussed in a multidisciplinary team. In light of the increasingly applied new cancer immunotherapies, in particular immune checkpoint-inhibitors and CAR-T cells, we may be more often confronted

with neurotoxicity including spinal cord side effects in the near future and successful management of this specific toxicity will be crucial to maintain a high quality of life in this cancer population.

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CHAPTER 1.9

SYSTEMIC AND INTRATHECAL ANTICANCER TREATMENT AND SPINAL TOXICITY

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Abstract

Spinal toxicity of the meninges, spinal cord, or radices are rare complications of intrathecal or systemic chemotherapy and immunotherapy. It is important to differentiate spinal toxicity due to anti-cancer agents from other causes, such as spinal cord metastases or an infectious meningitis/myelitis. Treatment of spinal toxicity usually involves withholding anti-cancer treatment. In the case of myelitis or polyradiculitis due to immunotherapy, additional treatment with immunosuppressive agents (e.g., corticosteroids) is required.

Keywords: methotrexate, cytarabine, intrathecal, targeted therapy, immunotherapy, arachnoiditis, myelopathy, radiculopathy

Introduction

Spinal toxicity due to anti-cancer agents is a rare complication of cancer treatment which is seen in children more often than in adults. It is described as a complication of both intrathecal and systemic chemotherapy,

in particular after treatment with methotrexate (MTX) or cytarabine for hematological malignancies.[1] Spinal symptoms can vary from mild asymptomatic forms of arachnoiditis/aseptical meningitis to irreversible myelopathy. Acute radiculopathy can occur after intrathecal administration of antibodies such as rituximab (anti-CD20). Polyradiculitis and myelitis are neurologic immune-related adverse events (irAE) that can prevail after treatment with immune checkpoint inhibitors. Spinal toxicity has not been described after treatment with small molecule tyrosine kinase inhibitors.

Toxicity of the spinal meninges, the spinal cord and its radices by anti-cancer agents should be differentiated from other causes of spinal dysfunction in the oncological patient such as metastatic tumor spread to the central nervous system (CNS), paraneoplastic syndromes, radiation-induced toxicity or infectious meningitis/myelitis.

Intrathecal chemotherapy

Methotrexate and cytarabine arabinoside (Ara-C) are frequently intrathecally administered chemotherapeutic agents in the prophylaxis and treatment of patients with hematological malignancies. Spinal toxicity can consist of arachnoiditis and/or myelopathy. Myelopathy is a rare complication of intrathecal chemotherapy in adults, and is more often described in children.[2] Arachnoiditis, i.e., chemical aseptical meningitis, can occur after intrathecal treatment with MTX or cytarabine, and is particularly described after intrathecal treatment with liposomal cytarabine (Depocyte®).

Symptoms

Symptoms of arachnoiditis due to intrathecal chemotherapy include headache, nausea, vomiting, neck stiffness and fever. Symptoms are often observed within 24 hours after intrathecal chemotherapy (MTX or cytarabine) and resolve after steroid administration.

In the case of MTX, the reaction is idiosyncratic, usually does not recur with subsequent cycles of intrathecal treatment and does not seem to be dose-related. Patients with an acute reaction are not predisposed to developing late or chronic neurotoxicity of the drug.

Symptoms of a myelopathy include bilateral leg weakness (and spasticity), pain and sensory loss (often with a distinct level), bladder/bowel dysfunction and gait difficulty.

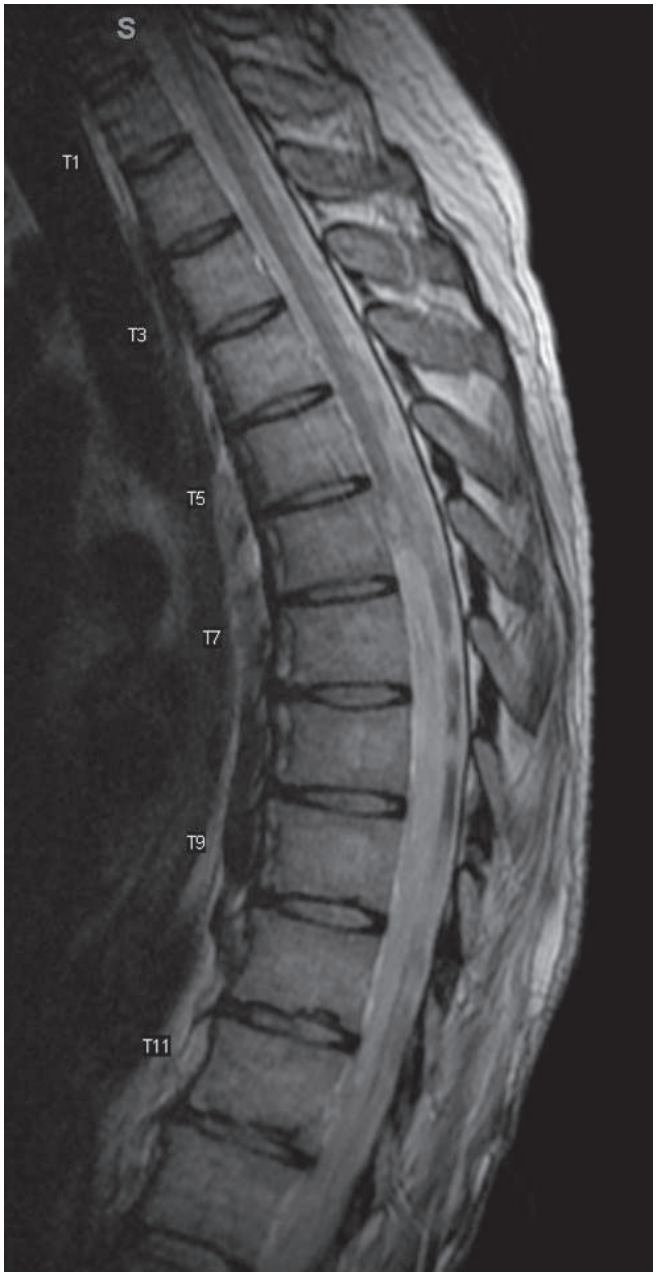
A myelopathy after intrathecal MTX can occur within hours to weeks after administration of the drug.[3] A conus medullaris/cauda equine

syndrome with bladder/bowel dysfunction and saddle anesthesia has been described in patients treated with intrathecal MTX and/or intrathecal cytarabine or with single-agent liposomal cytarabine.[4,5] Neurotoxicity of liposomal cytarabine appears to be more frequent than for intrathecal MTX, although no direct comparison has been carried out between the two agents.[5]

MR-imaging

MRI is the most sensitive radiologic technique in the diagnosis of myelopathy induced by intrathecal chemotherapy. MRI abnormalities include spinal cord swelling, T2 hyperintensity, and contrast enhancement. In the case of MTX-induced myelopathy, longitudinal hyperintensities in the spinal cord involve mostly the dorsal columns and to a varying degree the lateral corticospinal tracts.[6] Enhancement of the conus medullaris and cauda equina nerve roots can be seen.[4] However, (initial) MR-imaging can be normal and MRI abnormalities are not specific.[7] Figure 1-9-1 illustrates MRI spine abnormalities in a patient with a myelopathy after intrathecal MTX and intrathecal cytarabine.

Figure 1 (next page). MRI of the thoracal spine of a patient with acute myeloid leukemia treated with sequential intrathecal MTX (15mg, 8 courses) and intrathecal cytarabine (70mg, 7 courses). A sagittal T2 MR image shows a hyperintense spinal cord from Th6-Th11.



Cerebrospinal fluid

In the case of myelopathy due to intrathecal chemotherapy, the total protein concentration in cerebrospinal fluid (CSF) can be increased.[4] There is some evidence that elevated levels of myelin basic protein (MBP) in CSF reflect spinal cord damage rather than leukemic infiltration, as MBP is a protein produced by oligodendrocytes and is the major constituent of the myelin sheath of axons.[8] The most concerning clinical task is to distinguish spinal neurotoxicity from leptomeningeal leukemic/lymphoma infiltration of the spinal cord. The sensitivity of immunoflow cytometry and cytomorphological analysis of CSF is approximately 80%.[9]

This implies that diagnostic uncertainty regarding spinal toxicity versus leptomeningeal leukemic/lymphoma infiltration may persist in patients with spinal symptoms, an (ab)normal MRI and no malignant cells in the CSF. Other possible causes of a myelopathy are infectious meningitis/myelitis, radiation-induced myelopathy and paraneoplastic myelopathy. CSF examination should therefore include direct examination and culture for bacterial and viral analysis. It is important to know that liposomal cytarabine particles may be mistaken for leukocytes because of their aspect and size. Therefore, it must be specified to the laboratory when a patient is treated with liposomal cytarabine. If patients present with spinal symptoms early in the malignant disease course, paraneoplastic antibodies in CSF and plasma should be measured. Finally, one should realize that a combination of diagnoses (e.g., neurotoxicity and a relapse of leukemia/ lymphoma) can occur in individual cases.

EMG

In the case of spinal toxicity, EMG studies can show acute denervation changes in the leg muscles such as fibrillation potentials or positive sharp waves but usually these do not allow a clear distinction between a peripheral and central cause of the weakness early on in the course of the disease.

Pathological examination

Pathological examination of the spinal cord is, when performed, often unrevealing. Vacuolar degeneration and necrosis without inflammation has been reported in one patient.[10] In another patient, cord destruction, diffuse macrophage infiltration with destruction of the neuropil was found.[11]

Methotrexate

Epidemiology

Aseptic meningitis has been reported in 10-19% of MTX cycles, including 3% Common Toxicity Criteria (CTC) grade 3-4 after Dexamethasone prophylaxis.[12]

Myelopathy after intrathecal MTX is rare with no stated incidence, and it is only described in case reports and case series. It can develop over a variable time and with a variable rate from two days to up to seven months after one or multiple courses of intrathecal MTX.[4] Risk factors include the continuous exposure to chemotherapeutic drugs over a prolonged period of time and the combination with high-dose intravenous MTC.

The combination of intrathecal MTX and radiation therapy probably increases the risk of spinal toxicity.[1]

Etiology

The cause of the spinal toxicity of MTX is unknown. It may be incited by the preservative used in the diluent, but has also been reported in patients who were given intrathecal preservative-free MTX.[13] Alternatively, it may be due to local depletion of folate by MTX. MTX is an antimetabolite drug, known to inhibit the enzyme dihydrofolate reductase which catalyzes the conversion of dihydrofolate (DHF) to tetrahydrofolate (THF). It thereby inhibits the S-phase of the cell cycle. In the biologically active form, 5-methyl THF is a donor of the methyl group for producing methionine and, in turn, S-adenosylmethionine (SAM). S-adenosylmethionine is an essential substrate in the transmethylation and maintenance of normal myelin. As a consequence, intrathecal MTX treatment can induce demyelination by a pathogenic process of local SAM deficiency, resembling subacute combined degeneration due to a vitamin B12 deficiency.

It has been suggested that methylTHFreductase (MTHFR) polymorphism is a risk factor for MTX-induced myelopathy.[14] However, the detection of normal serum MTX levels in patients treated with high-dose intrathecal therapy, routinely used as a clinical surrogate of MTHFR polymorphism assessment, diminishes the likelihood of a MTHFR polymorphism underlying MTX-induced spinal toxicity.

Cerebral MTX neurotoxicity has been associated with increased plasma and CSF levels of homocysteine and depletion of folate. Homocysteine is known to be toxic to vascular endothelium and

homocysteine and its metabolites are N-methyl D-aspartate (NMDA) receptor agonists, which are known to be neurotoxic.[15]

Treatment

To decrease the risk and symptoms of aseptic meningitis/arachnoiditis by MTX, it is advised to start oral Dexamethasone 4mg twice a day as prophylaxis one day before intrathecal injection and maintained for a total of five days. As the risk of meningitis/arachnoiditis by MTX is low, Dexamethasone can also only be initiated once MTX-induced arachnoiditis occurs. In one patient with MTX-induced myelopathy, treatment with high-dose folate metabolites showed promising results.[16] Drachtman et al. reported that dextromorphan, a non-competitive antagonist of the NMDA receptor could be effective in MTX-induced neurotoxicity.[15] However, these treatment approaches are experimental and are not yet applied in clinical practice.

Cytarabine

Epidemiology

Arachnoiditis can occur after intrathecal cytarabine treatment but is more common with liposomal cytarabine (Depocyte®), the sustained-release preparation of cytarabine. The prevalence of arachnoiditis rises in patients treated with liposomal cytarabine to 60% of cycles in the absence of Dexamethasone prophylaxis and decreases to 15-23% of cycles (including 5% CTC grade 3-4) when Dexamethasone prophylaxis is added.[12] It can recur with subsequent dosing of the drug.

Myelopathy as a complication of treatment was described in 2.5% of patients treated with intrathecal liposomal cytarabine.[5] Several studies suggest that the neurotoxicity of cytarabine is significantly enhanced by concurrent intrathecal and high-dose systemic administration of cytarabine, whereas there are no reports of severe spinal cord toxicity when it is administered only systemically. It is therefore strongly advised to avoid simultaneous high-dose systemic and intrathecal cytarabine treatment.[17]

Etiology

Cytosine arabinoside (cytarabine, Ara-C) is a pyrimidine analog that is metabolized within tumor cells into Ara-cytidine 5’ triphosphate (Ara-

CTP), the active metabolite that inhibits DNA polymerase. Decreased DNA synthesis and repair, resulting from the inhibition of DNA polymerase is the primary action when cytarabine incorporates into the DNA. Cytarabine blocks progression from the G_1 to the S-phase and leads to cytotoxicity.

The pathological mechanism of arachnoiditis due to liposomal cytarabine is assumed to be inflammatory. The mechanism behind the neurotoxic effects (e.g., cerebellar or spinal toxicity) may be a direct toxic effect of cytarabine on the axonal and myelin metabolism or possibly be immune-mediated.[18]

Treatment

Oral Dexamethasone 4 mg twice a day is started the day before intrathecal (liposomal) cytarabine administration and maintained for a total of five days to diminish the incidence of arachnoiditis.

Prognosis of spinal neurotoxicity

There is a variable severity of disease and degree of recovery of neurotoxicity induced by intrathecal cytarabine. Arachnoiditis usually recovers after several days of Dexamethasone treatment.

In the case of myelopathy, prognosis varies widely: patients can recover completely, have remaining (mild) spinal symptoms, show permanent neurological disability sometimes with ventilator dependency or die because of spinal cord necrosis.[1] Generally, spinal cord atrophy with normal signal intensity is the long-term radiological outcome on MRI.

Thiotepa

Thiotepa is a chemotherapeutical agent that can be administered intrathecally in the case of leptomeningeal metastases from breast and ovarian cancer or lymphoma. Similar to MTX or cytarabine it can induce a mild, reversible arachnoiditis or in rare cases a myelopathy.

Systemic chemotherapy

Spinal cord toxicity, such as a myelopathy, has been described in patients treated with systemic high-dose MTX, (liposomal) cytarabine, fludarabine and cladribine.

Immune checkpoint inhibitors

Immune checkpoint inhibitors, including anti-cytotoxic lymphocyte associated protein 4 (CTLA-4), anti-programmed cell death (PD-1) and anti-PD-1 ligand (PDL-1) have emerged as a novel treatment for metastatic cancer. They have been found to be beneficial in the treatment of melanoma, non-small cell lung cancer and renal cancer in particular. The activation of the immune system by these agents can lead to immune-related adverse events (IrAEs). IrAEs most frequently occur in the colon, liver, lungs, skin and pituitary and thyroid gland. Neurologic and cardiac IrAEs are reported less frequently. The incidence of neurologic IrAEs was 4% with anti-CTLA-4 (ipilimumab), 6% for anti-PD-1 (nivolumab or pembrolizumab) and anti-PD-L1 (atezolizumab, avelumab or durvalumab) therapy together. The incidence of neurologic IrAEs tends to be higher (12%) in patients treated with a combination of anti-CTLA-4 and anti-PD-1 therapy. Neurological IrAEs that affect the spinal cord and its radices are transverse myelitis and polyradiculitis.[19–26] Other neurological IrAEs are meningoencephalitis, posterior reversible vasoconstriction syndrome (PRES), myasthenia gravis, peripheral neuropathies and myositis. Neurologic IrAEs mostly occur within twelve weeks after starting immunotherapy with symptoms progressing in days.[27] Usually, neurologic IrAEs occur in combination with systemic IrAEs.

Transverse myelitis

Transverse myelitis is described as an inflammatory disease of the spinal cord with acute or subacute, often bilateral motor or sensory symptoms in combination with autonomic deficits and a sensory level. Up till now, transverse myelitis has been described in two patients with metastatic melanoma after treatment with ipilimumab, and in one patient after treatment with ipilimumab and nivolumab. CSF examination showed a mild pleocytosis and elevated levels of protein. Viral and bacterial cultures were negative, and cytology showed no malignant cells. In all patients, ipilimumab or nivolumab was withheld and patients were treated with high doses of intravenous corticosteroids. Two patients showed gradual improvement of strength in the lower extremities, whereas the other patient did not. figure 2 shows the MRI of a patient with a myelitis due to radiation and atezolizumab.

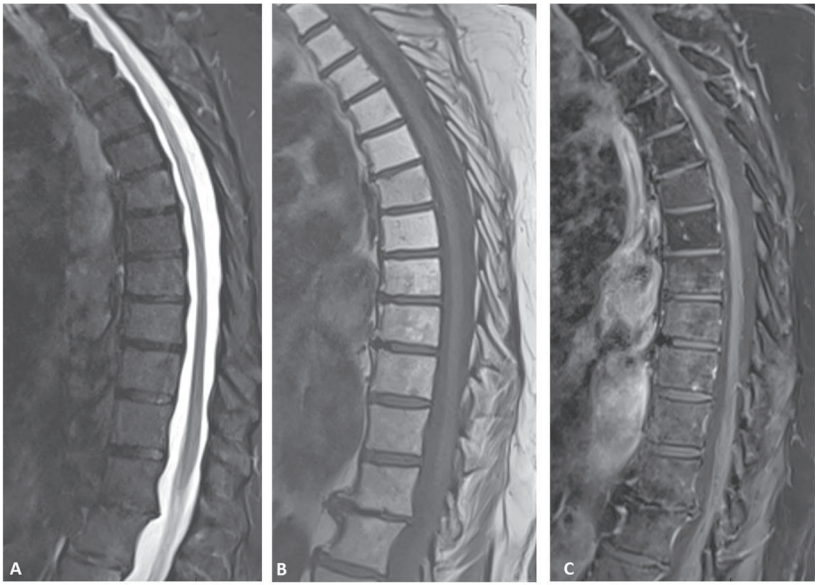


Figure 2. MRI of the spine of a patient with non-small cell lung cancer and myelitis after radiation for mediastinal lymph node metastases (nine months earlier) and seven courses of atezolizumab (anti-PD-L1). A sagittal T2 MR image (A) shows hyperintensity of both the upper and lower thoracic spinal cord (see arrows). A sagittal T1 without gadolinium (B) and with gadolinium (C) shows contrast enhancement of the complete spinal cord.

Polyradiculitis

Polyradiculitis (or meningo-radiculitis) usually starts with radicular pain, followed by sensomotor deficits with proximal and/or distal loss of strength of the legs more than arms. On an MRI of the spine, enhancement of the leptomeninges and/or the conus/cauda equina can be seen. To date, polyradiculitis has been reported in five patients treated with ipilimumab,[22,23,26,28] in two patients receiving pembrolizumab,[24,25] in one patient treated with a combination of ipilimumab and nivolumab and in one patient during nivolumab monotherapy.[24,25] In all patients, symptoms started within twelve weeks of starting immunotherapy.

To confirm the diagnosis of polyradiculitis, it is advised to perform MR-imaging of the spinal cord and CSF examination to rule out (leptomeningeal) metastasis and infection.

MRI may show enhanced gadolinium contrast of radices or the cauda equina roots (Figure 3). CSF examination usually shows elevated levels of protein and a mild, mostly lymphocytic pleocytosis. Electrophysiological nerves conduction study and electromyography may help to differentiate between a polyradiculitis and a demyelinating polyneuropathy.[29]

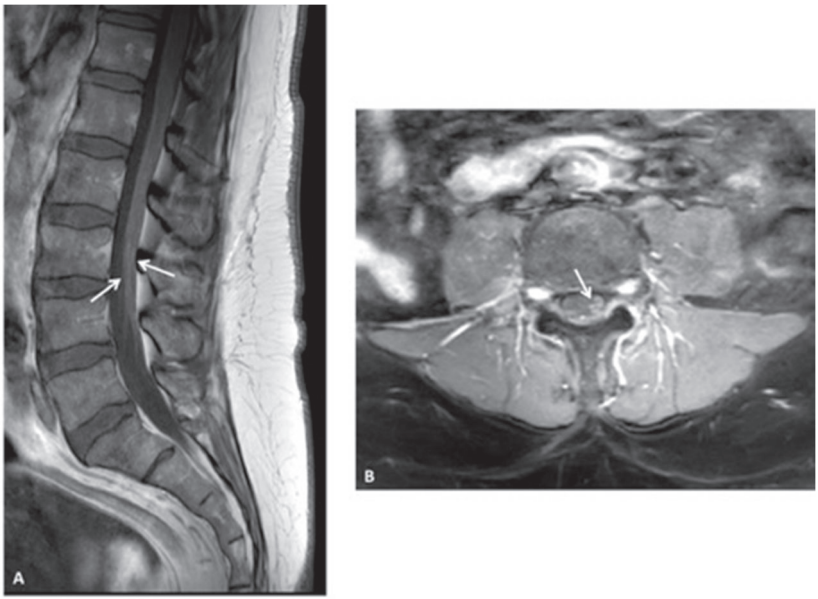


Figure 3. MRI of the lumbar spine of a metastatic melanoma patient with an immune-related polyradiculitis after two courses of ipilimumab and nivolumab. A MRI T1 with gadolinium (sagittal: A; transversal: B) shows contrast enhancement of the cauda equina (see arrows).

A prompt diagnosis of neurological IrAEs is necessary in order to start adequate treatment as soon as possible. At first, immunotherapy should be stopped and treatment with high-dose corticosteroids should be initiated. Patients who are unresponsive or only partially responsive to corticosteroids can be additionally treated with intravenous immunoglobulin (IvIg), plasmapheresis, anti-TNF-alpha antibodies, mycophenolate, or infliximab.[29]

Clinical improvement of patients with immune-related spinal cord toxicity is difficult to predict due to the limited number of patients described but may vary between 40-70%. However, neurological IrAEs

can be fatal and therefore timely and accurate diagnosis and treatment are important. Patients who experience severe neurological IrAEs appear to have higher tumor response rates and increased survival compared to those without IrAEs, even if immunotherapy is withdrawn. Therefore, intensive rehabilitation is warranted in these patients.[29,30]

Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor (CAR)-T cells are increasingly used as a treatment for relapsed and refractory hematological malignancies[31] and are being evaluated for their efficacy in the treatment of solid tumors in clinical studies. Impressive therapeutic response rates are accompanied by significant and often treatment-limiting toxicity.[32] Toxicity predominantly occurs as two related but distinct syndromes: cytokine release syndrome (CRS) and neurotoxicity. CRS is the most common complication in patients receiving CAR-T cell therapy. Clinically, it resembles sepsis with multiple organ failure in severe cases. CRS is triggered by the activation of CAR-T cells when they encounter their target cells. This is followed by a massive release of cytokines, sometimes called a cytokine storm. Symptoms usually start after the first day of T-cell infusion and may peak after one or two weeks.[27] CRS can affect any organ including the nervous system. CAR-T related encephalopathy is the most common CNS toxicity mediated by CAR-T and is responsible for significant morbidity and mortality. Up to 40% of the patients treated with CAR-T cell therapy may develop severe and occasionally fatal neurological symptoms. Frequent neurological symptoms are encephalopathy, aphasia, headache, and tremor.[27] Spinal toxicity of CAR-T cell therapy has not yet been described as a separate entity. However, in a recent study of 100 patients receiving CAR-T cell treatment, three patients developed allodynia and paresthesias of the back, trunk or hemibody. Whether these symptoms are caused by direct toxicity of the spinal cord or by CRS is unclear.[33]

Targeted therapy

Monoclonal antibodies

Rituximab is a chimeric anti-CD20 antibody, which has radically changed prospects for patients with systemic B-cell lymphoma.[34]

As intravenous rituximab has poor blood-brain barrier penetration, intrathecal administration may improve treatment results for leptomeningeal lymphoma. Bromberg et al. described five patients with painful,

lumbosacral paresthesia and paraparesis after intrathecal administration of rituximab (≤25 mg).[35] Symptoms occurred immediately after administration and resolved completely in all patients within a few hours. The exact cause remains unclear, but a direct interaction of rituximab with the spinal nervous structures is the most likely explanation for this adverse reaction.

Trastuzumab is an antibody directed against Human Epidermal Growth Factor 2 (HER2) and is mainly used in metastatic breast cancer. In a small study of patients receiving intrathecal trastuzumab, no neurotoxicity was reported, except for one patient experiencing cervical pain.[36] However, the origin of this pain or involvement of radices was not described. Another phase I study evaluating intrathecal trastuzumab in metastatic breast cancer is pending (ClinicalTrials.gov Identifier NCT 01325207). No spinal toxicity was reported in patients treated with systemically administered monoclonal antibodies.

Bispecific antibodies

Blinatumomab is an antibody that belongs to a new class of agents working as an engager of T-cell activity via binding to CD19 and CD3 (bispecific antibody (BAB)). It is approved for relapsed or refractory B-precursor acute lymphoblastic leukemia. As in CAR-T cell therapy, CRS is a frequent dose-limiting toxicity in treatment with blinatumomab.[37] Besides CRS, neurotoxicity is common (in approximately 50% of the patients), although no spinal toxicity was reported.[38]

Small molecule tyrosine kinase inhibitors

Small molecule tyrosine kinase inhibitors are increasingly used in the treatment of cancer with targetable mutations or translocations. Despite known CNS penetration, neurotoxicity is uncommon and there are no reports of spinal toxicity so far.[39]

Discussion

Although spinal toxicity of anti-cancer agents is rare, it can cause severe neurologic symptoms that impact quality of life and may be irreversible. A myelopathy or cauda equine syndrome can occur after intrathecal MTX but is more often described after intrathecal (liposomal) cytarabine. It is important to avoid concomitant intrathecal and high-dose systemic cytarabine to decrease the risk of spinal toxicity. When a myelopathy occurs during intrathecal chemotherapy, it should be stopped.

In the new area of immunotherapy, clinicians will be more and more confronted with neurologic IrAEs that can also involve the spinal cord (myelitis) and its radices (radiculitis). Withholding immunotherapy and starting immunosuppressive agents such as corticosteroids are the key elements of treatment of neurologic IrAEs, with frequent clinical improvement.

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PART 2:

EFFECTS ON THE PERIPHERAL NERVOUS SYSTEM

CHAPTER 2.1

THERAPY EFFECTS ON NERVE ROOTS

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Abstract

Metastatic nerve root compression is a frequent sign of malignancy.[1] However, effects of therapeutic interventions on nerve root function also have to be considered in differential diagnosis, as the cause determines further therapies. The distinction between neoplastic disease or therapy-related damage has important therapeutic consequences.

The nerve roots can be affected at several sites within the CSF space including the cauda equina, at the exit of the spine or the extraspinal part of the nerve roots.

Clinical symptoms can present as uni-, poly- or pseudoradicular symptoms and different pain syndromes. These symptoms are often complicated by diffuse pain projections or referred pain, sclerotomatic distribution and visceral components.

Pain syndromes in radicular lesions can be separated into local, neuropathic and nociceptive pain but can be mixtures of these.

Surgery and radiotherapy (RT) remain the most frequent causes of side effects, but also intrathecal (IT) chemotherapy (CT) has to be considered. Infections secondary to immunosuppression can also affect nerve roots.

Keywords: Cancer, nerve root lesion, intraspinal, extraspinal, dorsal root ganglion, surgery, chemotherapy, infections

Introduction

The nerve roots are the transition of nervous tissue from the spinal cord into the peripheral nervous system. Adjoining are the dorsal root ganglia (DRGs) and more distally the autonomic fibers. The nerve roots can be damaged within the spinal region, at their exit from the central nervous system (CNS) into the peripheral nervous system (PNS) and before their entry into the plexus or formation of the peripheral nerves.

The frequency of nerve root lesions is not well described as a side effect of tumor therapy. Local metastases in the vertebral column or adjacent structures are the main causes. A clinical presentation of sensorimotor symptoms and pain due to nerve compression or invasion is typical. The pain consists of somatic, visceral and neuropathic pain components.

Surgery or other mechanical interventions can damage the nerve roots at several sites. Sometimes nerve tissue needs to be sacrificed to allow access to or removal of a malignant tumor.

The local effect of RT on nerve roots is not well described. Most reports deal with RT-induced nerve injury, usually the delayed type. Multiradicular[2] involvement by RT can result in camptocormia due to polyradicular damage and dropped head syndrome. RT of nervous tissue also bears the risk of the development of malignant peripheral nerve sheath tumors (MPNST).

The effects of systemic CT on nerve roots are not well described, however, several drugs, in particular platinum drugs, exert their main effect on the dorsal root ganglia (DRG), which is further discussed in the chapter on neuropathies. IT CT can cause nerve root damage, however, despite the infrequent use of IT therapy detailed reports on the intraspinal nerve root toxicity are lacking. Reports describing complications after IT therapy have been published.[3,4]

The emerging use of immunotherapies also causes a variety of nerve root lesions. Currently, these reports are reduced to single cases and observations and the precise spectrum cannot be defined yet.

Hormonal therapies can also lead to root lesions, e.g., lipomatosis after the use of steroids can cause spinal lipomatosis which can affect nerve roots.[5] Osteoporosis due to steroid therapy can cause a collapse of the vertebral body and damage of nerve roots.

Infections, such as herpes zoster and also bacterial infections such as spondylodiscitis occur in immunosuppressed patients and are usually considered to be an indirect effect of cancer.

Table 2-1-1: The nerve roots divided into three compartments, damage due to surgery, RT and chemotherapy.

		Surgery	Radiotherapy	Chemotherapy	Other
Compartment I	Transition of nerve roots, "intraspinal" Part including dura	+	+	Chemotherapy Steroids	Immuno-therapy?
Compartment II	Exit of nerve root, including the dorsal root ganglion	+	+		Infection, (herpes zoster, spondylodiscitis) Collapse of vertebral body due to osteoporosis
Compartment III	Extraspinal-para-vertebral part before forming nerve plexus	+	+		Local tumors

For practical purposes, the damage of nerve roots will be topographically divided into three compartments and in each compartment, the different causes of lesions will be discussed. Due to the vicinity of structures, lesions can overlap these three compartments. Table 2-1-1 comprises the most important side effects of the three compartments.

1) Compartment I

The first compartment is defined by the very proximal anatomical part, as the nerve roots exit the spinal cord and enter the vertebral foramina.

Surgical damage of nerve roots can occur during a spinal surgical procedure and local interventions. Nerve roots may be directly or indirectly infiltrated due to metastasis.[6]

RT can have several effects on the nerve roots. However, histopathological examinations of previously radiated spines remain rare.

In humans, a radiation-induced radiculoplexopathy (RILP) has been described, following RT after several years.[7] The effects of radiation on the cauda equina depend on tolerance doses.[8] Lesions have been reported,[9] and may be difficult to distinguish from a lower motor neuron syndrome.[10,11,12]

The concept of the lower motor neuron syndrome describes a lesion of the second neuron, which is the anterior horn cell. This has been seen in RT but has also been postulated to occur in some diseases such as myeloma and lymphoma.

Damage of the intraspinal course of nerve roots is usually caused by leptomeningeal spread (LC), less frequently by infection. Typically, these lesions are multifocal and have a higher affinity for the lumbosacral roots due to sedimentation effects. LC is often combined with other symptoms such as cranial nerve deficits and CNS symptoms.[13] Histologically, a variety of patterns of damage from infiltration occur, including nodules and sleeve-like compression.

The precise mechanism of nerve damage by IT therapy remains unresolved, except for the development of fibrosis. Lesions of nerve roots in IT treatment are based on neuropathological observations.[14,15]

The sequels of inadvertent IT treatment with vinka alkaloids, and also MTX, are rarely fatal.[16,17]

Dural infiltration is rare in lymphoma and a definite clinical description distinguishing this syndrome from other conditions is missing. Dural infiltration has been observed in lymphoma and other cancers such as breast cancer[18] and can be focal or widespread.

Rarely, immune-compromised patients can also develop polyradiculitis and Guillain-Barré syndrome, also as a paraneoplastic effect.

Immunotherapy

Immune checkpoint inhibitors have been observed to cause mostly inflammatory neuropathies with PD-1, PDL-1 and CTLA-4 inhibitors,[19,20,21] motor polyradiculopathy was observed during pembrolizumab treatment.[22] Also, meningoradiculoneuritis has been reported.[23]

Invasive pain therapy

Other IT-applied drugs, in particular analgetics, can cause side effects.[24] Pseudotumorous inflammatory masses can be caused by opioid infusions and pseudoinflammatory lesions by catheters[25] and adhesions have been described.[26]

Infections

Immunosuppression, RT as well as concomitant diabetes mellitus can predispose for spondylodiscitis,[27] usually presenting as back pain. Local abscesses as differential diagnoses must also be considered.

Miscellaneous other causes of root damage such as chloroma,[28] nerve root amyloidoma,[29] and thickening of nerve roots due to infection have been described.

2) Compartment II

The second compartment comprises the structures from the vertebral column and the adjacent tissue, which are a frequent site of cancer metastasis depending on the type of cancer.[30] Local metastasis can induce a collapse of the vertebral body. Also, steroid therapy can have similar effects. Metastasis into nerve roots is infrequently reported and difficult to detect.[6]

Lymphoma may mimic primary nerve tumors and infiltrate nerve roots.[31] The same applies to leukemia. Solid depositions such as chloromas have been described.[28,32] Multiple myeloma has a propensity to appear/manifest in the vertebral column. Local pain and radicular pain developed due to root compression[33] can appear.

Surgery can damage nerve roots in local interventions such as vertebral body replacement. Also, spondylectomy and vertebral body replacement for metastases can damage nerve roots.

The effects of RT are similar to other compartments. Cavernomas mimicking meningeal spread,[34] and multilevel involvement causing radiation-induced late-onset camptocormia,[35] or dropped head syndrome, have been described.

As in all compartments, RT can induce peripheral nerve tumors (MPNST),[36] which have a long latency until they appear.[37]

3) Compartment III

The third compartment comprises the pre- and paravertebral structures.

The exit area of the nerve roots can be affected by paravertebral tumors. A good example is the Pancoast tumor, where often local or referred pain of the surrounding affected structures can be misleading.[38] Clinically, the involvement of the sympathetic fibers is relevant to distinguish it from isolated nerve root lesions and gives important clinical information on the site of the lesion. In addition, retrograde spread from metastasis and infiltration of brachial plexus tumors needs to be considered.

In particular in the lumbosacral region, due to the limited space, a distinction between root, plexus and peripheral nerve lesion can be difficult. An example is the lumbosacral triangle.[39]

Nerve roots can also be enlarged due to other causes such as amyloidoma[29] and primary nerve tumors, in particular after RT, such as MPNST.

Local infections such as herpes zoster can cause segmental weakness of the trunk muscles[40,41] and shoulder weakness.[42]

Local pain syndromes are usually the hallmark of nerve root tumor infiltration and can appear in all regions of the spinal cord.

Pain in the sacral region

Pain in the sacral region occurs frequently in cancer patients. In addition to metastasis to the vertebral column and nerve roots also metastases to the sacrum must be considered. This is important as the pain radiates and may mimic radicular distribution. The pain can be somatic, visceral and neuropathic.

The treatment of local tumors with RT often exceeds the tolerance dose of the tissue.[43] The toxicity of RT is derived from the RT dose of the

brachial plexus and is more difficult to estimate in the region of the sacrum and sacral plexus.

Surgical interventions in the case of metastatic cancer in the sacrum are rare. It is important to know that the risk of sacral fractures is increased in patients radiated with cervix carcinoma.[44]

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CHAPTER 2.2

PLEXOPATHIES

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Abstract

The nerve plexuses are usually divided anatomically into the cervical, brachial, lumbar, sacral and coccygeal plexus. Most reports focus on the brachial and lumbosacral plexuses. The clinical distinction between tumor recurrence and radiotherapy (RT) damage is a matter of concern for patients with previous cancer treatment.

Traditionally, the distinctions between tumor recurrence and RT effects were made on clinical examination and electrophysiology. Technology has changed the approach and imaging, in particular computed tomography, magnetic resonance imaging, positron emission tomography and ultrasound are helpful in detecting mass lesions affecting the nerve plexus.[1]

The present chapter describes the concept of nerve plexus damage, not only by surgical intervention and RT, but also by drug and immune therapies. In addition to the therapeutic effects, infections and unrelated events also need to be ruled out

Keywords: Cervical plexus, brachial plexus, lumbar plexus, lumbosacral plexus, sacral plexus, coccygeal plexus, surgery, radiotherapy, chemotherapy, immunotherapy, infections

Introduction

Nerve plexuses are proximal nerve structures, forming a complex network linking the radicular and autonomic system to individual (mixed) nerves. The position of the nerve plexus is intermediate between the nerve roots and the peripheral nerves, with the addition of autonomic fibers.

The brachial plexus is in close relation to the apex of the lung and the first rib, the lumbar plexus is ventrally positioned to the psoas muscle, and the sacral plexus is dorsal and in close proximity to the nerve roots and the individual nerves originating from the plexus, which can make a precise topographical localization difficult in this confined space.

The types of therapeutic interventions vary and include surgery, radiotherapy (RT), chemotherapy (CT) and immunotherapy. The main diagnostic challenge is the distinction between tumor involvement, recurrence or metastasis and less frequently the development of secondary tumors as malignant peripheral nerve sheath tumors (MPNST). Also, other unrelated causes such as infections have to be considered.

Furthermore, primary nerve tumors of the plexus[2] can pose an additional differential diagnostic challenge.

Principles of interventions

Several types of intervention such as surgery, RT, CT and other therapies can damage the nerve plexus.

Table 2-2-1: Interventions affecting the brachial plexus.

Plexus	Intervention	Comment
Cervical	Surgery RT Interventions Catheters and tubes	Confined and circumscribed space, vicinity with ENT interventions.
Brachial	Surgery RT CT Immunotherapy	Most frequently: lung and breast cancer. Recurrence versus late effects.

Lumbar	RT? Coagulation? Surgery	Anticoagulation.
Sacral	RT CT Intervention: surgery	Difficult to discriminate between root, plexus and nerve distribution. Pelvic pain.
Coccygeal	?	Loops and connection to sacral plexus.

Abbreviations: RT=radiotherapy, CT=chemotherapy, ENT=ear nose throat

Cancer therapies are based on surgery, RT, CT and also increasingly other concepts such as targeted therapies and immunotherapies. The principles of damage relating to the plexus are briefly summarized:

- Surgery: damage of nerve plexus
- RT: mostly delayed and late effects
- CT: rarely, depending on the type of administration
- Immunotherapy: emerging, usually inflammatory
- Hormonal therapy: rare
- Other: Infection and other non-related conditions.

Although the principles of interventions for nerve roots, plexus and individual nerves are similar, due to the localization, specific aspects will be mentioned.

Surgery

Surgical intervention usually aims to spare the nerve plexus depending on the tumor location. Rarely, individual nerves or nerve plexuses need to be sacrificed for tumor removal. Lesions of the plexus can result in a permanent loss of function and also in neuropathic pain syndromes.

During surgical interventions malpositioning or other inter- and perioperative mechanical traumas (e.g., due to catheters)[3,4] can also occur.

In addition, local interventions for cancer pain[5] can damage the brachial plexus. In dramatic circumstances such as metastasis and pain,

also extensive amputations, damage to the nerve plexus have been reported.[6]

Radiotherapy

The precise principles of RT are discussed elsewhere.[7] For the practical evaluations, type, dose cycles and type of radiation, the time and the characteristics of the RT field need to be considered. Generally, the "upper" brachial plexus is more prone to late effects of RT.

Overall, early and delayed effects are rare.[8] Late effects are more common, including a pre-fibrotic phase[9,10] followed by blood vessel damage. The dimension of RT damage extends beyond pure nerve damage and affects all other structures such as vessels and fibrous tissue and is summarized as radiation fibrosis syndrome.

Chemotherapy

There are several "classical" drugs and also new developments acting on different pathways such as alkylating agents, spindle inhibitors, antimetabolites and others, all of them having a different neurotoxic spectrum on the peripheral nerves. Focal nerve lesions and isolated plexus lesions are rare. Regional CT of the plexus is rarely used and has been used in the treatment of cancer pain.[11]

It is generally assumed that in cases of chemotherapy-induced neuropathy (CIPN), the peripheral nerves and plexus are more prone to pressure and positioning injury. Contrary to the increased appearance of severe neuropathies, following neurotoxic CT in patients with Charcot-Marie-Tooth (CMT), no reports of an increased incidence of plexopathies in those patients have been described. The new group of targeted therapies does not seem to affect the nerve plexus.

Other causes

Neoplastic:

The nerve plexus can be involved by the tumor, either as the primary site, involvement by adjacent tumors, metastasis or diffuse infiltration. The distinction can be difficult clinically, but usually imaging is helpful.

Infections:

Infections such as herpes zoster can cause motor deficits resembling brachial plexus lesions.

Unrelated causes:
Association of RT and neuralgic amyotrophy[12] have been reported.

1) Cervical plexus

The cervical plexus receives fibers from C1 to C4. There are several anastomotic connections with cranial nerves such as the accessory and hypoglossal nerve as well as with the sympathetic trunk. Several branches such as the greater auricular nerve, the transverse cervical nerve, the inferior occipital and supraclavicular nerves innervate the posterior region of the head and neck and can produce pain projection to the head as a misleading sign.

Neck dissections are predominately used in ENT procedures and can cause a variety of individual nerve lesions. Biopsies can also cause iatrogenic accessory nerve lesions. Depending on the site of the lesion, the sternocleidomastoid muscle only or the spinal portion can be affected. A focal lesion of the accessory nerve can result in shoulder pain.

Additionally, scar tissue and "post-radiation-fibrosis" often remain as severe impairments for patients. Neuropathic pain syndromes[13,14] are burdensome.

The combination of RT and CT can also cause multiple cranial nerve lesions,[15] sometimes in addition to lesions of the cervical and brachial plexus.

Rarely after surgery or RT cervical dystonia can develop.[16] Cervical dystonia can also be found in survivors with head and neck cancers and is often progressive but more responsive to treatment options aiming to strengthen and stabilize the cervical musculature. Treatment for cervical dystonia includes neuromuscular and proprioceptive retraining, myofascial release and restoration of range of motion with physical therapy. Medications such as pregabalin, gabapentin and duloxetine have also been found to help with neuropathic pain and spasm.

2) Brachial plexus

Brachial plexus lesions in cancer present with focal neurological deficits, local pain syndromes or both. Shoulder pain and ill-defined cervico-brachialgias occur. Upper sulcus tumors, or Pancoast tumors, also produce pain projections into the elbow and other sites, which can be misleading.

In neoplastic diseases the brachial plexus can be affected as the first sign of cancer (as in Pancoast tumors), or appear later in the course, due to metastasis.

In patients with pre-radiated brachial plexus the distinction between cancer recurrence and RT damage is important.

Pain can be a feature in neoplastic causes at the onset of the disease or as a late effect,[17,18] usually pointing to a neoplastic cause and interventions may be needed. Sensory symptoms and pain in brachial plexus surgery have been observed without prior RT [19] and, based on electrophysiology, nerve damage during the surgical intervention is suggested.

The improvements in RT techniques over the past decades have lowered the number of prominent side effects such as lymphedema[20] and the radiation fibrosis syndrome (RFS).[21]

In addition to sensory symptoms, pain and handicap, the cosmetic and psychological aspects also need to be taken into account.[22]

Surgery

Surgical cancer treatment can result in surgical damage to the brachial plexus. The extent depends on the site of intervention and has a wide spectrum from local damage to the need to sacrifice parts of or the whole plexus to enable tumor removal.

Lesions of the intercostobrachial nerve were frequent and some developed chronic postsurgical neuropathic pain (CPSNP),[23] depending on the technique of surgical intervention and other factors. With new and less invasive procedures the frequency declines. The intercostobrachial nerve originates from several nerve branches, which increases the risk of accidental damage. Patients present with shoulder pain, local pain and often restricted shoulder movement.

Positioning according to the needs of the surgical procedure can cause complete or partial brachial plexus lesions.[4,24,25]

Acute transient brachial plexus lesions may be caused by local hematomas, seromas, drains and local infections following local interventions.

Brachial plexus lesion has been described after a latissimus dorsi flap intervention.[26] Latissimus dorsi flaps also cause spontaneous movements such as twitching in the breast (“jumping breast”) [27], which are socially disturbing.

Radiotherapy

The incidence of RT-induced brachial plexopathy is decreasing due to improved RT techniques.[28] Radiation injury is most frequently observed in breast cancer, ENT tumors and in RT of tumors of the chest, neck or axillary region. In addition to the brachial plexus the recurrent and phrenic nerve can be damaged.[29]

The time of onset varies from months to years in RT-induced brachial plexopathy and is dose-dependent.[30] Conventionally, three types of RT injury are distinguished: early transient, early delayed and delayed plexopathy.

An exception is "ischemic" RIBP which is an exceptional neuropathy of sudden onset, with absence of secondary worsening. Only a few cases have been described and this syndrome is still controversial.

Delayed toxicity usually occurs at the earliest six months after RT. Paresthesias are frequent. RT-induced brachial plexus lesions involve primarily the upper trunk, which may be explained by the closeness to the radiation port. Additionally, skin lesions and lymphedema can appear and add further complications such as carpal tunnel syndrome, although this observation remains controversial.[31]

Electrophysiologically, several distinctive features have been described such as discharges, duplets, triplets, pseudomyotonia and myokymia.

Increasingly, imaging studies such as ultrasound, CT and MRI are used for discrimination. In ultrasound studies investigating elasticity allows the detection of fibrosis.[32]

As in the cervical plexus, the surrounding tissue is damaged, and according to the tolerance dose, additional symptoms appear, which cannot always be distinguished with certainty from myelopathy or nerve damage. Also, damage to the surrounding tissues, which have a variety of RT resistances, can contribute to damage.[33,34,35]

Focal radiation such as in stereotactic surgery and gamma knife therapy

(e.g., for the lung)[36,37] have been described and can cause focal brachial plexus lesions depending on the RT site.

As in all radiated nerves, the risk of development of an MPNST also remains in the radiated brachial plexus.

Chemotherapy

Systemic effects of CT on the brachial plexus are not established. The addition of cytotoxic CT may increase the risk of RT damage.[38,15,39]

Speculatively, patients with hereditary neuropathies such as CMT may be more susceptible to brachial plexus lesions, yet data are lacking.

The use of regional CT is less frequent than systemic applications, but several sites of nerve damage with plexopathies[40,41] have been identified.

Immune therapy

The side effects of immune therapy are different to toxic mechanisms. In immune-mediated neuropathies, either focal or systemic neuropathies can appear.[42] Also, brachial plexopathies have been observed in graft versus host disease[43] and engraftment syndrome.[44]

Lumbar plexus

Lumbar and sacral plexopathies are often termed "lumbosacral plexopathy," a nomenclature which is due to the partial common root supply by the L4/L5 segments but does not reflect the topographical relation of the principal main trunks.

Despite the distinguishable and separated location of the nerve plexus, the lumbar and the sacral plexus are connected with the lumbosacral trunk (fibers from L4/5).

The lumbar plexus is less frequently involved in cancer than the sacral plexus. It is situated ventrally on the psoas muscle and can be affected by hematomas (as in coagulation disorders or thrombocytopenia).

Rarely, malignant local tumors, the "malignant psoas syndrome," damage the plexus. A rare appearance is the "iliac syndrome," where a local hematoma in the iliac muscle causes pain and weakness, often combined with blood loss and anemia. As the main trunk of the femoral nerve is not involved, the patellar tendon reflex remains preserved as a misleading sign. The iliac syndrome is more difficult to detect. Diffuse pain in the groin and rapid blood loss are indicators. The knee jerk can remain elicitable, which can be clinically misleading.

The sacral plexus is confined to a narrow presacral space, with short distances between nerve roots, the plexus and peripheral nerves exiting the plexus. This can make a precise distinction between affected structures difficult.[45] As both sacral plexuses are positioned near the midline focal radiation can affect both sides, which can make the distinction more difficult.

Acute lumbosacral plexopathy following radiation has been described.[46]

Interventions

Surgery, endoscopy and local manipulations, including catheters, can damage local nerves such as the iliohypogastric, ilioinguinal, genitofemoral and pudendal nerves, leading to local sensory and or pain syndromes, which may be difficult to distinguish from other local pain syndromes.

Chemotherapy

As in the brachial plexus, the influence of systemic CT on lesions of the lumbar or sacral plexus is not well explored.

Individual lesions of pelvic nerves: are summarized in the chapter "mononeuropathies" where the peculiar anatomic relations with the sacral plexus are described.[45]

Sacral Plexus[47]

The location of the sacral plexus is presacral and near the midline, which makes bilateral RT damage possible.[48]

Often, osseous metastatic destructions of the sacrum can be found. The local neighborhood of the sacral plexus with nerve roots and the peripheral nerves often makes a precise neuroanatomical diagnosis difficult.

Regional and radiating pain syndromes, mimicking sciatic nerve lesions are often the clinical hallmark. Numbness in the perianal region as well as the involvement of the sympathetic fibers resulting in "hot and dry foot" are clinical signs. Local tumors and recurrences of gynecological and rectal carcinoma have to be excluded, but also other local tumors can occur.

Damage to the sacral plexus can be caused by local surgery to a variable extent. In some cases hemipelvectomy is also performed.[49]

Acute and transient sacral plexus lesions following RT are rare.[50] The occurrence of radiation-induced lumbosacral plexopathy can also present with an almost symmetric neuropathy distribution.[51] The additional involvement of sphincter function to symptoms of neuropathy is suggestive of a sacral plexus lesion.

The time and extent of prior RT treatment of the sacral plexus are important clinical data and determines the effects. Usually, RT lesions do not occur for several months, and are often, but not always, painless and characterized by additional autonomic features. Several RT dose

adaptations have been described in gynecological cervical cancer to avoid nerve damage. For the distinction from neoplastic disease or recurrence, imaging is helpful; EMG helps to characterize RT-induced electrical activity such as myokymia.

Immunotherapy

Few reports on lesions of the lumbosacral plexus have been observed in immunotherapies,[52] see also the chapter on immunotherapies (Chapter 2-4).

Cauda equina

Lesions of the cauda equina are an important differential diagnosis.

Cauda equina lesions can be caused by a variety of focal neoplastic lesions, such as leptomeningeal carcinomatosis, dural spread or local tumor with cauda compression, as well as malignant or osteoporotic lesions. The clinical picture is a flaccid paraparesis, often associated with pain.

In neoplastic involvement, bulky or nerve root thickening can be expected in MRI.

Local recurrence may mimic sciatica.[53]

RT poses a risk of damage to cauda equina fibers.[49] Few reports are available, possibly due to the often advanced state of cancer.

CT is discussed in the chapter on nerve roots (2-1.).

Infections

Infection, due to immunosuppression such as herpes zoster[47,54] can occur. If skin lesions are less prominent or absent, differential diagnosis can be difficult.

Sacral neoplastic lesions

Local tumor spread along regional nerves has been described predominately in prostate cancer and is increasingly described in other conditions ("perineural spread").[55]

Neoplastic local pain syndromes are often difficult to distinguish. Sacral metastasis not only produces local pain syndromes but can also affect sacral nerve roots.

Sacral metastases often present with local pain.[56]

Surgical interventions for sacral metastasis have been described in addition to RT but are a rare type of intervention, bearing the risk of additional root and nerve damage.

Coccygeal plexus

The coccygeal plexus[57] is often neglected but is important for the sensory pelvic innervation and chronic pelvic pain syndromes. The intervention of the ganglion (Walter's ganglion) has been described in pain syndromes.

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CHAPTER 2.3

CRANIAL NERVES AND MONONEUROPATHIES

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Abstract

The anatomical course of the cranial nerves (CNs) consists of parenchymal and intracranial segments, the site of the passage through the skull and the peripheral course outside of the skull. The individual nerves are formed distally of the nerve roots and in addition to motor and sensory fibers also receive autonomic fibers, to form so-called "mixed nerves," which proceed to their target organ. Most of the individual nerves are formed from nerve plexuses. The only exceptions are the intercostal nerves and the dorsal rami which originate directly from the nerve roots. Dysfunction of an individual nerve is generally termed "mononeuropathy."

Nerve damage can develop due to surgical damage, thermic interventions such as hyperthermia and cryotherapy, radiotherapy (RT), chemotherapy (CT) and immunotherapies and also due to the effects of endocrine treatment. Whereas cranial nerve (CN) lesions can occur in a number of conditions, mononeuropathies are usually rare as a direct effect of cancer. Peripheral nerve lesions occur at different sites and for different reasons. They can be confused with radicular or spinal symptoms and need a thorough differential diagnosis.

Keywords: Cranial nerve, mononeuropathy, nerve damage, mechanisms, upper extremity, trunk, lower extremity

1. Cranial nerves

Introduction

The cranial nerves (CNs) have an intracranial section with a zone of transition, they leave the cranium via foramina and have an extracavitary part. The first and second cranial nerve (CN) (olfactory and optic nerve) are generally considered to be an extension of the brain.

The intracranial section of the other CNs has a brain parenchymal (or spinal) part including the nucleus and the parenchymal tracts and an intracranial part at the base of the skull ending at the exit of the capsule of the skull. In addition, there is also a supranuclear control system.

The remaining CNs are considered to be part of the peripheral nervous system (PNS). The extracranial parts of the CNs are mixed peripheral nerves and several have anastomoses either with other CNs, the cervical plexus, or autonomic fibers. Autonomic fibers sometimes change from vessels to several CNs.

The CNs are vascularized by vasa nervorum and in some instances the angiosomic pattern for the support of their vasa nervorum is of relevance. An example is the ascending pharyngeal artery, which supplies several caudal CNs, and can be compromised by embolization.

The subsequent summary (Table 2-3-1) of the side effects of tumor therapy affecting CNs is symptom-based and does not follow the rigid CN classification. A more systematic list of possible causes for CN lesions is given in Table 2-3-2.

Table 2-3-1 CN lesions, symptom-based.

Symptoms	RT	Chemo	Other
Taste and smell	+	+	Frontal neurosurgery
Eye and vision Optic nerve Diplopia Macular damage	+	+	Targeted Immune checkpoint inhibitors
Focal sensory loss Facial pain			Exclusion of neoplastic cause

Symptoms	RT	Chemo	Other
Hearing	(+)	+	
Swallowing and caudal CNs	+	+	Infections, mucositis embolization

Mechanisms

Damage of CNs can be caused by surgical interventions inside and outside the skull. In general, intracranial lesions are predominately caused by neurosurgical interventions. Examples are facial and trigeminal nerve lesions such as after an operation on cerebellopontine tumors, or any other access in interventions at the base of the skull.

Surgical lesions outside of the skull are more likely due to other interventions and depend on the respective site. In particular, the neck region can be affected, but also all regions such as the base of the skull, the orbit and the cavities (e.g. sinus) and the facial skull (e.g., parotid surgery).

Surgery

CN lesions within the cranial vault or at the exit are usually part of neurosurgical procedures.

Interventions outside of the cranium refer to surgery in the orbit and the ear nose and throat (ENT) cavities. The main site of surgical lesions after their exit from the skull is the region of the neck, in particular the spinal part of the accessory nerve, causing shoulder dysfunction and pain.[1,2]

Of minor functional impact, but contributing to discomfort and pain, are lesions of the nerves of the cervical plexus.

Radiotherapy

CN damage due to RT covers a different spectrum and can involve the optic nerve and the chiasm, which is usually carefully protected from the RT beam. When radiation-induced optic neuropathy affects the anterior part of the optic nerve an acute “ischemic anterior optic neuropathy” with acute loss in visual acuity can occur. However, chronic damage to the

posterior portion of the optic nerve or chiasma is the most frequent "posterior radiation-induced optic neuropathy," with gradual impairment of visual acuity over the years after RT.[3] Other causes of RT damage are retinopathy[4] and maculopathy.[5]

A variety of RT-induced CN lesions has been described in RT of nasopharyngeal tumors.

Trigeminal neuropathy develops after cavernous sinus tumor irradiation, which is mainly targeted with meningioma and chordoma. Facial paralysis occurs after RT for parotid cancer.

Other CNs can be endangered, however, this can result in a long-term complication. Ionic radiation, also used for other purposes, causes damage to optomotor and trigeminal nerves.[6]

Late motor effects such as myokymia of facial muscles occur rarely[7, 8] as well as neuromyotonia of the extraocular muscles.[9,10,11,12] Also, tongue myokymia is a rare occurrence.[13]

Focal muscle weakness can also result from a radiation recall syndrome. Furthermore, calcification of the masseteric muscle and fibrosis have been observed, as well as trismus.[14]

Rarely, RT induces large vessel damage which can result in a devastating aneurysm, so-called "blow-out" syndrome, which can damage several CNs after rupture of the artery.[15]

According to Delanian[16] the nerve most frequently affected by RT is the hypoglossal nerve, followed by the glossopharyngeal and the vagus nerve; swallowing difficulties can occur.[17] Also, the vocal cords can be involved.[18] The hypoglossal nerve has a complex pathway from the brainstem to the tongue. Several extracranial sites of lesions have been described.[19] Tongue muscle atrophy can be observed, often as hemiatrophy.[20] Other injuries involve the glossopharyngeal nerve with swallowing impairment or the vagus nerve after thoracic RT for breast cancer.[21]

RT of the head and neck muscles can result in multiradicular lesions and produce a "dropped head" [16] syndrome.

Less frequent are RT-induced nerve tumors, or malignant peripheral nerve sheath tumors (MPNST), which can appear after a latency of several years.[22,23,24]

Cryotherapy and hyperthermia

Cryotherapy and hyperthermia are thermic interventions that can cause focal CN lesions, depending on the site of intervention.

Chemotherapy

Clinically CT-induced CN lesions are rare and a matter of exclusion, except isolated neuropathies in vinca alkaloids.[25] Several reports describe an optic nerve neuropathy in taxane chemotherapy.[26]

Acute, reversible and transient neurotoxicity manifests with paresthesias and dysesthesias in the perioral region which can be provoked by cold and may increase with cumulative dose (>540 mg/m^2) by oxaliplatin. Less frequently cumulative toxicity appears as jaw and eye pain, visual and voice changes in addition to sensory neuropathy.[27]

Local CT can produce isolated damage of CNs and resembles the pattern of focal and compartmentalized CT as observed elsewhere in the body. An example is optic nerve damage, after periocular cisplatinum injection.[28] Multiple CN lesions occur (Table 2-3-3) and the combination of CN dysfunction can be valuable for localization.

Immune therapies

The side effects of immune therapy are discussed in Chapter 2-4.

Immune therapies can affect the optic nerve and vision,[29] produce hearing loss[30] and can also induce headache.[31]

Other mechanisms

Vascular interventions

Local interventions such as embolization to treat base of the skull tumors can affect the vasa nervorum supplying the caudal CNs. The vascular supply of the caudal CNs is provided by the ascending pharyngeal artery. The embolization of this vessel can cause a dysfunction of lower CNs.[32]

Hemorrhage

Hemorrhage into CNs has been observed in leukemia,[33] but can also occur in therapy-related coagulation disorders.

Infections

The function of the caudal CNs can be severely impaired by local infection, resulting in swallowing problems. This is termed the "mucosatoxic syndrome."

Muscle function

Also, muscle function can be impaired. Rarely, directly by muscle metastases (e.g., in the eye muscles) or by calcification.[34]

Jaw pain

Jaw pain is a frequent feature of the treatment of osteoporosis, with biphosphonates and other substances such as VEGF inhibitors.[35,36]

Table 2-3-2 Causes of CN lesions in cancer patients.

	Neoplastic	Surgery	RT	CT	Other	Multiple CNs
I			+			
II	+		++	+	Targeted therapy, Immunotherapy	
III, IV, VI	++			+		+
V sensory motor	 +	+ +	+	+		
VII	+	+	+-		+	+
VIII		+	+	++	Immuno-therapy	+
IX	+	+			Infection	
X	+	+			Infection, autonomic disorder	+

XI		++	?			+
XII	+	+	+		+	

Abbreviations: RT=radiotherapy, CT=chemotherapy, CNs=cranial nerves.

Table 2-3-3 Multiple CN lesions can be a source of difficult differential diagnosis.

	Site of lesion			
	Parenchymal	Within cranium capsule	Exit zone	Extracranial
Neoplastic	+	+		+
Surgery		+		Various interventions, ENT
RT	?	+	+	Various: fibrosis, -blow-out syndrome
CT		IT therapy?		Focal CT
Immune-mediated				
Vascular				Blow-out syndrome
Muscle involvement				+

Abbreviations: RT=radiotherapy, CT=chemotherapy, IT=intrathecal, ENT= ear/nose/throat.

2. Mononeuropathies

Mononeuropathies are rare side effects of cancer therapy and even rarer as a direct effect (metastatic) of cancer. However, several neoplastic options such as oligoradicular involvement, plexus lesions and rarely solid nerve metastasis[37] into peripheral nerves, diffuse infiltration (lymphoma and leukemia) and nerve encasing metastasis can occur. Also, amyloidomas in conjunction with multiple myeloma have been described.

The most common cancer-associated mononeuropathies are listed in Table 2-3-4.

Table 2-3-4 Most common individual nerve lesions (mononeuropathies).

	Neoplastic	Surgery	Mechanical (e.g. positioning, catheters etc.)	RT	CT	Other	
Median nerve	Neurolymphomatosis		+			Hormonal therapy	
Ulnar nerve			+			Cryotherapy	
Radial nerve			+				
Intercostobrachial nerve		+	+				
Axillar nerve		+	+				
Long thoracic nerve		+	+			Infection	

Intercostal nerves	+	+				Infection, herpes zoster, cryotherapy, thermo-ablation	
Abdominal nerves		++	+				
Pelvic nerves: e.g. Pudendal, obturator nerve	+	++		+	+		
Femoral nerve		+	+				
Sciatic nerve	+	+	+	+			
Peroneal nerve		+	+				
Tibial nerve		+					

Abbreviations: RT=radiotherapy, CT=chemotherapy.

Surgery

Surgery can cause direct nerve damage either unintentionally or deliberately when nerve structures are sacrificed to enable a better approach to the tumor, or within a resection or amputation of an affected part of the body. Any surgical intervention on a peripheral nerve or plexus results in scar tissue and fibrosis and can cause secondary complications such as neuroma formation and neuropathic pain syndromes.

An example of surgical damage is the intercostobrachial nerve, which can be damaged by lymph node extirpation of the axilla due to its variable course. Local neuropathic pain syndromes can develop. As this occurs often postoperatively, it can be confused with local infection and swelling. Consecutively, also shoulder movement is reduced due to local pain, which makes the discrimination difficult and is a good example of the need for pin-point discrimination of symptoms and signs of peripheral deficits in cancer patients. Other examples are the intercostal nerves, the long thoracic nerve and the cutaneous nerves of the lower abdomen and pelvis.

Mechanical damage

Peripheral nerves can also be damaged by malpositioning and hypoperfusion. Also, the local application of thermal interventions (heat and cryotherapy) can damage peripheral nerves. Hyperthermia[38,39] has been shown to damage peripheral nerves experimentally.

Mechanical damage to nerves can also be caused by venipuncture,[40] tubes, catheters and endoscopic investigations. Loss and amputation of parts of the body as in the limbs can result in phantom pain.

The principles of radiation-induced nerve injury are also valid for peripheral nerves. As an early effect also a transient conduction block (CB) following RT has been described in NCV studies.[41]

The development of RT injury is usually delayed for several months or years. In addition to fibrosis, vascular damage of nerve vessels has also been noted, resulting in dysfunction and also neuropathic pain syndromes.

Local RT of extremities and primary nerve tumors

RT of primary nerve tumors: RT is part of the treatment protocols of several nerve tumors. Some, but not all tumors are radiosensitive. Any RT intervention can increase fibrosis, induces vasculopathy and also risks the development of an MPNST. Also, collateral damage to peripheral nerves

located in the vicinity of tumors (e.g., sarcomas of limbs) may cause mononeuropathies.

Post-RT effects on nervous tissue can also cause fasciculations and myokymia.[42]

Contrary to chemotherapy-induced neuropathy (CIPN), the issue of individual nerve lesions (mononeuropathies) has not been well described in the literature. For vinca alkaloids, individual nerve lesions were observed. For the other groups of chemotherapeutic agents it can be assumed that the nerves damaged by CIPN may be more susceptible to local irritation, in particular to pressure.[43] In hereditary neuropathies such as Charcot-Marie Tooth neuropathies, the risk of developing a more severe form of neuropathy has been described,[44,45] however, no systematic studies are available for individual nerves.

In some instances of local perfusion of tumors isolated limb nerve lesions have been observed. Also, local pressure on the nerves (cuffing and ischemia) may have the principal role in this damage. A rare issue is local CT, targeted at limb perfusion such as on the peroneal nerve.[46]

Immune therapy

Vasculitic neuropathies presenting as multiplex types are rare but have been described with immune therapies.[47]

Hormonal therapy

Hormonal treatment with tamoxifen in breast cancer patients seems to be associated with an increased risk for carpal tunnel syndrome (CTS).[48] Although observed infrequently, symptoms can be confused with arthralgia[49] and other musculoskeletal pain syndromes which occur in some CT, in particular taxanes.

Hemorrhage

Rarely, hemorrhages into peripheral nerves have been observed.[50] Local neoplastic infiltrates, nerve metastasis and amyloid depositions rarely occur.

Graft versus host disease

In graft versus host disease (GVHD) multiple entrapment syndromes have been described.[51]

Paraneoplastic causes

Paraneoplastic involvement of individual nerves is not usually considered part of "classical" paraneoplastic syndromes. More relevant seems to be the influence of weight loss [52] for an increasing risk of pressure palsies.

Peripheral nerve lesions

Subsequently, individual nerve lesions of the upper and lower limbs as well as the trunk will be delineated separately.

a) Upper extremity

The upper extremities (UE) can be damaged by positioning, pressure and cuffs as well as catheters, intravenous or intraarterial interventions. Extravasates of CT can cause local tissue damage and subsequent fibrosis can also cause nerve damage.

Also lymphedema, in particular in the UE[53,54,48,55] can have negative effects on the peripheral nerves and cause multiple entrapment syndromes.[56]

RT is usually only applied for local tumors of the hand and arm. Focal irritation such as CB or secondary late lesions such as fibrosis or nerve tumors can occur. The local perfusion with CT of tumors can result in focal nerve damage.

Also, prior CT may cause increased susceptibility to nerve damage.[57]

Other conditions resembling peripheral nerve lesions

In some patients, usually drug dependent, a "hand foot" syndrome appears[58], late effects from CT include Raynaude syndrome,[59,60] finger necrosis can be caused infrequently by gemcitabine.[61] Also nail changes, resembling autonomic disorders, following CT were described.[62]

Musculocutaneous nerve

Weakness in the distribution of the musculocutaneous nerve can be caused by muscle[63] or nerve metastasis.[37]

Median nerve

Median nerve lesions at the wrist, such as CTS have been observed due to lymphedema,[53] which are frequent with aromatase inhibitors.[54,48,55] Rarely, a transient CB due to local RT has been observed.

The frequency of CTS is also increased in multiple myeloma,[64] also amyloid depositions can appear.[65] For the other individual nerves, apart from the general mechanisms, no specific lesions were identified.

Ulnar and radial nerve

The ulnar and radial nerves are usually damaged by malpositioning during interventions. Cutaneous nerves of the forearm can be affected by mechanical interventions and effusions.

b) Trunk

The apical trunk is connected with the cervical/brachial plexus and the caudal part with the lumbosacral plexus. Anatomically, the pulmonary cavity is separated by the diaphragm from the abdominal cavity, which is caudally confined by the pelvic floor. Nerve lesions can occur on the surface of the trunk (such as by surgery or RT), or within the trunk (e.g., recurrent tumors).

RT is more confined to the superficial parts of the trunk, however more extensive "axial neurological injuries" have also been described as a rare complication in "dropped head" syndrome and late-onset cervico-scapular muscle atrophy combined with cervical paraspinal and shoulder girdle muscle weakness.[66]

CT with prior RT can induce radiation recall syndromes[67,68] appearing as focal muscle weakness.

Surgery can damage peripheral nerves in all parts of the trunk. Examples are the long thoracic and thoracodorsal nerves[69] in lung surgery and the intercostobrachial nerve in breast surgery. Intercostal nerves can be damaged by thoracic interventions. In the region of the neck and

shoulder branches from the cervical and brachial plexus can be affected such as in approaching the apex of the lung ("Pancoast surgery").

The abdominal nerves can be damaged not only by surgery but also by endoscopy and minimally invasive procedures such as endoscopic interventions.[70]

The nerves around the pelvis can be damaged in surgical interventions (such as ilioinguinal, iliohypogastric, genitofemoral nerves). Traumatic and surgical peripheral nerve lesions are often the source of neuropathic pain and often ill-defined symptoms, due to overlap in the distribution of these nerves.

Radiotherapy

Focal lesions (e.g., brachial plexus), large RT fields can cause complex damage, not only of the nerve, but also the surrounding tissue.

Physical Heat/Cold therapies

Local heat, general hyperthermia and cryotherapy are used for local interventions, as therapy[71] and can cause nerve lesions. Intercostal nerve damage (as used in pain therapy) can be associated with cryotherapy and radiofrequency ablation.[72]

Other interventions

Large local perfusions, such as local CT in the peritoneum can cause generalized neuropathy. This is documented by several observations but no systematic study.[73]

Dorsal scapular nerve

The dorsal scapular nerve to the rhomboids or the suprascapular nerve to the supraspinatus and infraspinatus are important for shoulder function in many cancer survivors.[74] They can be damaged by extensive RT, such as in examples of the mantle field RT.

Phrenic nerve

The phrenic nerve can be damaged by surgery, CT and RT,[75,76,77] Phrenic-RT[78] and by thermal interventions such as cryotherapy.

Diaphragmatic weakness can also develop after cervical high-dose RT for head and neck cancer. Also RT of the brachial plexus can result in a phrenic nerve paresis.[79]

CT: Phrenic nerve lesions have been described in capecitabine CT[75] but also as a late effect of RT[78] and in thalidomide treatment.[80]

In patients treated with immune checkpoint inhibitors, phrenic nerve lesions were described.[81]

Nerves of the pelvis

In addition to lesions of the sacral plexus, which is discussed in the chapter on plexus (chapter 2-2), several individual nerves of the pelvis can be affected. These are usually mainly branches from the lumbar plexus such as the ilioinguinal, iliohypogastric, genitofemoral,[82] femoral, obturator nerve , or from the sacral plexus such as the pudendal[83] posterior cutaneous femoral, sciatic nerve and other branches. The "inner" pelvic nerves, some of which are purely autonomous, such as the hypogastric plexus, the hypogastric nerve, the inferior hypogastric plexus and the splanchnic contribute to pelvic dysfunction and pain syndromes. The precise topography in MRI has been established for most, but not all nervous structures.[84,85]

Pelvic surgery can damage these nerves and other interventions such as RT can potentially have a more diffuse and less focused site of damage. It is important to follow the anatomical distributions, in particular of the autonomic nerves, which reach far beyond the sacral plexus. Conventional NCV/EMG, except for the pudendal nerve investigations,[86] are usually not helpful and are not universally available. Multimodal electrophysiological monitoring may help.[87] Lesions of the obturator nerve will be discussed below.

Symptoms include various pain syndromes, bladder, anal sphincter and sexual dysfunction. Urinary dysfunction may be as high as 27%, sexual dysfunction may also reach 11–55%. RT of patients with prostate cancer also seems to increase the risk of incontinence.[88] Surgical interventions need to consider the pelvic nerve anatomy.[89]

The issues of incontinence and also sexual dysfunctions are of major importance for the patient. Several studies on sacral surgery and sacrifice of the sacral nerves[90] indicate that unilateral preservation of the sacral nerve roots may sustain continence.

Pelvic surgery is not only important for rectal cancer but is also performed for several other cancer types such as prostate,[91] cervix uteri,[92]

urinary, bladder[93] and others. Information on risks and recovery seem to accumulate from prostate cancer.[94]

Pain syndromes in the pelvis are often difficult to discriminate and define. The issue of peri-and postoperative pain, recurrence and infiltration and also sequelae of RT are often difficult to discriminate. Pain in and around the pelvis is an important issue in cancer pain.[95,96,97]

Pudendal nerve

The nerve originates from S2-S4 and passes through the sciatic foramen and pudendal canal. Its terminal branches are the inferior rectal nerve, the perineal nerve (innervating the external urethral sphincter muscles, bulbocavernosus, perineum, and dorsal aspect of scrotum/labia), and the terminal branch of the pudendal nerve (providing sensory innervation to the clitoris, glans penis, dorsal region of the penis). Pudendal nerve dysfunctions, such as sexual dysfunctions or incontinence have been described after RT of the pelvis, and in particular in prostate cancer.[98,99,88]

Obturator nerve

The obturator nerve can be damaged in prostate and gynecological surgeries. It can clinically result in the characteristic sensory deficits, but also weakness in the adductor muscles resulting in a gait disorder. The nerve can be also be directly affected by cancer[100] or involved in perineurial spread.[101]

c) Lower Extremities

Peri-surgical procedures can damage peripheral nerves and muscles which can be caused by local pressure usually during malpositioning. Compartment syndromes have been described in isolated limb perfusion[102] and also in pelvic surgery.[103] Additional coagulation disorders can cause hemorrhages in muscle and nerve.

Surgical lesions of the lower extremity nerves are rare. The most likely nerve lesion would be the femoral nerve at interventions at the groin.[104,105,106] Lesions of the sciatic nerve are rare, as well as of its distal branches. The obturator nerve is rarely damaged in pelvic surgery or in prostate surgery. Due to its rarity and often discrete presentation, it can be overlooked. Imaging the distribution of muscle damage can help[100,107,108] localizing the source of damage.

The lower extremity is also prone to damage by pressure and by positioning in patients with progressed disease and in a cachectic and emaciated state. In addition, a concomitant neuropathy, e.g., by chemotherapy, may make pressure lesions more likely. The term "malignant foot drop" has been used in conjunction with local nerve tumors. An increase of peroneal lesions in cancer patients has been systematically evaluated, and possibly related to weight loss.[109]

Other mechanical possibilities for nerve damage are lower leg lymphedema[110] and also pressure stockings.[111]

Radiotherapy

Lower limb nerves can be within the field of radiation. In particular, RT of pelvic tumors might cause damage to the proximal parts of the femoral and sciatic nerve. The lesion is usually delayed or late and is caused by vasculopathy and fibrosis.

These nerve trunk lesions have been described as the result of local RT[112,113,114] usually have a delayed onset and are caused by fibrosis.[115]

Chemotherapy

Local perfusion of the lower limbs can cause mononeuropathies. This is a rare type of intervention, compared to systemic CT, but needs to be considered if weakness occurs after regional CT.

Immunotherapy

Mononeuropathies per se, or in the context of multiplex neuropathies, have been described.[116] The frequency and relevance are not clear yet, as large studies are missing.

Vasculopathy

Vascular interventions, in particular embolization or regional CT[73] have been described. Edema[117] and compartment syndromes can occur.[118]

Individual nerves

Depending on the etiology such as positioning, surgery, RT, CT and immunotherapies, individual nerves can be affected. In clinical practice, the appearance of a lower leg nerve paresis, without any reasonable

therapeutic interventions also needs the consideration of a drug-induced vasculitis (immune checkpoint inhibitors), and of a rare neoplastic cause such as meningeal carcinomatosis, nerve metastases, encasement of nerves by a tumor, in hematological diseases neurolymphomatosis[119] and neuroleukemiosis.

Other Complex disorders

More complex dysfunctions of the lower extremities result in sensory and motor symptoms, gait pain and gait disorders. Rarely, “tingling” and paresthesia can be an initial symptom of nerve damage.[120] Despite a possible association with treatment, other causes, in particular neuropathies and entrapment syndromes, need to be ruled out. A common source of concern is the hand and foot syndrome,[58] although erythromelagia can present as a rare paraneoplastic syndrome, it has not been observed due to chemotherapy

Pruritus

Painful pruritus can be a presentation of neuropathic pain. Following RT of the sacral plexus the detection of the hot and dry foot[121] can be helpful in regard to etiology.

Stem cell transplantations, Graft vs Host Disease:

Following blood and stem cell transplantations several neuromuscular complications have been reported.[122,123,124,125]

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Chapter 2.4

Polyneuropathies and Ganglionopathies due to Neurotoxic Anticancer Treatments

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Abstract

The involvement of peripheral nerves by chemotherapy is a major potentially dose-limiting adverse event of a wide variety of anticancer agents. Chemotherapy-induced peripheral neurotoxicity (CIPN, including both peripheral nerves as well as dorsal root ganglia neuron damage) can be long-lasting and only partially reversible. Preventive or symptomatic treatments are usually ineffective, and new neuroprotective agents are proposed that would either prevent or ameliorate CIPN.

CIPN usually presents as symmetric sensory impairment, which is distributed in a stocking and glove-like distribution. Pain can be a feature but motor symptoms are scarce. CIPN affects can be quite debilitating, and significantly reduce the quality of life of affected patients and limit their daily life activities.

Usually, most drugs have a cumulative neurotoxic effect, while in only a few cases do early, acute symptoms can occur. Worsening of CIPN after treatment withdrawal can be a clinically relevant event, particularly after the administration of platinum drugs (the “coasting” effect).

New immune modifying has shown potential for inducing immune-mediated neuropathies, resembling Guillain-Barrè Syndrome.

Overall, the proper identification, assessment and management of CIPN is emerging as a prominent clinical problem, particularly in view of the increasing number of long-term cancer survivors and of the possible impact of chronic CIPN.

Keywords: Peripheral neuropathy, dorsal root ganglia, long-term toxicity, adults, children, recovery, economic cost

Introduction

Cancer remains a major cause of death in developed countries, with an estimated annual incidence of at least fifteen million new cases worldwide and approximatively eight million deaths, with marked regional differences. India, China, and other East and Central Asian countries account for nearly half of them (The Cancer Atlas, http://canceratlas.cancer.org/). According to the American Cancer Society data released in 2018, cancer is the second most common cause of death in the US, exceeded only by heart disease, and 1.7 million new cancer cases are diagnosed in the US every year (excluding carcinoma in situ of any site and basal cell or squamous cell skin cancers). Prostate, lung and bronchus, colon and rectum, urinary bladder in men and breast, lung and bronchus, colon and rectum, uterus in women are the most frequent cancers, accounting for more than 50% of new cases each year. These cancers (and several other less frequent malignancies) are potentially treated with antineoplastic drugs able to induce damage to the peripheral nervous system.

Moreover, cancer treatment has rapidly evolved over recent years and this favorable evolution, coupled with more active screening programs and more precise diagnostic tools allowing earlier and more effective identification of cancer, has resulted in a marked improvement in cancer patients' survival (Fig. 1). In fact, over the past three decades, the 5-year relative survival rate for all cancers combined increased by 20% among white people and 24% among black people (data released in 2018 by the American Cancer Society).

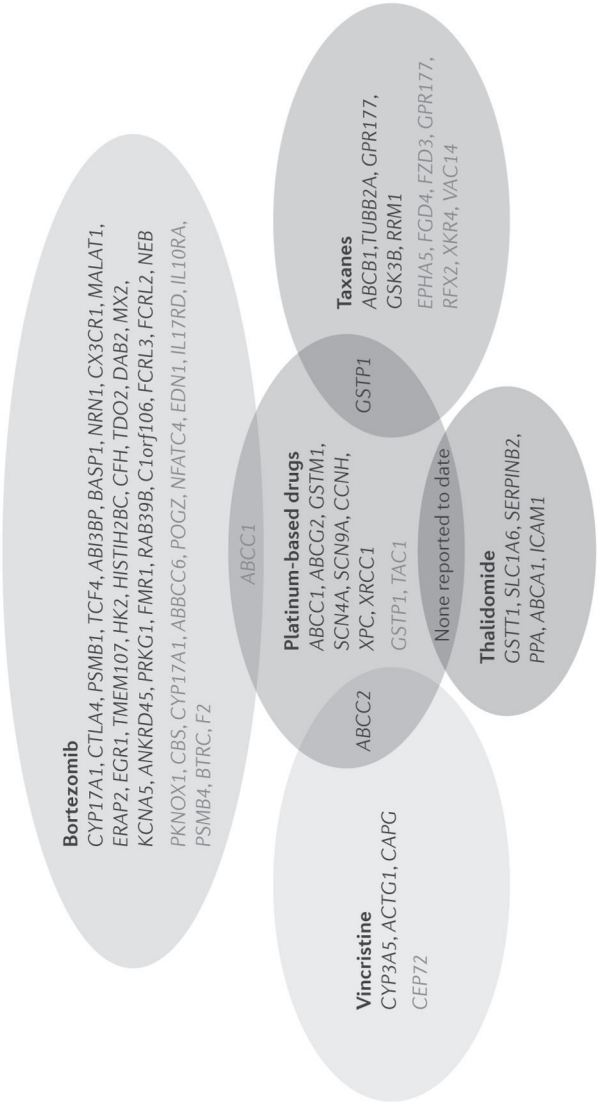


Fig. 1 Examples of the large number of genes potentially associated with CIPN. Several genes investigated since 2011 are associated with an increased risk of chemotherapy-induced neuropathy (CIPN), classified by neurotoxic agent in this figure. Gene names in red were identified in genome-wide association studies; those in black were identified in candidate-gene studies (reprinted with permission from Argyriou AA (87))

This improvement in cancer survival, and the consequent increased number of patients living after exposure to neurotoxic agents, allowed the emergence of the problem of long-term/permanent side effects of treatment. Cancer patients are prepared to deal with serious side effects during antineoplastic treatment, and generally they can accept them since they are fighting against a life-threatening disease. However, once they complete their treatment and are cured (or at least enter the long-term survival period), the importance of persistent treatment-related side effects increases and in most cases they request more careful management, particularly if these toxicities have an impact on daily life activities and have no effective symptomatic treatments. Long-term treatment-related neurological complications are among the toxicities that more severely compromise the quality of life (better "quality of survival") and the functional status of patients. Central nervous system side effects are frequent and, among common toxicities of anticancer drugs, one of the most challenging and debilitating is damage of the peripheral nervous system, and impairment may be permanent.

The clinical features of chemotherapy-induced peripheral neurotoxicity (CIPN) are fairly well established, at least for the drugs with a longer history, and awareness of its importance is increasing among oncologists, pain specialists, neurologists and, in general, healthcare providers. However, in several settings, the complexity of the problem is still underestimated, and most aspects are not properly considered by the treating physicians or by basic researchers. For instance, the interpretation of the widely used acronym "CIPN" that is frequently used to describe "chemotherapy-induced peripheral neuro*pathy*" is sometimes misleading and the description as "chemotherapy-induced peripheral neuro*toxicity*" is definitely more pertinent. The difference between the two definitions is remarkable, since it implies a precise understanding of the real target of antineoplastic drugs within the peripheral nervous system and of the pathogenesis of the signs and symptoms experienced by patients, which might be secondary to damage not only of the peripheral nerves, but also of the dorsal root ganglia (DRG), and possibly even of the spinal cord. In this chapter, the main features and the pathogenesis of CIPN secondary to the administration of different neurotoxic drugs, the socio-economic burden of CIPN, and the available therapeutic options for preventing its onset or treat its symptoms will be described.

Clinical relevance of CIPN and open issues

The development of more effective supportive treatments (e.g., growth factors to prevent hematological side effects, anti-emetic drugs to alleviate nausea and vomiting, physical prevention to limit hair loss, etc.) has allowed a remarkable reduction of the impact on patients' daily life of several previously dose-limiting side effects due to anticancer chemotherapy. Unfortunately, this is not the case for CIPN, which has now become one of the most severe side effects of many treatments. The impact of CIPN on patients' daily quality of survival is now clearly emerging.[1] Moreover, patients often believe that the real burden of CIPN on their quality of life is underestimated by healthcare providers.

There is now a fairly general agreement among healthcare providers that CIPN is frequent and that it might be a severe medical problem, since it can cause treatment delays or even withdrawal, induce symptoms which are difficult to treat and interfere with daily life over a long period of time, in several cases life-long.[2] However, several issues are still unsettled in clinical practice, including more homogenous education and agreement on the assessment among examiners.[3] These differences in CIPN recognition affect not only daily clinical practice but also the results of clinical trials, which are often inconsistent.

For instance, an important issue is that CIPN can be the cause of intense pain, but the real spectrum and importance of pain relevance in CIPN has not yet been reliably assessed,[4,5] even if in a cross-sectional analysis of patients with stable symptoms its incidence based on self-reported questionnaires was remarkably high.[6] Methodological aspects are potentially important since, still too frequently, the interpretation of the symptoms reported by patients is confused and misleading. In fact, disturbing but not really painful, symptoms (e.g., paresthesias) are often considered in the assessment, thus including a possible source of bias in the results. In most clinical trials the planned assessment methods were not specifically designed to capture the presence of pain, although it is particularly relevant, at least with some drugs such as bortezomib and taxanes. Moreover, another reason for the difficult characterization of this symptom is the presence of pain of different origins in cancer patients.

Another problem that may also lead to inconsistent results in clinical trials could be the incomplete acknowledgment of the presence of acute symptoms and signs during the course of the same treatment (e.g., cold-induced paresthesias, cramps and muscular spasm in oxaliplatin- or myalgias in taxane-treated patients)[7] overlapping with chronic symptoms. This aspect is highly remarkable since there is no firm evidence that acute

and chronic symptoms/signs have the same pathogenesis, however, their relevance is definitely different for patients.

An additional and troublesome aspect of CIPN is that its severity is extremely variable among patients treated with the same drugs/schedules and bearing cancers of the same type and grade. This variability led to the hypothesis that individual genetic background could be a determinant for a more severe course of CIPN, and several pharmacogenomics studies have been performed in different treatment settings. Despite extensive investigation and the identification of a number of putative candidate genes (Fig. 2-4-1), it should be admitted that at the moment this approach has failed to provide reliable information for clinical practice. The only case where a clear increase in susceptibility to vincristine-related CIPN can be predicted through genetic screening is the presence of Charcot-Marie-Tooth disease, an inherited neuropathy associated with different gene mutations with a prevalence of approximately 1:2500 cases in the US.[8]

Several methodological reasons, besides the absence of a genetic difference explaining the different susceptibility to CIPN, might be at the basis of the overall negative results of these investigations. In fact, the earliest genetic studies were mainly focused on targets more likely to be related to the antineoplastic activity of the investigated drugs (e.g., DNA repair mechanisms, influx/efflux cellular systems, resistance genes), and it is possible that they simply failed to identify proper targets. Moreover, several studies were performed in small cohorts of patients, and they were neurologically assessed with improper methods. Several of these possible sources of bias have now been more clearly identified, and this is reflected by the improved design of the latest studies so that it is likely that a definite answer will be provided quite rapidly. Fig. 2 summarizes the results of a critical analysis of possible errors that flawed CIPN pharmacogenomics studies.

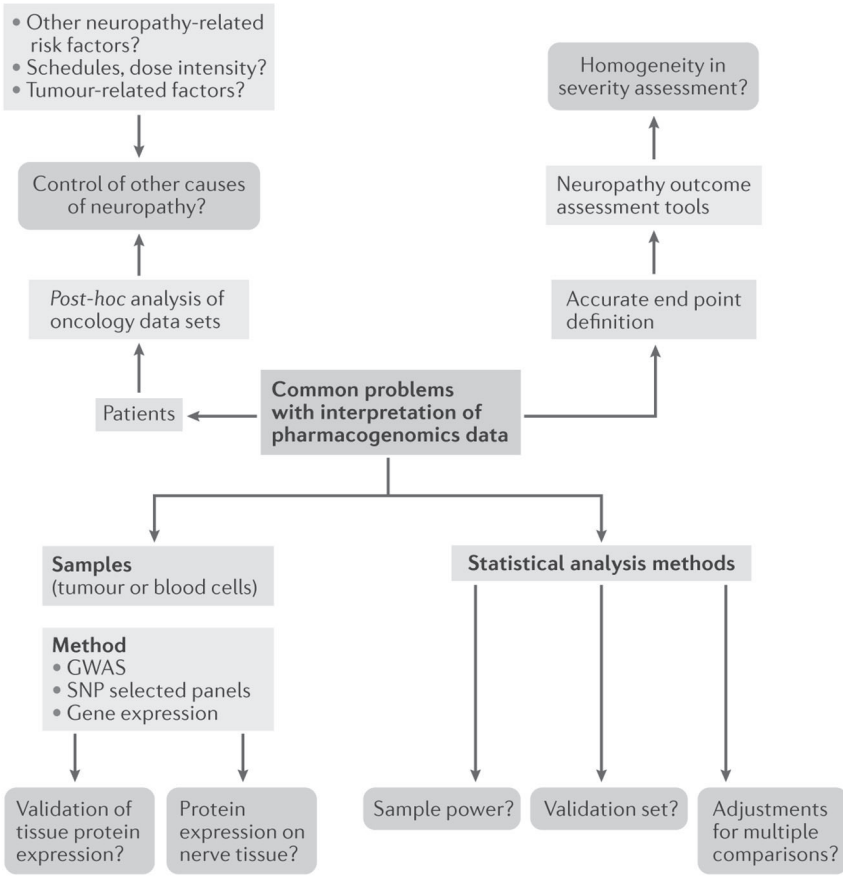


Fig 2: Summary of several methodological drawbacks of CIPN pharmacogenetic trial design which should be improved in future studies, to enable the management of CIPN to be informed by genetic associations. GWAS, genome-wide association study; SNP, single nucleotide polymorphism. (reprinted with permission from Argyriou AA (87)

Based on all the previous observations there is no doubt that CIPN is not only a clinical challenge but also a typical multidisciplinary medical issue. However, while this aspect is becoming more and more accepted in the research setting, a real multidisciplinary approach still remains difficult to implement in clinical practice for logistic, economic and cultural reasons, and real and effective collaboration among specialists is still

infrequent. Finally, another critical aspect that should be carefully considered and properly addressed in order to have a really comprehensive approach to its management is the very different perception of CIPN that exists between healthcare providers and patients.[3]

The pathogenesis of CIPN

The pathogenesis of CIPN has been investigated mostly using rodent models (Fig. 3, see colour centrefold) or neuronal/neuronal-like cellular systems *in vitro*.

The first *in vivo* model of chronic CIPN was established in 1992 using cisplatin,[9] and since then several different laboratories have contributed to the design and evaluation of animal models reproducing the neurotoxic effect of all the conventional anticancer drugs, apart from thalidomide.[10] Most of the studies on the pathogenesis of CIPN are driven by the deeper knowledge of the mechanism of action of anticancer drugs against tumor cells that are highly replicating, are supported by altered and increased angiogenesis, and can develop effective modulation of their capacity to cope with the drugs leading to resistance. However, these features are not all shared by peripheral nervous system cells (particularly by neurons), and this might raise concerns on the appropriateness of this approach. Therefore, a parallel search for "unexpected" targets of neurotoxic anticancer drugs (at least in some cases) should be pursued. For instance, for several neurotoxic anticancer drugs, mitochondrial damage and subsequent oxidative stress affecting DRG neurons have been proposed, but while this hypothesis is based on fairly sound rationale in some cases, the evidence is less convincing with other drugs.[11]

Platinum-based anticancer drugs are alkylating agents capable of causing nuclear damage. This damage, such as to DNA cross-links, is the basis of their anticancer activity and has been correlated with electrophysiological abnormalities in peripheral nerves.[12] Platinum drugs can reach the DRG neurons in view of the limited efficacy of the blood-nervous system barrier at that site and can bind to nuclear as well as mitochondrial DNA. While it is unlikely that interaction with nuclear DNA plays a fundamental role in DRG neuron damage since they are non-replicating cells, it has been demonstrated that inhibition of the replication and transcription of mitochondrial DNA can be responsible for mitochondrial degradation after exposure to cisplatin.[13] Platinum drugs have also been associated with oxidative stress in DRG neurons. The role of DNA binding on DRG satellite cells has never been fully investigated, although cisplatin-induced pathological changes have been reported in

animal models.[14] Besides sharing these effects with the other platinum drugs, oxaliplatin is also able to interact with ion channels, and this is probably the reason for its acute neurotoxicity, causing axonal hyperexcitability and increased cold sensitivity. The role of oxaliplatin-induced DRG changes in pH level is still to be clarified, but it is possible that it can concur to DRG neuron damage. In a preclinical study *in vitro,* it was demonstrated that treatment with oxaliplatin at clinically-relevant concentrations leads to acidification of the cytosol of mouse DRG neurons, leading to sensitization of TRPA1 channels, and thus providing a possible mechanistic explanation for acute toxicity of oxaliplatin. This effect was reproduced *in vivo* after a single injection of a therapeutically-relevant dose of oxaliplatin.[15]

Particularly based on studies regarding platinum drugs, the investigation on the role of cellular transporters involved in the influx and efflux of neurotoxic drugs in the peripheral nervous system provided additional information potentially useful for a better understanding of CIPN. Selective accumulation of cisplatin and oxaliplatin within DRG neurons has been reported to be due to copper transporter 1 (CTR1) and organic cation transporters (OCTs, OCTNs)[16] and their pharmacological modulation or genetic knock-out have allowed prevention of oxaliplatin-related CIPN in animal models.[16]

The obvious target of taxanes, as well as of epothilones, vinca alkaloids and eribulin is tubulin, and their effect in cancer cells is primarily directed toward the inhibition of the mitotic spindle thus preventing their replication. The abundance and functional importance of neuronal cytoskeleton tubulin makes it a reasonable target to explain neurotoxicity through inhibition of anterograde fast axonal transport.[17] However, the reasons why the sensory fibers are affected more severely than the motor fibers, as clearly demonstrated by clinical practice, are still unknown.

Also, increased oxidative stress has been suggested as a possible neurotoxicity mechanism for taxanes, able to target neuronal and non-neuronal cells in the peripheral nervous system since it was reported to contribute to macrophage and microglial activation in the DRG, peripheral nerves, and spinal cord.[18] According to this hypothesis, oxidative stress could contribute to increased local production of pro-inflammatory cytokines (TNF-alpha and IL-1beta) and to decreased production of anti-inflammatory cytokines (IL-10 and IL-4),[19] eventually leading to painful CIPN. Moreover, different animal studies suggested a direct toxic effect also on DRG neurons.[20,21]

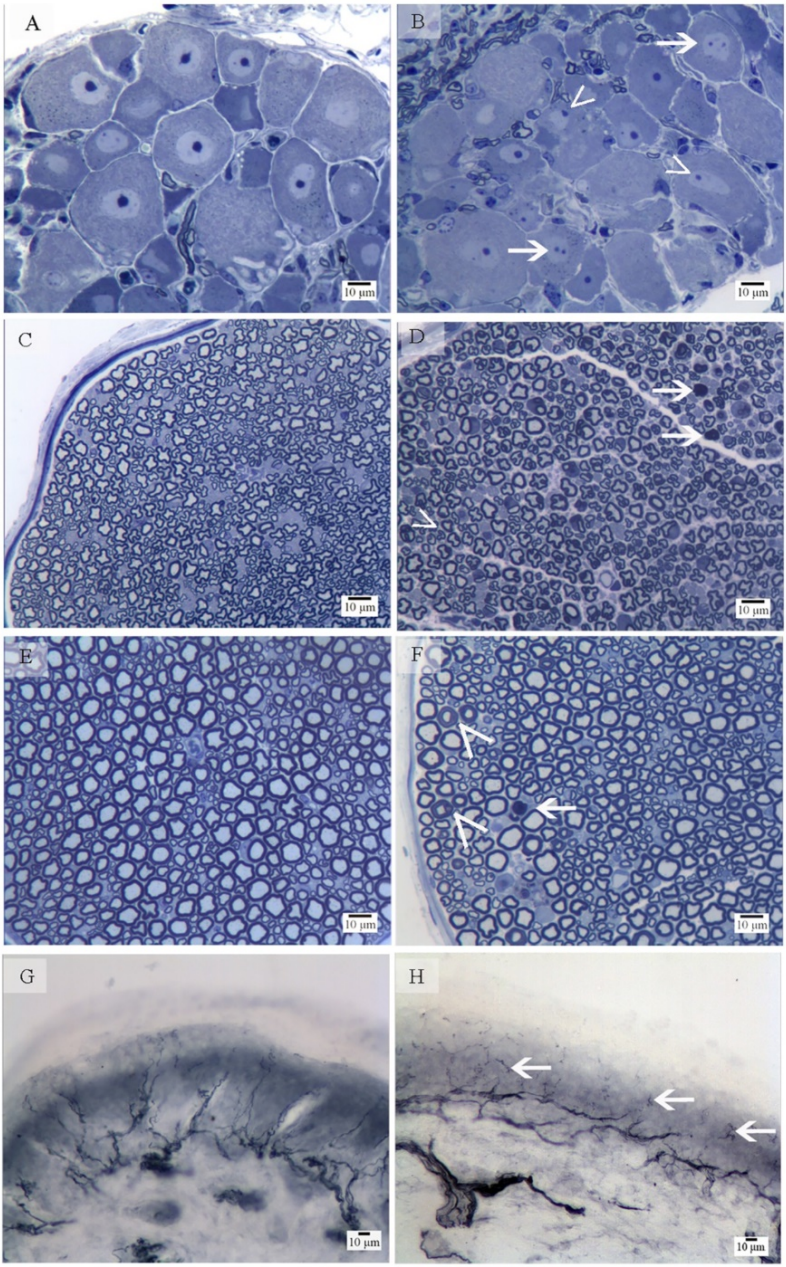
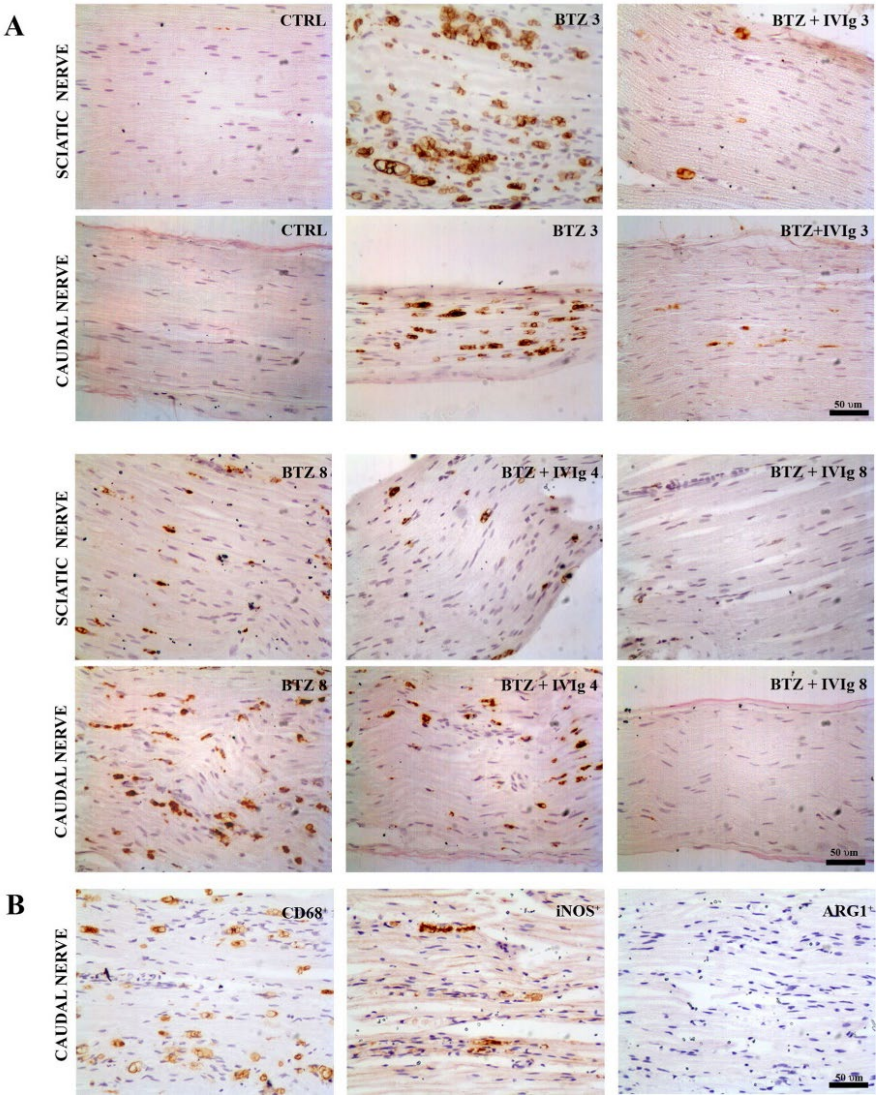


Figure 3 (previous page): Representative images obtained from CIPN animal models. Morphological analysis of light microscope images from control dorsal root ganglia (A), caudal nerve (C), sciatic nerve (E) and skin (G) compared to those obtained from oxaliplatin-treated Balb-c mice (B, D, F, H). B: multiple (arrows) and eccentric (arrowhead) nucleoli can be observed; D and F: degenerating fibers (arrows) and myelin derangement (arrowheads) are indicated; H: arrows point at the site of unmyelinated fiber density reduction in the epidermis *(reprinted with permission from Marmiroli (82)*)

Figure 4 (next page): Immunolocalization of macrophage infiltration in the peripheral nerves of bortezomib (BTZ)-treated rats. An anti-CD68 antibody has been used to stain macrophages and show the effects of intravenous immunoglobulins (IVIg) treatment in inflammatory infiltration in peripheral nerves. A: after 3 and 8 weeks of BTZ treatment, both sciatic and caudal nerves show a massive macrophage infiltration which is almost completely abrogated by the preventive co-treatment with IVIg (BTZ + IVIg 3; BTZ + IVIg 8). In the therapeutic setting, when IVIg were delivered after the onset of peripheral damage induced by BTZ (BTZ + IVIg 4), a milder reduction of CD68+ infiltrating cells was achieved in both sciatic and caudal nerves. B: representative immunohistochemistry for iNOS and ARG1 after 3 weeks of BTZ treatment. Most infiltrating macrophages (CD68+) are iNOS+ pro-inflammatory M1 type while a very limited amount of them are ARG1+ anti-inflammatory M2 type. Scale bar 50 mm *(reprinted with permission from Meregalli C (88)*)



Several additional explanations besides tubulin damage have been proposed for vinca alkaloids peripheral neurotoxicity, mostly based on vincristine-related preclinical studies. Endogenous opioids, key players in nociception, are decreased in the spinal cord and DRG of animals treated with vincristine. Central glia (particularly astrocytes) are activated following vincristine administration and overproduction of reactive oxygen species as well as an alteration in calcium homeostasis that might result from dysregulation of mitochondria activity have also been reported.[22] It is important to note that none of these mechanisms have ever been correlated with the severe autonomic dysfunction caused by vincristine administration.

Thalidomide (and its metabolites) exerts pleiotropic actions, thus the understanding of the origin of its peripheral neurotoxicity is extremely difficult. Part of this difficulty is also related to the absence of any animal model of thalidomide-related CIPN, probably because thalidomide's neurotoxic metabolites are species-specific so their effects in humans might not be the same as in rodents.

Based on the well-established thalidomide anti-angiogenic activity, it has been suggested that one of the mechanisms of thalidomide-induced CIPN is capillary damage and secondary ischemia of nerve fibers (although the typical changes correlated with ischemic neuropathies of different origins, as well as endoneurial vessel alterations have never been described). Moreover, thalidomide could reduce DRG neural cell survival by downregulation of tumor necrosis factor alpha (TNF-alpha), triggering inhibition of nuclear factor kappa B (NF-kB) and subsequent acceleration of neuronal cell death. Interestingly, NF-kB inhibition has also been proposed as one of the main effects of bortezomib to explain its neurotoxicity.[23]

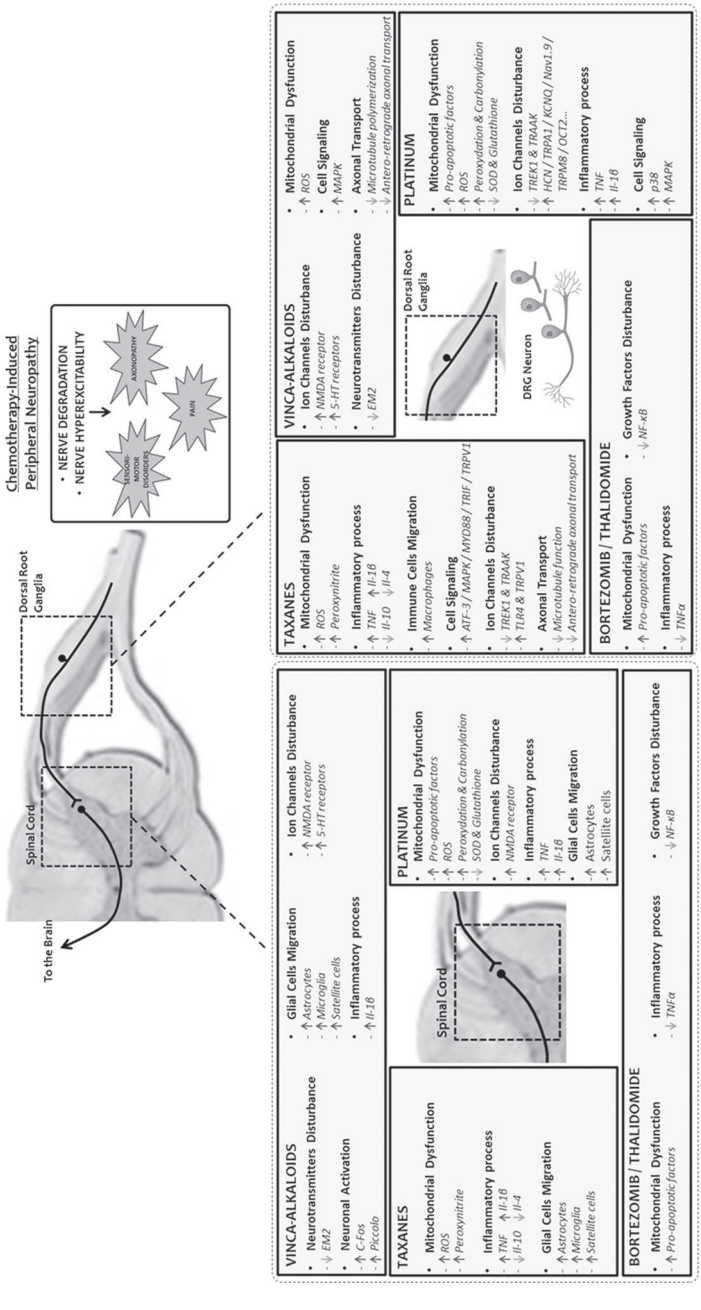
The pathologic hallmarks of bortezomib-induced CIPN in animal models are represented by alterations in the spinal cord, DRG and peripheral nerves, where the damage involves mostly Aδ and C nerve fibers.[24] Despite its specific target represented by the proteasome, bortezomib-induced CIPN might occur via a proteasome-independent mechanism,[25] possibly also involving mitochondrial dysfunction in this case.[11] Moreover, and similar to what was suggested for thalidomide, bortezomib induces transient calcium release from the intracellular store, leading to mitochondrial calcium influx and caspase-related apoptosis.[26] Dysregulation of neurotrophins through the inhibition of NF-kB activation may also contribute to CIPN following bortezomib administration.[26] Since a higher ratio of polymerized versus soluble tubulin was found in cancer cells in *in vitro* studies,[27] this mechanism has been investigated in animal

models of bortezomib-related CIPN. In these models, remarkable increases in tubulin polymerization were demonstrated in DRG and peripheral nerves. Remarkably, these changes had a different dynamic from that demonstrated for proteasome inhibition, thus suggesting that they can be independent of the direct effect of bortezomib on this fundamental intracellular organelle and instead be due to direct interaction with tubulin.[28]

As a recent new line of research, there is great interest in ascertaining whether reciprocal crosstalk between the nervous and immune systems occurs in CIPN and this might provide an important contribution, particularly in those cases with more prominent neuropathic pain. Recent studies tend to suggest that complex neuroimmune interactions occur, depending on the chemotherapeutic drug, dose, schedule, and timing. The most compelling evidence suggests an increase in pro-inflammatory cytokine expression and changes in immune signaling pathways. These data, however, originated from animal models and no firm evidence has yet been provided in humans. In an animal model of bortezomib-related CIPN, the co-administration of high-dose human immunoglobulins (a very effective immunomodulating treatment widely used in clinical practice to treat inflammatory neuropathies such as Guillain-Barrè Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyradiculoneuropathy, CIDP) significantly reduced intraneural macrophage infiltration and allodynia, with significant protection also against bortezomib-induced reduction in intraepidermal nerve fibers density (Fig. 4, see colour centrefold).

However, besides those previously described, several other possible mechanisms of the basis of CIPN pathogenesis have been proposed. Fig. 5 summarizes most of them in relation to the onset of CIPN secondary to the administration of different drugs.

Fig 5 (see next page): Summary of possible mechanisms of the pathogenesis of CIPN. Schematic summary of most of the mechanisms reportedly involved in CIPN pathogenesis (reprinted with permission from Kerckhove N (89)



Clinical features of CIPN

The most relevant aspect of the clinical features associated with the neurotoxicity of different conventional antineoplastic agents are summarized in Table 2-4-1.

Platinum drugs

Cisplatin is the first-in-its-class platinum-based antineoplastic drug. Its cytostatic properties were discovered by Barnett Rosenberg in the late 1960s, while he was carrying out experiments to analyze the effects of electric fields on bacterial growth and observed that bacterial proliferation was reduced when a platinum electrode was used. Multiple cellular events contribute to the cytotoxic effect of cisplatin as well as of the other platinum-based drugs, although DNA platination is a crucial step driving the incapacity of replicating cells to divide.

Since 1978, when cisplatin was first approved in the US to treat cancer, CIPN has emerged as a major side effect in its clinical use and, subsequently, carboplatin (1986) and oxaliplatin (1996) entered into generalized clinical practice with the aim of improving efficacy, but also of reducing peripheral neurotoxicity. Nedaplatin, lobaplatin and heptaplatin received only regional approval in some countries. Despite having been on the market for more than four decades, due to its efficacy cisplatin is still indicated (generally in combination with other antineoplastic drugs or radiation therapy) particularly in the treatment of testicular, ovarian cancer, bladder and cervical carcinoma, squamous cell carcinoma of the head and neck, small and non-small cell lung carcinoma. Carboplatin has its principal indication in advanced ovarian carcinoma of epithelial origin (also as second line when other treatments have failed) and small cell carcinoma of the lung, while oxaliplatin is the cornerstone of colorectal cancer, but it is also used in different tumors of the gastrointestinal tract.

While at the earliest stages of cisplatin use nephrotoxicity, mostly due to tubular toxic damage, was the main dose-limiting side effect in its clinical use, now hydration and diuretics have minimized its severity, and peripheral neurotoxicity has emerged as a major issue. Cisplatin peripheral neurotoxicity has two distinct clinical presentations: ototoxicity and sensory impairment in the limbs.

Cisplatin-induced hearing loss is primarily in the high frequency range and it is due to damage of the hair cells of the Corti organ of the cochlea. It is bilateral, dose-dependent, permanent and particularly frequent in

children. Moreover, children (typically undergoing treatment for brain tumors, such as neuroblastoma) show greater risk of developing hearing loss following cisplatin treatment than adults, particularly when it is combined with myeloablative carboplatin administration [29] and its occurrence could affect early speech development and hamper social integration. There is no effective treatment to prevent cisplatin-induced ototoxicity.[30]

Sensory impairment in the limbs is another very frequent occurrence in cisplatin- as well as oxaliplatin-treated patients, while its occurrence is less frequent in patients receiving carboplatin. Distal, symmetrical loss of perception, numbness, tingling and sensory ataxia resulting in unbalance worsened by eye closure and frequent falls are the typical clinical features observed in platinum drugs-treated patients, which are intensity- and cumulative dose-related. Neuropathic pain is very rarely a clinically relevant effect of the administration of platinum drugs. However, in nearly all of the subjects treated with oxaliplatin (but not with cisplatin or carboplatin) the occurrence of acute neurotoxicity is also very common, represented by a combination of symptoms including distal and oropharyngeal cold-induced paresthesias, cramps, and muscular spasms, lasting in most cases no more than 48-72 hours after drug delivery. It is still uncertain if there is a causal relationship between acute and chronic oxaliplatin-induced peripheral neurotoxicity, although it has been demonstrated that subjects with more intense acute manifestations in the hours after oxaliplatin administration are also those with a more severe long-term CIPN.[31]

Apart from the severity of CIPN during treatment, a highly relevant aspect of platinum drugs peripheral neurotoxicity is represented by the progressive worsening of chronic signs and symptoms occurring after treatment withdrawal. This clinical course, known as the “coasting” effect is very difficult to predict in its duration, time of progression and severity, and this aspect is both challenging for the treating physician and extremely difficult to be accepted by patients.

The incidence and the severity of long-term CIPN have been mostly assessed in oxaliplatin-treated patients, and there is now convincing evidence that symptoms are still present in a great number of patients more than one year after therapy termination.[32]

Antitubulin drugs

The importance of tubulin in the formation of the mitotic spindle during mitosis and cell replication prompted the development of several

different classes of "antitubulin" anticancer drugs, and this remains a target also for several compounds under development. However, since tubulin is also the fundamental component of microtubules and these cytoskeleton structures are highly involved in the proper flux of axonal transport, it is not surprising that nerve fiber damage is a frequent side effect of their use.

Vinca alkaloids

Vinca alkaloids are a group of antimitotic and anti-microtubule agents that were first derived from the periwinkle plant *Catharanthus roseus* (basionym *Vinca rosea*) and other vinca plants. Vinca alkaloids including vincristine, vinblastine, vindesine, and vinorelbine can now be produced synthetically. These drugs inhibit microtubule formation thus leading to cytoskeleton disaggregation in axons and among them (which share the same peripheral neurotoxicity profile, but with remarkably different severity), vincristine is the agent more frequently associated with clinically-relevant CIPN.

Vincristine was approved by the US Food and Drug Administration (FDA) in 1963 and it is used particularly in leukemias (including acute and chronic lymphocytic leukemia, acute myelogenous leukemia and blastic crisis of chronic myelogenous leukemia), Hodgkin's disease and non-Hodgkin's lymphomas, multiple myeloma. It is also used in adult solid tumors (including breast carcinoma, small cell bronchogenic carcinoma, head and neck carcinoma and soft tissue sarcomas) and pediatric solid cancers (including Ewing's sarcoma, embryonal rhabdomyosarcoma, neuroblastoma, Wilms' tumor, retinoblastoma and medulloblastoma). Despite the most common clinical feature of vincristine-related CIPN in both adults and children being sensory impairment,[33] distal weakness (particularly in the lower limbs) and cranial nerve involvement are also not infrequent. Typically, vincristine-treated patients report impairment in touch and thermal/pain perception, while sensory ataxia is relatively rare. Besides these somatic features, vincristine administration is associated with a peculiar capacity to target the autonomic nervous system. In fact, autonomic impairment can be particularly frequent and severe in vincristine-treated patients,[34] with different clinical features including cardiovascular and genitourinary symptoms/signs (e.g., orthostatic hypotension, bladder dysfunction). However, the most worrisome autonomic impairment has the features of paralytic ileus and constipation can be particularly severe.

Taxanes

Taxanes are a class of diterpenes originally identified from plants of the genus Taxus (yews). Paclitaxel (the first-in-class taxane entered in clinical practice) was originally derived from the Pacific yew tree, and taxanes are still difficult to synthesize because of their numerous chiral centers. The main mechanism of action of the taxanes is the disruption of microtubule function through reduced depolymerization obtained by the stabilization of GDP-bound tubulin in the microtubule.

Paclitaxel was approved for medical use in 1993, and the semi-synthetic parent drug docetaxel followed in 1995. Paclitaxel and docetaxel are particularly indicated (often in combination with cisplatin or carboplatin) to treat ovarian, breast, prostate, gastric, pancreatic, head and neck, and non-small cell lung carcinoma. The peripheral neurotoxicity profiles of paclitaxel and docetaxel are very similar, although the latter seems to be slightly less neurotoxic in most settings [35]. Similar to vinca alkaloids, taxanes also induce a distal sensorimotor neuropathy without any relevant autonomic dysfunction. Animal studies indicate that DRG neuron cell bodies are also damaged by taxane administration.[35]

Another taxane indicated particularly for the treatment of breast, pancreas, and non-small cell lung cancer is nab-paclitaxel, an albumin-bound paclitaxel nano-formulation developed to improve efficacy and reduce the toxicity of paclitaxel. Reduced peripheral neurotoxicity has been suggested for this modified drug, but this assumption still needs to be confirmed, also because the comparison with the schedules and actual dose of paclitaxel delivered is difficult.[36]

Besides sensorimotor impairment, taxanes (particularly paclitaxel) induce the so-called “taxanes acute pain syndrome” (previously reported as “arthralgia-myalgia syndrome”) in a significant proportion of patients. Pain begins within two to seven days after paclitaxel, but the worst pain occurs on days three to four, and can last for several days. Patients report pain in their legs, feet, hips, abdomen, back, arms, shoulders, hands, neck, and chest; in 10-20% of patients this pain can be very severe. Remarkably, since some paclitaxel regimens are given weekly and this pain continues for several days, patients can suffer from paclitaxel-induced pain almost constantly throughout the chemotherapy cycle. The basic mechanisms of this painful syndrome are unknown, but the disease has never been associated with any structural alteration of muscles or joints. It has been suggested that it is an uncommon presentation of neuropathic pain caused by taxanes-induced nerve injury, possibly with subsequent sensitization of nociceptors into the central nervous system.

Epothilones

Epothilones were originally identified as metabolites produced by the soil-dwelling myxobacterium Sorangium cellulosum and the structure of epothilone A was determined in 1996 using X-ray crystallography. Like taxanes, epothilones bind to the αβ-tubulin heterodimer subunit. Once bound, the rate of αβ-tubulin dissociation decreases, thus stabilizing the microtubules. Furthermore, epothilone B (and probably all the other parent drugs) can induce tubulin polymerization into microtubules without the presence of GTP. Epothilones can be effective on taxanes-resistant cancer cells.

Ixabepilone, the only epothilone entered in clinical practice so far, was approved in October 2007 by the US FDA for use in the treatment of aggressive metastatic or locally advanced breast cancer no longer responding to currently available chemotherapies. However, in November 2008, the European Medicine Agency (EMA) refused a marketing authorization for the drug, mostly because of an unfavorable risk-to-benefit assessment, where the major risk was CIPN. Several synthetic epothilone analogs are currently undergoing clinical development for the treatment of various cancers. Although the clinical features of epothilones-induced CIPN are very similar to those following taxanes administration, with sensory impairment more severe than motor damage, pain is much rarer. Interestingly, a faster recovery from CIPN after drug withdrawal, compared with taxanes, has been reported.[37]

Eribulin

Eribulin mesylate is a more recent antitubulin agent belonging to the class of halichondrins. It is a fully synthetic macrocyclic ketone analog of the marine natural product halichondrin B, derivates from Japanese marine sponge Halichondria okadai. It acts primarily by suppressing microtubule dynamic instability at low concentrations and promoting microtubule disassembly at high concentrations. In addition to its cytotoxic, antimitotic-based mechanisms, preclinical study models suggest that it also exerts complex effects on the biology of surviving cancer cells and residual tumors that appear unrelated to its antimitotic effects, such as vascular remodeling that modify tumor perfusion. Eribulin mesylate was approved by the US FDA in 2010, to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline- and taxane-based

chemotherapies, and it was subsequently approved for the treatment of liposarcoma.

Also in the case of eribulin, CIPN has the features of a sensorimotor neuropathy.[38] However, eribulin was found to be less neurotoxic than vincristine and in animal studies comparing CIPN induced by eribulin, paclitaxel, and ixabepilone at equivalent doses, it induces less severe nerve damage[39] and allows more rapid and complete recovery.[40] In a head-to-head clinical trial vs. the epothilone drug ixabepilone in patients with relapsed breast cancer, eribulin-induced CIPN incidence after controlling for pre-existing neuropathy was similar to that observed in ixabepilone-treated patients. However, patients treated with eribulin developed sensorimotor impairment later and recovery was also delayed,[38] thus suggesting a different neurotoxicity profile.

Immunomodulatory drugs (IMiDs)

With the term "immunomodulatory drugs" (IMiDs) a class of compounds characterized by the presence of an imide group in their chemical structure is indicated. The IMiDs used in anticancer treatment include thalidomide and its analogs lenalidomide and pomalidomide.

Thalidomide and pomalidomide are indicated for combination chemotherapy in multiple myeloma patients and in myelodysplastic syndrome, a precursor condition to acute myeloid leukemia, while lenalidomide is also used to treat mantle cell lymphoma.

Thalidomide is definitely more neurotoxic than lenalidomide and pomalidomide, but the full spectrum of the mechanism of action of thalidomide as well as that of its neurotoxicity remains highly debated. It is known that IMiDs inhibit the production of interleukin-6, TNF-alpha, immunoglobulin G and vascular endothelial growth factor (VEGF), thus producing strong anti-angiogenic effects. Moreover, they co-stimulate T and NK cells and increase interferon gamma and interleukin-2 production, but it is not clear if and how these effects can be related to CIPN onset. Under this perspective, experimental studies *in vitro* showed IMiDs induced damage of microtubules, suggesting a still uncovered mechanism to explain axonal damage.[41]

Thalidomide-related CIPN is characterized by a cumulative, dose-dependent, distal sensory neuropathy, with milder motor impairment only in a small subset of patients [42]. Pain or autonomic system impairments are extremely rare in IMiDs-treated patients and recovery after drug withdrawal is generally complete. It is possible that with respect to CIPN, thalidomide benefits from the strict monitoring regimen enforced by

several State regulations in view of the thousands of babies worldwide born with malformed limbs when the drug was marketed as a safe sleeping pill for pregnant women in the 1960s, thus allowing detection of CIPN onset at its earliest stage and preventing irreversible damage.

Proteasome inhibitors

The first proteasome inhibitor entered in clinical use was bortezomib, approved by the US FDA in 2003 for the treatment of multiple myeloma, with subsequent extension of this indication to mantle cell lymphoma. Bortezomib inhibits the proteasomal activity in a reversible way by binding the catalytic site of the 26S proteasome. Its introduction in the treatment of multiple myeloma represented a breakthrough advance in the treatment of this hematological malignancy. However, since the earliest clinical trials CIPN emerged as a major side effect in bortezomib-treated patients. Distal, sensory impairment with a stocking and glove distribution is frequent among bortezomib-treated patients, and it can be severe, with a hardly predictable onset during the treatment.[43] As with most of the other neurotoxic anticancer agents previously described, motor or autonomic impairment is very rare. However, the hallmark of bortezomib-related CIPN and the major clinically relevant side effect is neuropathic pain affecting the same regions where sensory impairment occurred.

While originally bortezomib was delivered only intravenously, subsequent studies demonstrated that, at least in some specific clinical settings, subcutaneous administration was equally effective but less neurotoxic. However, additional clinical trials specifically addressing this important issue raised some concerns on the extent of the greater safety of the subcutaneous administration of bortezomib, rather suggesting that bortezomib-induced CIPN is dose-dependent and might be reduced more effectively by lower intensity schedules rather than by administration route.[44]

It is important to note that CIPN does not seem to be a class-effect of proteasome inhibitors. In fact, the irreversible proteasome inhibitor carfilzomib, available for the treatment of multiple myeloma since 2012 and acting by inhibiting the chymotrypsin-like activity of the 20S proteasome, shows similar non-neurological side effects, including anemia, thrombocytopenia, fatigue, dyspnea, and nausea, but it is remarkably less neurotoxic than bortezomib.[45] This important difference in neurotoxicity raised the possibility that intracellular structures other than the proteasome might be targeted by bortezomib, and also in this case tubulin emerged as a possible target in animal models.[28]

"Targeted drugs"

The US National Cancer Institute defines targeted therapies as "…the foundation of precision medicine… that targets the changes in cancer cells that help them grow, divide, and spread," thus pointing to highly specific effects. Most targeted agents are either small-molecule drugs or monoclonal antibodies. Small-molecule drugs are small enough to enter cells easily, and they are used for targets that are inside cells, while monoclonal antibodies are designed to attach to specific targets found on cancer cells or to "mark" cancer cells so that they will be better seen and destroyed by the immune system. Other monoclonal antibodies directly stop cancer cells from growing, cause them to self-destruct or carry toxins to cancer cells. Given their size and structure, monoclonal antibodies are drugs that are not able to enter cells easily and they attach to specific targets on the outer surface of cancer cells.

A basic, but unfortunately incorrect, concept describing targeted drugs is that they are so highly precise as to be devoid of off-target side effects, including CIPN. By contrast, increased use of targeted drugs allowed the identification of a wide range of side effects, some of which involved the peripheral nervous system. Frequently the proper assessment of targeted drugs-related CIPN is difficult because patients have already received neurotoxic first-line chemotherapy regimens, or targeted drugs are co-administered in association with neurotoxic drugs. Although in some cases targeted drugs-related CIPN may present with the distal, sensorimotor clinical picture previously described with conventional chemotherapy agents, other types (often severe) of neurotoxicity manifestations have been reported.

Acute, mainly motor radiculo/neuropathies resembling GBS, have been reported in patients treated with several monoclonal antibodies designed to target different surface cellular antigens such as alemtuzumab, a monoclonal antibody that targets the CD52 antigen (currently approved for relapsed/refractory and high-risk untreated chronic lymphocytic leukemia) and rituximab, a monoclonal antibody against CD20 antigen (originally developed to treat rheumatoid arthritis and B-cell non-Hodgkin's lymphoma). Despite this form of acute and severe neurotoxicity that has been described mostly after monoclonal antibodies use, it is not peculiar of this class of targeted drugs. For instance, it has been reported after the administration of nelarabine, a prodrug of arabinosylguanine nucleotide triphosphate (araGTP) which causes inhibition of DNA synthesis and cytotoxicity [46]. Another prodrug that has been associated with severe motor CIPN (although with features different from those of GBS, since the damage here was predominantly axonal, and not

demyelinating) is brentuximab vedotin, a CD30-specific antibody-drug conjugate with remarkable activity in relapsed or refractory Hodgkin's lymphoma and anaplastic large cell lymphoma. The two step mechanism of action of brentuximab vedotin is based on primary binding of the conjugate to CD30 on tumor cells, followed by molecule internalization with subsequent release of the potent antitubulin agent monomethyl auristatin E (MMAE) into lysosomes. CD30 is not expressed by axons, Schwann cells or myelin, but nevertheless clinical studies indicate that CIPN (with predominantly sensory features) is a frequent, although overall manageable, complication of treatment with early complete resolution in about 50% of patients, while most of the remaining patients have a delayed recovery.[47,48] In a small proportion of patients, for still unclear reasons, very severe motor impairment has been reported after brentuximab vedotin administration and the examination of a nerve biopsy obtained from one of these patients disclosed severe axonopathy with a nearly complete and diffuse disappearance of axonal microtubules.[49]

Polatuzumab vedotin, another antibody-drug conjugate containing MMAE, was associated with CIPN in most patients with indolent non-Hodgkin's lymphoma.[50] To quantify the correlation of conjugate exposure and treatment duration with CIPN risk, a time-to-event model was developed and it suggested that CIPN risk increased with conjugate exposure and treatment cycles.[50]

A frontline development in cancer treatment is immunotherapy, and cancer immunotherapy has progressed considerably in the last few years, mostly thanks to improved understanding of the factors that promote or inhibit T cell response. Immune checkpoints are inhibitory molecules that play a key role in dampening the T cell responses preventing autoimmunity. Two well-characterized immune checkpoints are cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death 1 (PD-1). Understanding the role of CTLA-4 and PD-1 has led to the development of immune checkpoint inhibitors aimed at improving antitumor immune response. The PD-1 blocking antibodies nivolumab and pembrolizumab are now approved for use in multiple cancers including melanoma, non-small cell lung cancer, and head and neck cancer. While immune checkpoint inhibitors have been increasingly used in patients with metastatic cancers with favorable oncological outcomes, there have also been increasing numbers of cancer survivors who have developed immune-related adverse events. Neuromuscular disorders are the most common neurological complication reported in PD-1 inhibitor-treated patients. Myasthenia gravis, immune-mediated myopathies, and GBS are among the commonly reported immune-related neuromuscular

complications, but also cranial nerve palsies, CIDP and vasculitic neuropathies have been reported.[51] Ipilimumab was the first CTLA-4 blocking antibody approved for the treatment of metastatic melanoma in 2011 [52]. Also ipilimumab, although less frequently than PD-1 inhibitors, has been associated with GBS,[53] as well as with cranial nerve palsies.[54]

The pathogenesis of "targeted" drugs peripheral neurotoxicity is unknown, although it has been suggested that a major role might be attributed to their capacity to interact with the immune system.[55] If this hypothesis is confirmed it will be extremely challenging to create reliable animal models to be used to better understand the underlying mechanisms. Therefore, based on these observations it seems reasonable to advocate careful neurological monitoring during the administration of "targeted" drugs to ascertain as early as possible the onset of CIPN and to design prospective clinical trials to ascertain their real toxicity profile, alone or in combination treatments.

Long-term effects of CIPN

While most of the clinical information regarding CIPN focused on early and late CIPN symptoms and signs, i.e., those ensuing during treatment or immediately after its completion, a high level of attention is now being given to long-term or permanent impairment. Data are now already very solid for several of the most widely used neurotoxic treatments associated with improved prognosis of the treated cancer. This is the case particularly for breast cancer treated with taxane-based chemotherapy and colorectal cancer treated with oxaliplatin-based schedules. From recent studies, it has emerged that taxane-induced peripheral neuropathy is common among breast cancer survivors, and a correlation has been demonstrated between CIPN severity and an increased rate of falls among breast cancer survivors.[56] In an exercise trial of cancer survivors including more than 450 women, nearly half of those with CIPN symptoms experienced worse physical functioning, altered walking patterns, and more falls than women without CIPN.[57]

Similar impacts of CIPN were observed among a group of patients treated with oxaliplatin for colorectal cancer two to eleven years prior to the assessment.[58] The study evidenced that several different aspects of daily life were impaired by long-term CIPN, including trouble hearing, opening a jar or bottle because of loss of strength in the hands, tingling in toes and feet, and difficulty walking up the stairs or standing up from a chair.

Long-term analysis was also performed in other cancer populations, such as ovarian cancer survivors. In a study performed on 348 women diagnosed with ovarian cancer between 2000 and 2010 who were evaluated using the EORTC quality of life questionnaire and the ovarian-cancer specific questionnaire (QLQ-C30 and EORTC QLQ-OV28 including three items about neuropathy), 191 women returned their answers. Of all the 191 women, the 129 women who received taxane/platinum drug chemotherapy more often reported having tingling in the hands and feet and feeling numbness in the fingers and toes and other symptoms including fatigue and pain. These women reporting more neuropathy symptoms had more often experienced the disease and treatment as being a burden and were more worried about their health. Also, more cycles of chemotherapy, more recurrences and a shorter period since the last treatment were associated with a higher neuropathy score.[59]

In order to achieve a broader view on the possible extension of long-term CIPN to different peripherally neurotoxic drugs, more than 500 patients with incident exposure to at least one of 28 chemotherapeutic agents associated with the development of peripheral neuropathy living in Olmsted County, Minnesota were identified within the period 2006–2008. The five more frequently used drugs in that cohort had been paclitaxel, carboplatin, cisplatin, vincristine, and oxaliplatin. More than half of the patients were determined to have CIPN and those with CIPN surviving longer than five years (n=145) continued to have substantial impairments and were more likely to be prescribed opioids than those without CIPN.[60]

CIPN in children

Since the treatment of pediatric cancers has improved at an even faster rate than in adults, and several peripherally neurotoxic drugs are also used in these settings, it is not surprising that CIPN is not only common among adults, but also among children. Over the last few decades the decline in mortality has been impressive, with the overall five-year childhood cancer survival rate reaching 80% for nearly all cancer types.

Given longer life expectancy, not only the immediate but also the long-term disability may be substantial when chemotherapy is administered in childhood. According to a recent review there is a population of nearly 400,000 long-term survivors in the US alone.[61] Nevertheless, pediatric CIPN has been largely under-investigated compared to adult CIPN. There is, therefore, a compelling need to improve the available knowledge through more accurate assessment, monitoring, and careful characterization of long-lasting side effects of treatment for childhood cancer.

Among conventional antineoplastic drugs known to be potentially and severely neurotoxic on the peripheral nervous system, cisplatin and vincristine are those more frequently used in children, often in combination, for the treatment of solid and hematological malignancies. However, several other neurotoxic drugs already widely available for adult cancer patients are under investigation for possible future use.

Despite its wide use, little is known from a large series of patients regarding the incidence and characteristics of cisplatin related CIPN in children. Similarly, for carboplatin, frequently used with cisplatin in combination therapy, information is very limited. From the available data it seems confirmed that, as occurs in adults, carboplatin is less neurotoxic in children than cisplatin, and also in heavily pre-treated patients.[62] Oxaliplatin is not used as standard therapy, but in pediatric phase I and II trials presented CIPN with the same clinical features described in adults (i.e., sensory neuropathy with cold-related dysesthesia, muscle cramps/spasms and jaw pain). In pre-treated patients, acute peripheral neuropathy was a dose-limiting toxicity,[63] while this event is very uncommon in adults.

In a large retrospective review including six trials for a total of more than 4500 patients, approximatively 10% of the children treated with vincristine had severe or disabling peripheral neurotoxicity graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE grades 3 and 4), with an evident cumulative dose-toxicity relationship. According to other reported studies, neuropathy of any NCI-CTCAE grade affected 80 to 100% of patients treated with vincristine and neuropathic pain was reported in up to 35%.[64,65]

Peripheral neurotoxicity is likely to become a serious side effect of treatment also with other microtubule-targeting agents. The administration of paclitaxel either as three, six or twenty-four-hour infusions was tested in pediatric phase I trials and CIPN was the dose-limiting toxicity presenting as transient paresthesia in a glove and stocking distribution. Transient, severe myalgia was also common.[66] From these earlier experiences it seems that a dose-toxicity relationship is present[66] and that lower and more frequent doses may be associated with reduced neurotoxicity.[67] As in adults, docetaxel seems to be slightly less neurotoxic also in children, while the data on epothilones are still too limited to draw any firm conclusion about their safety in children.[68,69]

Bortezomib has been used in phase I and II trials for refractory or relapsed hematological malignancies,[70] but also to prevent antibody-mediated rejection in cardiac and renal transplantation. Overall, the

incidence of CIPN in these patients was approximately 20%,[70,71] with only a few cases reporting painful sensory neuropathy.

Another neurotoxic drug already used in different clinical settings is thalidomide. In fact, this agent has been used in children primarily in the treatment of inflammatory conditions such as rheumatoid arthritis, refractory inflammatory bowel disease, graft versus host disease and also as part of anti-angiogenic therapy for particular pediatric brain tumors.[72] Thalidomide-related CIPN presenting with painful distal paresthesia and sensory loss, sometimes associated with proximal muscle weakness and muscle cramps, is frequently a dose-limiting side effect in these patients.

It is now clear that survivors of childhood cancer treated with neurotoxic drugs acting on the peripheral nervous system carry a significant risk of having long-term reduced performance in strength, motor tasks and dexterity and balance as well as decreased preference for physical activity compared to controls.[73,74] Most of the data available so far refer to long-term CIPN after the administration of vincristine, cisplatin and thalidomide. In vincristine-treated children with acute lymphoblastic leukemia, electrophysiological evidence of persistent motor or sensorimotor axonal neuropathy was evident in 30–33% of subjects up to seven years following treatment.[33,75,76] Interestingly, an additional 27% reported subjective symptoms of neuropathy without abnormalities in nerve conduction studies. Long-term data are less easily available for cisplatin-treated patients, but at least one-third of adolescents and young adults tested at a median of eight months after completion of their cisplatin therapy had sensory axonal neuropathy with clinically-evident impairment in vibration perception threshold and deep tendon reflexes.[74] At approximately the same time from the end of treatment clinical and electrophysiological deficits were observed in children following administration of thalidomide.

Regarding the long-term effect of exposure to neurotoxic chemotherapy for the treatment of solid cancers in childhood, in a large series of 531 survivors of extracranial solid tumors assessed at least ten years post-diagnosis the prevalence of sensory and motor impairment was 20% and 17.5%, respectively. Vinca-alkaloid exposure was associated with an increased risk of motor impairment while platinum exposure was associated with an increased risk of sensory impairment without evidence of a dose response. Vincristine and cisplatin exposure is related not only to long-term motor and sensory impairment at the neurological examination, but survivors are also at increased risk of functional performance limitations.[77]

Treatment for CIPN

Despite extensive investigation and several promising results obtained in animal models, prevention or symptomatic treatment of CIPN still remain unmet clinical needs, and dose reduction or treatment modification are the only feasible options to limit the severity of CIPN and prevent long-term side effects when neurotoxic agents are used. This problem has been addressed by several extensive literature reviews, in the form of systematic analysis such as the Cochrane review on platinum drugs,[78] as well as under the auspices of scientific societies such as the American Society for Clinical Oncology (ASCO) that released the results as guidelines.[79] From these reviews it is clear that only moderate evidence in favor of duloxetine use as symptomatic treatment of CIPN can be proposed on evidence-based criteria. However, antioxidants (e.g., reduced glutathione, vitamin E, alpha lipoic acid), anticonvulsants (mainly pregabalin and gabapentin), tricyclic antidepressants, and even opioids are used in clinical practice. It is possible that the currently incomplete knowledge of the pathogenesis of CIPN plays a major role in this unsatisfactory situation, but several flaws in the methodological design of the clinical trials performed to test neuroprotective agents are also probably relevant.[80] To support the need for more careful design of the next clinical trials, the example of the proposed use of calcium/magnesium infusion to prevent oxaliplatin-related CIPN is paradigmatic, since it required several subsequent clinical trials with improved quality at each step before unequivocally discarding its efficacy.[81]

A similar improvement is also required in the field of preclinical investigation, leading to the use of models that more and more closely mimic the human clinical setting in terms of dose intensity, method of administration, PK/PD, and methods of assessment strictly focused on the most relevant features of any different kind of CIPN. To this aim, solid knowledge of the animals selected for the study is also a critical issue, since it has been demonstrated that simply the selection of different mice strains can lead to different results.[82]

The socio-economic burden of CIPN

As it occurs in most diseases with acute and severe onset, followed by a chronic course with long-term or permanent symptoms, signs, and related impairment in daily activities, CIPN not only has a medical impact, but it also carries important effects at the socio-economic level. This aspect was investigated only marginally, but it immediately emerged as

potentially highly relevant. A study on patient recall from medical services performed in 2001 on a cohort of forty-two CIPN women with ovarian cancer showed that the medical costs directly attributable to CIPN were nearly USD 700 per episode, but that overall indirect costs (e.g., patient and caregiver work loss and paid caregiver costs) were over USD 4,000 per episode.[83] A subsequent study demonstrated that patients with a neuropathy have healthcare costs triple those of controls.[84] Despite this study not being specifically designed to investigate CIPN, its results were in substantial agreement with the previous investigation. Lema et al.[85] attempted to estimate the potential impact on patients who are at risk of the development of CIPN (and particularly those with neuropathic pain) based on an analysis of actual usage of peripherally neurotoxic anticancer drugs in combination with cost per event. The study reports that the IMS health database indicated that about 2.6 million outpatient prescriptions were written in the US in 2007, and a little over 3 million prescriptions were written in 2008. The authors assumed an average of three treatment cycles per patient, and this led to an estimated one million outpatients at risk of developing chemotherapy-induced neuropathic pain. Based on the total cost per neurotoxicity event previously reported the estimated cost of the problem was considered to be approximately 2.3 billion USD.

On these background investigations, the first study specifically designed to assess health outcomes as well as the healthcare and work loss cost burden of CIPN in different tumor types were performed in 2012, and demonstrated that CIPN patients have average extra healthcare costs of USD 17,344 with outpatient costs being the highest component.[86] This result allows some projections regarding the enormous socio-economic cost of CIPN, since it is predicted by the World Health Organization that the number of cancer patients is expected to increase to 30 million by 2040 and at the moment more than 50% of these patients are potential candidates for treatment with one or more drugs toxic to the peripheral nervous system. This estimate leads to a possible cost of several billion USD.

A great proportion of these cancer cases will occur in less developed countries, and this will have important epidemiological relevance for CIPN risk. In fact, while it is likely that patients living in more developed countries will be treated in the future with new, more expensive and, hopefully, less neurotoxic drugs, the present conventional anticancer agents will probably become the way to access low-cost, but effective anticancer treatment in less developed parts of the world and CIPN will remain a relevant medical and socio-economic issue.

Conclusions

Despite considerable efforts in preclinical and clinical research, CIPN remains a rather elusive entity for oncologists and neurologists. In the preclinical investigation of CIPN pathogenesis, a fundamental step to identify potential targets in the development of specific neuroprotectant agents, the unique opportunity to investigate a disease with a precise onset and a definite cause has not yet been fully exploited.

In clinical practice it is now evident that CIPN is a severe, and sometimes persistent, impairment in the quality of survival of cancer patients, who are strongly asking researchers to join their efforts and provide solutions.

This goal can successfully be achieved only through intensive collaboration between basic researchers and clinicians creating networks able to share knowledge and recruit large numbers of patients in order to provide regulatory agencies and pharmaceutical companies rationale-based information allowing the design of less neurotoxic drugs and the testing of effective neuroprotectant agents.

Table 2-4-1: Most frequent symptoms and signs associated with the administration of conventional antineoplastic drugs

DRUG	SYMPTOMS/SIGNS
Platinum drugs	
Cisplatin (Carboplatin has a similar, but less severe neurotoxicty profile)	• Large myelinated nerve fibers more severely involved than small myelinated/unmyelinated nerve fibers • Early reduction/loss of DTR • Despite preclinical evidence of DRG neuron damage, rarely the clinical features are those of a typical ganglionopathy, and distal, symmetric, upper and lower limb impairment with loss of all sensory modalities are much more common • Sensory ataxia and gait imbalance are frequent • Neuropathic pain is rare • Coasting* phenomenon is frequent and frequently long-lasting
Oxalipatin	**Chronic** • Similar to cisplatin in clinical picture and severity **Acute** • Cold-induced, transient paresthesias in mouth, throat and limb extremities • Cramps/muscle spasm in throat muscle • Jaw spasm
Antitubulins	•

Taxanes	• Pathological evidence of axonopathy in sural nerve biopsies • Distal, symmetric, upper and lower limb impairment with loss of all sensory modalities • Distal, symmetric weakness in lower limbs can also occur but is generally mild • Gait unsteadiness is possible due to proprioceptive loss • Reduction/loss of DTR • Neuropathic pain and paresthesias at limb extremities are relatively frequent • "Taxanes acute pain syndrome" (previously "arthralgia-myalgia syndrome") is frequent, possible expression of atypical neuropathic pain
Epothilones	• Similar to taxanes, but neuropathic pain is less frequent, and recovery is reported to be faster
Vinca alkaloids (particularly Vincristine)	• Pathological evidence of axonopathy in sural nerve biopsies • Distal, symmetric, upper and lower limb impairment with loss of all sensory modalities • Autonomic symptoms may be dose-limiting (e.g., orthostatic hypotension, constipation, paralytic ileus) • Reduction/loss of DTR • Distal, symmetric weakness in lower limbs progressing to foot drop • Neuropathic pain/paresthesia at limb extremities is relatively frequent
Eribulin	• Similar to epothilones, less severe in animal models and recovery is reported to be faster
Thalidomide	• Mild to moderate, distal symmetric loss of all sensory modalities • Reduction/loss of DTR • Weakness is rare • Relatively frequent neuropathic pain at limb extremities
Bortezomib	• Neuropathic pain can be dose-limiting • Mild to moderate, distal symmetric loss of all sensory modalities • Reduction/loss of DTR • Mild distal weakness in lower limbs is possible, but very rarely clinically-relevant

DTR = deep tendon reflexes; * Coasting = worsening of neuropathy signs/symptoms over months after drug withdrawal.

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CHAPTER 2.5

NEUROMUSCULAR TRANSMISSION

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Abstract

Neuromuscular transmission disorders such as myasthenia gravis and Lambert–Eaton myasthenic syndrome are rare in cancer patients. In recent years, myasthenia gravis has become a clinically relevant complication of cancer treatment with immune checkpoint inhibitors. Myasthenia gravis can appear after initiation of treatment and is frequently associated with additional muscle manifestations. So far myasthenia gravis has not been reported with conventional cytotoxic treatments.

Lambert–Eaton myasthenic syndrome (LEMS) can appear as a paraneoplastic disorder usually by a small-cell lung carcinoma. To date, LEMS has not been reported as a complication of cancer treatment.

Keywords: myasthenia gravis, Lambert–Eaton myasthenic syndrome, cancer, thymus, drug side effects, immune therapy

Myasthenia gravis is a prototypical autoimmune disorder that impairs neuromuscular transmission at the postsynaptic site. Several subtypes exist, defined by age of onset, antibody status and distribution of symptoms but importantly, myasthenia can also be a paraneoplastic syndrome as it is caused by a thymoma in 10% of patients.[1]

Several drugs can impair neuromuscular transmission and thus worsen existing or unmask subclinical myasthenia gravis. In particular, certain antibiotics such as telithromycin , fluoroquinolones, macrolides and aminoglycosides should be avoided.[1] Also, some drugs, e.g., d-penicillamine, may cause myasthenia or myasthenia like symptoms.[2] Until

recently, myasthenia was an ultra-rare complication of cancer treatment, only observed in a few cases of bladder cancer treated with intravesical Bacille Calmette-Guerin.[3,4] However, since the introduction of targeted immunotherapy and the development of immune checkpoint inhibitors (ICI), which dramatically changed the landscape of solid tumor therapy, myasthenia has become a more frequent and clinically relevant side effect of cancer treatment.[5]

Immune checkpoint molecules, specific receptors expressed on T-cells, are relevant regulators of immunologic homeostasis. They modulate T-cell maturation and play a key role in the maintenance of self-tolerance and thereby prevent the development of autoimmunity. ICI can act by blocking programmed death-1 receptor (PD-1), its ligand (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4). Currently used ICI, their mechanisms of action and their indications are listed in Table 2-5-1.

Table 2-5-1: Approved immune checkpoint inhibitors (ICI): mechanism of action and indications[6]

CTLA-4	Ipilimumab	Melanoma
PD-L1	Pembrolizumab Nivolumab	NSCLC, small-cell lung cancer, head and neck carcinoma, RCC, Hodgkin lymphoma, cervical carcinoma, PMBCL, urothelial carcinoma, hepatocellular carcinoma, gastric cancer
PD-1	Atezolizumab Durvalumab Avelumab	Urothelial cancer, NLCLC, Merckel cell carcinoma
CTLA-4 and PD-L1	Ipilimumab + nivolumab	Metastatic melanoma, RCC, colorectal cancer

CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; NSCLC, non-small-cell lung cancer; PD1, programmed cell death-1; PD-L-1, programmed cell death-ligand 1; PMBCL, primary mediastinal large B-cell lymphoma; RCC, renal-cell carcinoma.

However, the inhibition of these immune checkpoint molecules not only dramatically prolonged survival in patients with solid tumors, but also resulted in a wide range of autoimmune side effects including hepatitis, colitis, pneumonitis, dermatitis, nephritis, endocrinopathies, hypophysitis and autoimmune-neurological complications such as

encephalitis, transverse myelitis, immune-mediated neuropathies, myositis and myasthenia gravis.

Neuromuscular complications have been reported in up to 6% of treated patients,[7] the majority involving the central nervous system, However, several case series reported myasthenia gravis in patients treated with ICI.[8,9] The frequency of myasthenia was 0.12% in a two-years post-marketing safety survey in patients treated with nivolumab[8] and 0.15-0.20% in all PD-1 inhibitor-treated patients in Europe or America.[10] A disproportionality analysis using the World Health Organization pharmacovigilance database Vigibase compared adverse events reported in patients treated with ICI with the full database.[5] Myasthenia was reported in 0.47% (228 patients) of ICI treatments vs. 0.04% in the full database, resulting in a reporting odds ratio (ROR) of 16.5 [95% CI 14.5–18.9]. The ROR for myasthenia was higher than that for encephalitis (ROR 10.4), peripheral neuropathy and meningitis (ROR 3.1).

Myasthenia developed more frequently in patients treated with anti-PD-1/PD-L1 than with anti-CTLA-4 ICI.[5,8,9] In Vigibase,[5] 86.4% of cases with myasthenia were reported with anti-PD-1/PD-L1 monotherapy, 6.14% with anti-CTLA-4 monotherapy and 7.46% with combination therapy. Men (60.98%) were more frequently affected that women (39.2%), mean age of onset was 70.28 ± 10.50 years and 39.67%, 25.45% and 13.59% occurred in patients with lung cancer, malignant melanoma and renal-cell carcinoma (RCC), respectively.

It is suspected that ICI cause myasthenia by activating T-cells autoreactive to AChR molecules, which then results in the production of pathogenetic antibodies via B-cell activation.[8,10] Antibodies against acetylcholine receptor antibodies, which are present in approximately 70% of idiopathic myasthenia, were reported in 59%[9] and 83%[8] of ICI myasthenia. Interestingly, two patients with subclinical myasthenia and AChR-antibodies were AChR-antibody negative following ICI treatment despite developing myasthenic symptoms.[7] To date, antibodies against muscle-specific kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4), which can be found in idiopathic myasthenia, have not been reported in ICI-associated myasthenia.

Myasthenia was a *de novo* presentation in the majority of cases, but exacerbations of pre-existing myasthenia and subclinical myasthenia have also been described.[9] Patients usually developed generalized myasthenia, displaying the typical symptoms of the disease: diplopia, dysphagia, dysarthria, dyspnea, proximal weakness and fatigability, with variable and fluctuating severity. Myasthenic crises, life-threatening due to respiratory insufficiency and dysphagia, appear to be more frequent than in idiopathic

myasthenia.[8] Besides clinical symptoms and signs and the detection of AChR-antibodies, the diagnosis of myasthenia is supported by a significant decrement during repetitive nerve stimulation, increased jitter in single fiber electromyographic recordings or a positive response to edrophonium injections.[1]

Of all neurological side effects, myasthenia has the earliest onset, occurring within two to fifteen weeks (Kao) or a median of 29 days[5] after starting therapy. Of note is that creatine kinase (CK) elevation is frequent (up to 87%) in ICI-associated myasthenia[10] and concomitant inflammatory myopathy and myocarditis have been reported in up to 50%,[8] although a larger series found additional myositis in 16% and myocarditis in 10%.[5] CK values in one series of nivolumab-related myasthenia were 4,799 ± 4,415 U/l,[8] CK values >1000 U/l should raise the suspicion of myositis or myocarditis. Another indication of additional myositis is proximal weakness which does not fluctuate and is irresponsive to treatment. In these cases, needle EMG can show signs of an irritable myopathy, which is not seen in idiopathic myasthenia. Muscle biopsies of affected muscles that show immune-mediated inflammatory myopathy and infiltration of muscle fibers with $CD8^+$ T-cells have been reported in nivolumab-related myasthenia/myositis cases. Myocarditis has to be suspected when abrupt onset heart failure or arrhythmias occur. Elevated troponin T, abnormal ECG or echocardiogram and myocardial biopsy, which also shows $CD8^+$ T-cell infiltrates, help to secure the diagnosis.

In addition to stopping the treatment with ICI, treatment of ICI-associated myasthenia follows the same principles as the treatment of idiopathic myasthenia; pyridostigmine, steroids, intravenous immunoglobulin or plasma exchange.[1,11] Pyridostigmine is usually the first drug given orally in a daily dose of 180–360 mg; higher doses may be harmful. Although some effect of pyridostigmine is seen in most patients, prednisone is usually necessary to fully control symptoms. Dose regimes vary between 1 mg/kg/day and a starting dose of 10 mg/day. A higher dose may result in a more rapid response, however it carries the risk of a transient deterioration a few days after treatment initiation. Additional immunosuppression is generally used because of a steroid-sparing effect; the most frequently used drugs are azathioprine, mycophenolate-mofetil, or methotrexate, and in selected cases ciclosporin, tacrolimus or cyclophosphamide may be necessary to control the disease. Refractory myasthenia can be treated with rituximab or eculizumab. The efficacy of the latter has been demonstrated in a randomized controlled trial.[12]

Myasthenic crisis needs treatment in an intensive care unit. Besides respiratory support and symptomatic treatment, myasthenic crisis can be

treated with either intravenous immunoglobulins or plasma exchange, which had comparable efficacy in controlled studies.

Many patients respond favourably to treatment; however, the prognosis is worse than in idiopathic myasthenia. In a review of thirty published cases, fifteen improved with treatment, twelve died, one was refractory and two resolved spontaneously. Myasthenic crisis in ICI myasthenia is seven times more frequent than in idiopathic myasthenia[10] and more prevalent in patients with elevated CK levels. A fatality rate of 19.3% was cancer related in only a few.[5,10] The prognosis seems worse when myasthenia presents with myositis and myocarditis (death rate, 62%) than with myositis alone (20.7%) or with myocarditis alone (33%)[5]. In those who died of myasthenia, the median time to death was forty-three days.[5]

In conclusion, myasthenia is a rare but clinically relevant complication of cancer treatment with ICI. Myasthenia occurs early after initiation of treatment, is frequently associated with additional muscle manifestations such as myositis and myocarditis and carries a rather poor prognosis. Of note is that myasthenia has not been reported with conventional cytotoxic treatments.

A presynaptic neuromuscular transmission disorder, the Lambert–Eaton myasthenic syndrome (LEMS), also occurs in the context of cancer. It is a paraneoplastic disorder in approximately 50–60% of cases, commonly caused by a small-cell lung carcinoma.[13] To date, LEMS has not been reported as a complication of cancer treatment.

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CHAPTER 2.6

MYOPATHIES AND CANCER

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Abstract

Fatigue and muscle weakness are common symptoms in patients with cancer. Usually, such symptoms in this patient subgroup are due to the presence of cancer-related cachexia; a multiorgan process characterized by a dramatic reduction of body weight mostly at the expense of generalized loss of muscle mass and adipose tissue. Although its pathogenesis remains complex and not entirely understood, cachexia, when present, is the most likely explanation for the reduced muscle strength and limited physical performance these patients may have during their disease process. However, as important as recognizing cachexia as the main, and frequently only, contributory factor to muscle fatigue and muscle weakness in cancer patients, it is also crucial to consider the potential occurrence of neuromuscular complications which are often susceptible to specific treatments that improve patient's quality of life and prognosis. Thus, invasion of the structures of the peripheral nervous system by tumoral cells (infiltrative tumoral disease), impairment of such structures by immune attack due to their molecular mimicry with cancer cells (paraneoplastic syndromes) or toxic effects exerted by cancer treatments are not uncommon, and a prompt diagnosis and initiation of specific treatments and correct management may provide enormous benefit to patients.

Certain cancer treatments may exert a deleterious effect on skeletal muscle and cause a myopathy. Thus, myositis may occur as an immune-related adverse effect of checkpoint inhibitor agents within the first three months of therapy, or as a manifestation of chronic graft-versus-host disease that usually occurs at least three months after an allogenic blood or bone marrow transplant (as treatment for hematological malignancies). Radiation-induced myopathy is usually a painless and non-inflammatory myopathy affecting those muscles that were within the radiation field; a peculiarity of this myopathy is that it may clinically debut decades after completion of radiation treatment which emphasizes the importance of gathering a detailed history about cancer treatments that patients may have received in the remote past. Although not specific for cancer patients, steroid-induced myopathy, critical illness myopathy, and myopathies caused by electrolyte disturbances (whether or not directly related to cancer treatments) need to be considered as potential causes of muscle weakness in the proper clinical settings because of their frequency and good prognosis when preventative measures and correct management are initiated. Chemotherapy, although a well-known cause of polyneuropathy in cancer patients, rarely causes myopathy and other etiologies to account for a patient's muscle weakness will need to be explored.

Furthermore, we reviewed in this chapter those myopathies that carry an increased cancer risk. Thus, inclusion body myositis (the most common myopathy in patients older than 45 years of age) associates with a higher risk of lymphocytic leukemia, and myotonic dystrophy type 1 (the most frequent muscular dystrophy in adults) has been associated with thyroid, ovary, and colorectal cancers, among others. Lastly, myositis (i.e., dermatomyositis) and immune-mediated necrotizing myopathies have an increased risk for several malignancies including lung and breast cancers, and myositis-myasthenia overlap syndrome associates with thymomas; the prognosis of these myopathies often depends on the successful treatment of their associated cancers or tumors.

Keywords: immune checkpoint inhibitor-related myositis, radiation-induced myopathy, myositis related to chronic graft-versus-host disease, sarcopenia, chemotherapy, steroid-induced myopathy, critical illness myopathy, myopathy-associated cancers

Introduction

The peripheral nervous system is a complex and well-organized structure that includes spinal nerve roots, plexuses, peripheral nerves,

neuromuscular junctions, and skeletal muscles. Primary tumors of the peripheral nervous system are uncommon. However, neuromuscular manifestations in patients with cancer, either directly or indirectly related to the presence of malignancy are frequent. They may sometimes be overlooked or attributed to the constitutional syndrome, cachexia or fatigue that these patients commonly have. It is important to identify neuromuscular complications in the patient with cancer because they may affect quality of life, increase morbidity and mortality, affect prognosis, and their proper management may improve outcomes.

A detailed history and examination are key to determining whether a neuromuscular syndrome is present and to suspect potential causes or contributory factors responsible for it. The differential diagnosis in a cancer patient who develops a neuromuscular disorder is broad and includes: 1) direct infiltration of the peripheral nervous system by tumor cells (e.g., lymphomatous cells invading peripheral nerves), 2) neuromuscular paraneoplastic syndromes that may manifest prior to or following a cancer diagnosis (e.g., dermatomyositis or Lambert–Eaton myasthenic syndrome), 3) neuromuscular toxicity of cancer therapies (e.g., chemotherapy-induced polyneuropathy), and 4) multifactorial neuromuscular complications due to critical illness status, immobility, malnutrition and cachexia that cancer patients often suffer from (e.g., critical illness myopathy).

In this chapter, we specifically focus on the side effects of different modalities of cancer therapy affecting skeletal muscle (cancer therapy-induced myopathies). Thus, we discuss immunotherapeutic agents such as checkpoint inhibitors that may cause myositis within the first months of treatment or radiation therapy that may be responsible for a myopathy that occurs years after completion of treatment. Also, we will review those chemotherapeutic drugs, that although polyneuropathy is usually their most frequent neuromuscular complication, have also been associated with myopathies in some case reports. Steroid-induced myopathy has also been included in this chapter since steroids are often part of the treatment of the patient with cancer. Furthermore, we dedicate a section to the myositis associated with chronic graft-versus-host disease as a complication of allogenic hematopoietic cell transplantation which is the treatment for certain types of hematological cancers. Although not specific, critical illness myopathy may be seen in patients with cancer, particularly in those who undergo surgical procedures as part of their cancer treatment or develop a life-threatening complication during the course of the disease and need to stay in the intensive care unit for prolonged periods of time. We would like to raise awareness of critical illness myopathy for two

reasons; first because patients with this type of myopathy often undergo unnecessary work-up to identify the cause of their muscle weakness, and second but not less important, because early mobilization, physical therapy, and avoidance of myotoxic agents when possible may prevent patients from developing or exacerbating their motor deficits. Lastly, we summarize those primary myopathies that are associated with an increased cancer risk and in which cancer treatment may complicate the clinical course of these patients (e.g., general anesthesia in patients with myotonic dystrophy type 1, who have an increased cancer risk and may need a surgical procedure as part of cancer treatment, has been associated with an increased risk of perioperative respiratory failure).

1. Myopathy associated with immune checkpoint inhibitors

Immune checkpoint proteins refer to T cell receptors (and ligands) that trigger either co-stimulatory or inhibitory signals upon recognition of an antigen presented by an antigen-presenting cell or tumor cell. The balance between co-stimulatory and inhibitory signals is key to maintain self-tolerance and defend the human body from foreign substances (e.g., infection). However, tumor cells may be able to escape from the human immune response and become resistant to immunity. One modality of immunotherapy to treat tumors is directed to amplify the T-cell immune response by using antagonists of the inhibitory signals, so-called checkpoint inhibitors (CPIs).[1]

The use of CPIs in the treatment of malignancies has increased in recent years, and as a result the immune-related adverse effects (irAEs) associated with them have also increased. There are different groups of CPIs based on the inhibitory T cell signaling that they act on.[2] Thus, ipilimumab blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), pembrolizumab and nivolumab block programmed cell death 1 (PD-1) on the T-cell, and atezolizumab, avelumab, and durvalumab block programmed cell death-ligand 1 (PDL1) on the antigen-presenting cell or tumor cell (Figure 2-6-1). They are currently used to treat cancers such as melanoma, renal cell carcinoma, mesothelioma, and lung cancer. Unfortunately, this boost of the immune T cell response does not selectively attack tumor cells, but it may also attack other organs disrupting the innate immune self-tolerance that protects healthy human tissue in normal conditions. As a result, irAEs may develop; some of these are associated with significant morbidity and increased mortality, and discontinuation of CPI therapy is sometimes needed despite the risk of

tumor progression. Non-neurological irAES are the most frequent adverse effects (approximately 10–15% of patients treated with PD-1 inhibitors) and may affect gastrointestinal (e.g., colitis), endocrine (e.g., hypothyroidism), cardiovascular (e.g., myocarditis), pulmonary, renal, genitourinary, dermal, and hematopoietic systems. Neurological irAEs are

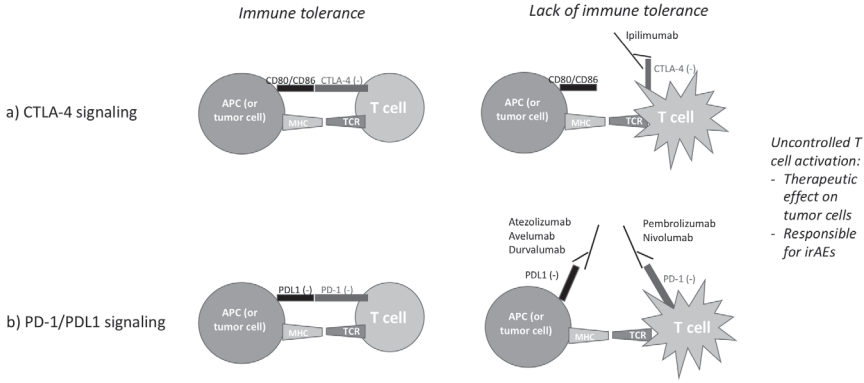

Figure 2-6-1: Effect of immune checkpoint inhibitors (CPIs). In normal conditions, a balance between positive and negative co-stimulatory signals between antigen-presenting cell (APC) and T cells allows for immune tolerance. In patients with cancer, tumor cells may act as APCs and escape from immune attack because the balance between positive and negative co-stimulatory signals remains intact. Check point inhibitor (CPI) drugs disrupt this balance resulting in an uncontrolled T cell response that will attack tumor cells (desirable therapeutic effect) but also other organ tissues leading to undesirable immune-related adverse events (irAEs). Examples of CPIs are: ipilimumab that blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), pembrolizumab and nivolumab that block programmed cell death 1 (PD-1) on the T-cell, and atezolizumab, avelumab, and durvalumab that block programmed cell death-ligand 1 (PDL1) on the antigen-presenting cell or tumor cell.

less common (approximately 1–4% of patients taking PD-1 inhibitors) and of these neuromuscular complications are by far the most frequent irAEs (they account for approximately 60–75% of the total neurological complications developed by patients taking PD1-inhibitors).[3–6] In this section, we will focus on neuromuscular irAEs associated with CPI therapy, and more particularly on CPI-related myopathies.

Neuromuscular complications associated with CPIs usually occur within the first three months following initiation of therapy and may affect peripheral nerves (e.g., Guillain-Barré syndrome), neuromuscular

junctions (more frequently in the form of myasthenia), and skeletal muscle (mostly myositis). Also the presence of overlap syndromes is not uncommon—myasthenia and myositis, myositis and myocarditis, or any other combination. A large recent retrospective series of 81 patients with neuromuscular complications associated with CPIs reported 30 with new-onset or exacerbation of previously diagnosed myasthenia gravis (mostly generalized and acetylcholine receptor-seropositive myasthenia), 29 with neuropathy (Guillain-Barré syndrome was the most common phenotype within this group), and 22 with myopathy (one patient had a hypothyroidism-related myopathy, whereas the majority developed myositis). [6] About half of the patients developed myasthenia and myositis. Thus, skeletal muscle appears to be the organ more commonly affected in patients with CPI-related neuromuscular complications. The combination of two CPIs appeared to be associated with increased risk of myositis. In addition, concomitant myocarditis was seen in six patients with myositis alerting to the coexistence of both in a frequency higher than would be expected by just coincidence; this association has been associated with poor prognosis.[7–13]

The typical phenotype of patients with CPI-related myositis is characterized by myalgias as the initial symptom followed by proximal arm and leg weakness progressing within the first two months after initiation of CPI therapy. Axial weakness (predominantly affecting neck extensor muscles and leading to a dropped head syndrome), ptosis and extraocular muscle weakness causing diplopia, and bulbar muscle weakness are common. Some also develop concomitant myocarditis resulting in dilated cardiomyopathy and heart failure, and ventilatory insufficiency due to the involvement of diaphragm muscle. Creatine kinase (CK) can be markedly elevated (e.g., five to fifty times normal). Myositis-associated and specific autoantibodies are often negative. Electromyography studies (EMG) on weak muscles demonstrate increased insertional activity and abnormal spontaneous activity in the form of fibrillation potentials and positive sharp waves with early recruitment of short-duration and low-amplitude motor unit potentials as also seen in other types of myositis. The characteristic morphological features on muscle biopsies are characterized by a severe necrotizing myopathy with multifocal clusters of necrotic myofibers, significant macrophage and T cell infiltrates (predominantly CD8+ lymphocytes), and strongly MHC-I and C5b-9 staining of the sarcolemma of necrotic fibers[9] (Figure 2-6-2).

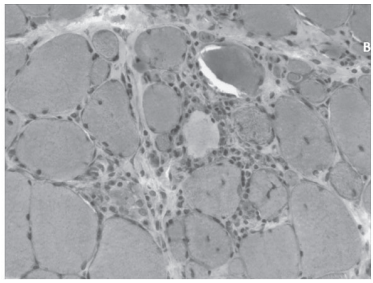

Figure 2-6-2: Myositis associated with immune check point inhibitor therapy. Muscle biopsy (hematoxylin and eosin) demonstrates clustered necrotic muscle fibers and predominantly endomysial inflammatory infiltrates in a patient receiving immune CPI therapy.

Weakness in a CPI-treated patient mandatorily prompts consideration of a myositis, myasthenia, or polyneuropathy as an irAE of this therapy. It is important to also consider if the myopathy might be a paraneoplastic syndrome as opposed to an irAE secondary to CPI therapy; the former would support the continuity of tumor therapy, whereas the latter would prompt discontinuation of this therapy. In theory, CPI therapy may aggravate a pre-existing and subclinical autoimmune response in the patient with cancer converting a clinically silent myositis into a clinically evident myositis rather than causing a *de novo* myositis. In general, clinical improvement following discontinuation of ICP therapy favors an ICP-related myositis if ICPs play a causative or aggravating role in the pathogenesis of myositis.[14–17] It is also important to consider myocarditis as a contributing cause of a patient's weakness.

A 3-Hz repetitive nerve stimulation study on a clinically weak muscle showing a higher than 10% decrement in the amplitude from the first to the fifth compound motor action potential, and the presence of positive acetylcholine receptor antibodies in blood (which are positive in two-thirds of patients with CPI-related myasthenia) would favor the coexistence of myasthenia and myositis. In addition, high troponin T levels, abnormal cardiac MRI or echocardiogram, and endomyocardial biopsy when clinically indicated showing necrosis of cardiomyocytes and inflammatory infiltrates would suggest a concomitant myocarditis.

Management of irAEs needs to be individualized based on tumor progression and severity of adverse effects. Thus, cautious assessment of the risks and benefits regarding discontinuation of CPI therapy is crucial. In general, the treatment of irAEs includes discontinuation of the offending drug (which may be enough in some cases) and/or the initiation

of immunomodulatory therapies such as corticosteroids, intravenous immunoglobulins (IVIG), plasma exchange (PLEX), and steroid-sparing immunosuppressive therapy. A short course of intravenous corticosteroids (methylprednisolone 1 gm/d for 3–5 days) followed by oral prednisone (1–2 mg/kg/d) is the first-line treatment for CPI-related myositis. In the presence of concomitant myocarditis, a higher prednisone dose may be required (4mg/kg/d). High-dose prednisone is maintained until stable clinical recovery is reached or until no further improvement occurs, it is then followed by a slow taper with close monitoring of symptoms and examination (and CK levels) since a relapse during this period may occur which would require increasing prednisone up to the minimal effective dose. IVIG or PLEX may be considered as adjuvant therapies if clinical response to steroid therapy is incomplete or if the full prednisone dose cannot be maintained in time (e.g., uncontrolled diabetes as side effect of steroids). Also, a steroid-sparing agent is often started to facilitate steroid taper. Methotrexate, which we usually use in the treatment of other types of immune-mediated myositis, has been used as a steroid-sparing agent in ICP-related myositis.[9] We usually recommend methotrexate 7.5–25 mg/week divided into two doses taken 24 hours apart to minimize side effects. It is important to be aware of the important side effects steroid-sparing agents may have since they may exacerbate already existing conditions in the patient with cancer. Thus, hepatotoxicity, pulmonary fibrosis, infection, neoplasia, leukopenia, and gastritis are some of the side effects associated with methotrexate. Daily folic acid supplementation to prevent myelosuppression, blood tests including cell blood count with differential and liver enzymes, and pulmonary function tests prior to and periodically during methotrexate treatment are recommended to monitor for potential side effects. In addition to close monitoring of the patient's symptoms and examination, CK may help to make early adjustments to the therapy regimen. Thus, a significant increase of the CK level even in the absence of clinical decline will alert the clinician to the need to intensify treatment in anticipation of a possible relapse, especially during steroid taper. Whether resuming the same CPI agent at lower doses or initiating a different class of CPI at a later time ameliorates or prevents irAEs developing again is unknown and decisions in this regard need to be individualized after careful risk and benefit assessment.

2. Radiation therapy-associated myopathy

The goal of radiation therapy is to kill fast-dividing tumor cells while minimizing the area of exposure to protect normal and radiosensitive

organs from radiation toxicity. There are multiple factors that determine radiation toxicity such as the volume of irradiated tissue, daily and cumulative dose, and frequency of treatment. Although the pathophysiology of radiation toxicity is not entirely understood, there are three stages that have been described to explain the fibrotic process that tissue may undergo when exposed to radiation therapy. The first phase is called the pre-fibrotic phase and it is characterized by the dysfunction of endothelial cells resulting in increased vascular permeability, edema, focal inflammation, and sometimes local ischemia due to vascular thrombosis events. The second stage is characterized by the presence of activated fibroblasts leading to increased connective tissue in a patchy distribution within a disorganized extracellular matrix; this process may be perpetuated in time due to an ongoing inflammatory response. The third stage is called the fibroatrophic phase and is characterized by a dense extracellular matrix that is poorly vascularized and friable. This last phase may occur many years after completion of radiation therapy and is responsible for most of the neuromuscular complications associated with radiation therapy.[18,19]

Radiation-induced neuromuscular complications are commonly seen in survivors of head and neck cancers or survivors of Hodgkin lymphoma who received mantle radiation therapy which includes all lymph nodes from the jaw to the diaphragm muscle within the radiation field. In these situations, cervical spinal cord, cervical nerve roots, brachial plexuses, peripheral nerves (e.g., phrenic nerves, suprascapular nerves, long thoracic nerves) and cervical paraspinal and proximal upper limb muscles are susceptible to radiation-induced damage. The term myelo-radiculo-plexo-neuro-myopathy is often used to summarize the broad involvement of peripheral nervous system structures that radiation toxicity may cause in these patients. In this section, we will specifically focus on radiation-induced myopathy although it often coexists with damage of neural structures.[18,19]

Radiation-induced myopathy usually manifests years or even decades after completion of radiation therapy as a complication of the fibroatrophic stage. Thus, a detailed history of remote cancer and specific treatments that the patient received (including radiation dose and exposure field when possible) is crucial to suspect radiation-induced skeletal muscle damage. Survivors of head and neck cancers and Hodgkin lymphomas who were treated with radiation therapy are more likely to develop neuromuscular complications given the inclusion of important peripheral nervous system structures within the radiation field. These patients may develop gradual and painless weakness of neck extensors and proximal muscles of upper limbs accompanied by progressive muscle atrophy of cervical paraspinal,

periscapular, and shoulder girdle muscles. Thus, dropped head syndrome is a known late complication of radiation therapy. CK is usually normal. Electrodiagnostic studies often reveal a combination of neuropathic and myopathic features. Thus, concentric needle EMG may demonstrate reduced insertional activity in severely fibrotic muscles, abnormal spontaneous activity in the form of myokymic discharges (an electrical feature of motor nerve impairment) and early recruitment of small motor unit potentials (as seen in myopathies) that are interspersed with reduced recruitment of large motor unit potentials (as seen in neurogenic disorders). Biopsy of an affected muscle may also reveal a combination of non-specific neuropathic and myopathic changes such as scattered atrophic myofibers and central nuclei, respectively. Interestingly, nemaline rods have been observed in an irradiated muscle of one patient with radiation-induced dropped head syndrome.[20] Unfortunately, there is no effective treatment for radiation-induced myopathy. Cervical collar and physical therapy are the main pillars of management.

In addition, it is important to be aware of the radiation call phenomenon which refers to an acute inflammatory response on a previously irradiated tissue following administration of specific medications such as chemotherapeutic agents. Thus, although most of the radiation call reactions affect the skin (dermatitis), myositis has also been reported following treatment with gemcitabine. This reaction may occur days or years after completion of radiation therapy and following initial or repeated doses of gemcitabine. Thus, localized muscle pain and swelling in a remotely irradiated muscle tissue following gemcitabine administration should prompt the clinician to consider a radiation call reaction in the form of myositis.[21–24] The treatment of this reaction includes discontinuation of the drug and symptom management with anti-inflammatory and/or steroid treatment for rapid symptom control. Re-challenging the patient with the same chemotherapeutic drug has been described in the literature with good results in some cases.[25, 26]

3. Chemotherapy-associated Myopathy

Cancer patients receiving chemotherapy frequently report fatigue (90–100% of patients) which probably has a multifactorial cause in this patient group. Fatigue is a complex symptom that not only refers to subjective physical tiredness but also intellectual exhaustion. Although it is sometimes difficult to differentiate muscle fatigue from muscle weakness, especially in a cancer patient who may have a constitutional syndrome, it is important to establish the difference to avoid unnecessary work-up and

to initiate proper management. Muscle fatigue is defined by loss of muscle force that is restored by rest; whereas, muscle weakness is the loss of muscle force that is not reversible by rest. One can argue that patients with myasthenia have muscle fatigue, however most of the time this muscle fatigue is accompanied by some degree of muscle weakness in our experience, and the common presence of ocular symptoms (diplopia, ptosis) in these patients would prompt the clinician to favor myasthenia rather than cancer-related fatigue in these situations. Symptomatic treatments for fatigue in cancer patients include nonpharmacologic and pharmacologic approaches. Thus, cognitive-behavioral interventions, sleep therapy, exercise, and medications such as modafinil and methylphenidate can be considered.[27, 28]

Chemotherapy has also been associated with sarcopenia which is defined as the loss of muscle mass accompanied by a reduction in muscle strength or reduced physical performance. Thus, sarcopenia is an aging-related process that chemotherapeutic agents may accelerate, and it affects all muscles to some degree without a specific distribution pattern. Although these patients may present muscle weakness on examination it correlates with generalized loss of muscle bulk, unlike in myopathies where muscle weakness precedes muscle wasting affecting predominantly proximal muscles, at least in early stages.[29]

The most frequent neuromuscular side effect of chemotherapeutic agents is polyneuropathy rather than myopathy which is uncommon. Furthermore, when any cancer patient (whether or not they are receiving any cancer treatment modality) develops a myopathy we should consider a broad differential diagnosis prior to concluding that chemotherapeutic agents (or other treatment) are directly causing the patient's muscle weakness. Thus, electrolyte imbalance which may be related or unrelated to treatment (e.g., hypokalemia as a result of severe diarrhea) may cause a myopathy and metabolic correction in these cases will restore the patient's muscle strength. Hypokalemia, hypocalcemia, and hypophosphatemia can complicate the clinical course of cancer patients and be responsible for their muscle weakness. Thus, identification of electrolyte abnormalities and their correction is mandatory, especially in this patient group. In addition, there are two other types of myopathies that need to be considered in patients with cancer: critical illness myopathy and steroid-induced myopathy. We will discuss both later in this chapter.

Although uncommon, some chemotherapeutic agents have been associated with myopathy in some case reports. Thus, vincristine (an antimicrotubular agent) has been reported to cause a neuromyopathy in three patients whose muscle biopsies revealed necrotic muscle fibers,

myophagocytosis, and occasional myofibrillary subsarcolemmal masses.[30] Imatinib (a tyrosine kinase inhibitor) caused myalgias in up to 50% of patients whereas its association with polymyositis is debated.[31] Alpha-interferon (an antiviral drug) has been associated with polymyositis and dermatomyositis.[32,33] Hydroxyurea (a ribonucleotide reductase and DNA synthesis inhibitor) has been reported to cause myositis in one patient and has also been associated with amyopathic dermatomyositis in several reports.[34,35] Finasteride (a 5-alpha reductase inhibitor) has been reported to cause myalgia, hyperCKemia, and myositis.[36,37]

4. Steroid-induced Myopathy

Glucocorticoids, and particularly fluorinated glucocorticoids (dexamethasone, betamethasone, triamcinolone), may cause myopathy due to their catabolic effect on skeletal muscle by the degradation of myofibrillar proteins, inhibition of growth factors, myostatin stimulation, and mitochondrial dysfunction among other pathogenic mechanisms. There are two forms of steroid-induced myopathy: acute and chronic.[38]

Acute steroid-induced myopathy often occurs in intensive care units in critically ill patients who may be intubated, have sepsis, and are receiving neuromuscular non-depolarizing agents. Thus, the acute form of steroid-induced myopathy is frequently part of a critical illness myopathy that we will discuss later in this chapter. Special caution needs to be taken with methylprednisolone, in that although it is a nonfluorinated glucocorticoid it is frequently used in inpatient settings and it may cause acute muscle weakness in these patients. Of note, and unlike chronic steroid-induced myopathy, myalgias may be present and CK may be elevated in patients with acute steroid-induced myopathy.[39]

Chronic steroid-induced myopathy is more common, it occurs in outpatient settings, and the groups at risk of developing this myopathy are the elderly, cancer patients, patients with respiratory diseases, and physically inactive patients. Although fluorinated glucocorticoids are associated with a higher risk of causing this type of myopathy, nonfluorinated preparations such as prednisone and prednisolone are commonly used, and in our experience, most of the patients with chronic steroid-induced myopathy we have seen were taking prednisone. Also, the chronic use of inhaled steroids in patients with respiratory diseases have been associated with this type of myopathy. The minimum prednisone dose or treatment duration that is associated with a higher risk of developing this type of myopathy varies among patients. In general, prednisone or an equivalent drug in doses of 40–60 mg/d for more than

one month may result in muscle weakness. These patients complain of slowly progressive, proximal, and painless muscle weakness that predominantly affects pelvic girdle muscles and it can be accompanied by muscle atrophy. CK is usually normal. Electrodiagnostic studies are usually normal, at least in the early stages, which can be explained by the selective involvement of type 2 muscle fibers which do not contribute (or contribute very little) to the recruitment of motor units on concentric needle EMG. However, in later stages, a non-irritable myopathic pattern with early recruitment of small motor unit potentials in weak muscles may be observed. The typical pathological finding on muscle biopsy reveals a selective atrophy of type 2 muscle (in particular, type 2B fibers) (Figure 2-6-3). Treatment consists of discontinuation or reduction in corticosteroid dose if possible and initiation of a regular physical therapy regimen. Substitution of fluorinated glucocorticoid with a nonfluorinated glucocorticoid may be considered. It is important to know that recovery of strength may take months or years after discontinuation of steroid therapy.[38,40,41]

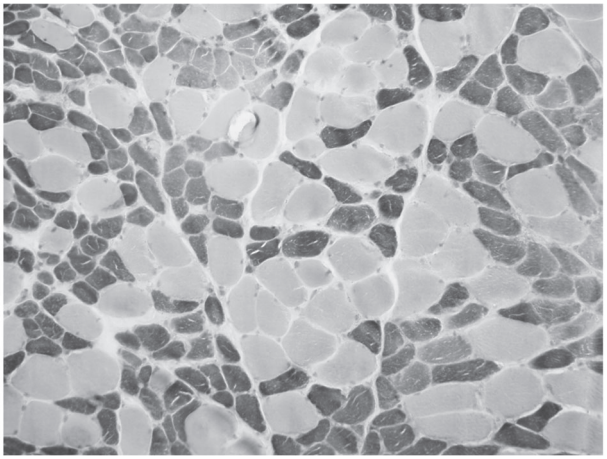

Figure 2-6-3 Steroid-induced myopathy. A 77 year old woman who had been taking daily high-dose prednisone for approximately five years developed proximal muscle weakness. A muscle biopsy of a clinically weak gluteal muscle revealed atrophy of type 2 muscle fibers (dark fibers) on ATPase 9.4 staining (200X).

5. Myopathy associated with chronic graft-versus-host disease

Chronic graft-versus-host disease (cGVHD) is a multiorgan inflammation occurring at least three months after allogenic blood or bone marrow transplantation which is the treatment for certain hematological cancers. The pathophysiology of this cancer treatment-related complication is not entirely understood; one of the hypotheses is that alloreactive T cells attack the thymic tissue of the host, and as a consequence, there is a loss of peripheral immune tolerance by the host autoreactive T cells which then attack several tissues leading to the characteristic multiorgan inflammation. It is important to consider cGVHD in any patient with symptoms involving different organs and a history of bone marrow transplantation, even if the transplant occurred years ago, which is sometimes the case. The organs more frequently involved are skin, eyes, mucosa, gastrointestinal tract and liver. Neurologic manifestations are fortunately rare, they may also occur years after transplantation, and although the central nervous system may be affected, neuromuscular complications are more frequent, affecting approximately 8% of patients. Thus, neuropathy, myasthenia, and more frequently myositis (incidence of 2–3%) are known to be clinical manifestations of cGVHD.[42–44]

Myositis associated with cGVHD is characterized by proximal muscle weakness. Muscle pain is common and may be associated with concomitant fasciitis. Dysphagia may also occur due to the involvement of striated muscles of the upper esophagus and pharynx. Other clinical features include myocarditis and respiratory symptoms. Some patients develop a dermatomyositis-like rash around the eyes (heliotrope rash), chest, over the knuckles (Gottron papules), and extensor surfaces of the joints.[44, 45] It may coexist with other organ involvement (dermatitis, hepatitis, etc.) which will help to raise the diagnostic suspicion. CK is often elevated, although it can be normal in the early stages. Myositis-specific antibodies are usually negative. As in other types of myositis, needle EMG of weak muscles often demonstrates increased insertional activity and abnormal spontaneous activity in the form of fibrillation potentials and positive sharp waves with early recruitment of short-duration and small-amplitude motor unit potentials. Histopathological features of a biopsied muscle reveal segmental necrotic fibers and endomysial, perimysial, and perivascular inflammatory T cells that rarely may invade non-necrotic muscle fibers.[46] There have been some reports documenting whether these infiltrating T cells were donor or recipient T cells; the former appears to better support a cGVHD-related myositis

whereas the latter may suggest other types of myositis. These chimerism studies may have a diagnostic and prognostic value since cGVHD-related myositis appears to be more responsive to immunosuppression than other types of myositis.[47,48]

It is important to mention that not all myopathies occurring after bone marrow transplantation are cGVHD-related myositis. Thus, steroid-induced myopathy, necrotizing myopathies, and anti-MDA5-associated dermatomyositis have been also reported in these patients.[47]

There are no controlled studies investigating the best therapeutic regimen for cGVHD-related myositis**.** As in other myositis, corticosteroids are often the first line of treatment; they may lead to improvement of strength within four to six weeks. Once the patient fully recovers or improvement reaches a plateau a slow steroid taper with close monitoring is advised to minimize the risk of relapses.[49] Intravenous immunoglobulin (IVIG) can be also considered. A steroid-sparing agent is often started at the same time as steroid initiation. In refractory cases, rituximab is used. Although usually not related to myositis, muscle cramps (more frequently attributable to motor nerve hyperexcitability) are often reported by patients with cGVHD. Symptomatic treatment for cramps including channel-blocking agents (such as gabapentin or carbamazepine) or muscle relaxants (such as baclofen) may be considered.[44,50]

6. Critical illness Myopathy

Patients with cancer may become critically ill during their disease for various reasons which can be directly or indirectly related to their cancer or treatment. Thus, uncontrolled pain requiring high doses of intravenous opioids, respiratory compromise due to direct cancer invasion of airways or by treatment with sedation and potent analgesics, or a life-threatening infection and sepsis in the setting of chemotherapy-induced neutropenia are common complications seen in cancer patients for which they require prolonged stays in the intensive care unit. Critically ill patients often require mechanical ventilation, sedation, and neuromuscular blocking agents which increase the risk of developing a critical illness myopathy. Also, glucocorticoid administration, hyperglycemia, and female gender (probably due to a lower muscle mass than men) have been associated with a higher risk of developing critical illness myopathy.

One of the challenges for the clinician is to detect muscle weakness in these critically ill patients who are often intubated and under sedative and neuromuscular blocking effects. The clinical suspicion for critical illness myopathy sometimes occurs when the patient cannot be extubated despite

successful treatment and resolution of the primary condition for which they were originally started on mechanical ventilation. It is then when a consultation with the neurology team is often requested because the patient is alert, understands and follows commands well, however they cannot move their limbs and are still fully dependent on mechanical ventilation. Examination then demonstrates a flaccid quadriparesis that predominantly involves proximal and pelvic girdle muscles, absent or reduced deep tendon reflexes, and respiratory weakness due to diaphragm involvement which has been an inactive muscle while receiving mechanical ventilation support. Electrodiagnostic studies can be helpful to support the suspicion of critical illness myopathy, however, they are challenging too because of the presence of external artifacts in intensive care units, and also because these patients frequently have edemas in distal limbs due to prolonged immobilization. Nerve conduction studies are characterized by prolonged duration and diminished amplitudes of the compound motor action potential at distal and proximal stimulation sites (without evidence of temporal dispersion that would suggest a demyelinating neuropathy instead) with a specificity close to 100% when these findings are seen in more than one nerve.[52] Also, reduced muscle membrane excitability on direct muscle stimulation is typical for this condition and it is thought to be caused by impairment of muscle sodium channels; thereby some consider this type of myopathy a channelopathy. On the other hand, conduction velocities (although sometimes slowed due to low body temperature) and sensory nerve action potentials (although more susceptible to artifacts) are usually normal or at least much less impaired than motor nerves. CK may be elevated (two to three times normal). Muscle biopsy findings may reveal necrotic muscle fibers, selective atrophy of type 2 muscle fibers, and a characteristic selective loss of thick filaments (myosin) on electron microscopy.

Awareness of this condition, preventative measures, and early initiation of treatment are key to minimize motor deficits in these patients. Thus, it is important to be aware that any patient in an intensive care unit is at risk of developing this type of myopathy and that minimizing contributory factors, when possible, and initiating early mobilization will help to minimize the risk. Interruption of sedation on a daily basis, reduction of sedative, neuromuscular blocking agent, and glucocorticoid doses, moderate control of glycemia to avoid hyper and hypoglycemia, and physical therapy have been proposed as preventative and therapeutic measures. Furthermore, mobilization of hemodynamically stable patients, even when they are still receiving mechanical ventilation support, has been associated with better outcomes.[53,54]

Although both critical illness myopathy and critical illness polyneuropathy may coexist, the former is more frequent, it better accounts for proximal muscle weakness that these patients develop, and it is fortunately associated with higher recovery rates.

7. Myopathies associated with an increased cancer risk

The skeletal muscle side effects of cancer treatments may be more pronounced in those patients with an underlying myopathy. Thus, certain precautions and closer monitoring of muscle strength and respiratory status of those patients with myopathies who need treatment for cancer is recommended. In general, a patient with myopathy has the same cancer risk as the general population, and therefore they should undergo the recommended malignancy screenings as would subjects without myopathy. However, there are some myopathies that are associated with an increased risk for specific types of cancer. [55–62] (Table 2-6-1). Also, some of these myopathies are well known to have an increased risk of cancer therapy-related complications. For example, patients with myotonic dystrophy type 1 have high sensitivity to anesthetics, sedatives, and opioids drugs that are often used as part of the treatment for cancers which these patients also have an increased risk for.

Table 2.6: Myopathies associated with an increased tumor or cancer risk.

	Type of tumor/cancer	Malignancy screening	Precautions during tumor/cancer treatment
Myotonic muscular dystrophy type 1	Thyroid, endometrium, ovary, melanoma, colorectal, testis.[55]	Thyroid stimulating hormone level in blood, pelvis ultrasound, skin inspection, and colonoscopy may be considered.	Anticipate an increased anesthetic risk, slow awakening from anesthesia, and increased drug sensitivity to opioids and sedatives. Awake extubation and postoperatively monitoring in ICU is highly recommended.[56]
Sporadic inclusion body myositis	T cell large granular lymphocytic leukemia/B cell chronic lymphocytic leukemia.[57]	Complete blood count with differential.	-----
Dermatomyositis	Lung, ovary, breast, colorectal, cervical, bladder, nasopharyngeal, esophageal, pancreatic, colon, and kidney. *Tif-1 antibodies are associated with cancer with a 70% sensitivity and 89% specificity.*[58]	Chest, abdomen, and pelvis CT or whole-body PET during the first 3-5 years following diagnosis, especially if presence of antibodies	-----

Immune-mediated necrotizing myopathies	Lung, ovary, breast, kidney, GI tract. *HMGCR antibodies or the absence of myositis-specific antibodies are associated with increased cancer risk.* *Association of SRP antibodies and cancer is weaker.*[59]	associated with malignancy or refractory myositis.	-----
Idiopathic myositis and myasthenia (overlap syndrome)	Thymoma[16]	Chest CT	Stabilization of myasthenic symptoms prior to thymectomy.
Late-onset sporadic nemaline myopathy	Monoclonal gammopathy[60,61]	SPEP with IFE	-----
Glycogen storage disease type 1a (von Gierke disease)	Hepatocellular adenoma/adenocarcinoma[62]	Abdominal CT and/or liver US	-----

Conclusions

Patients with cancer often have fatigue, cachexia, or sarcopenia that need to be differentiated from muscle weakness related to a myopathy which is less frequent. In our experience, the most common myopathies in cancer patients, and although not specific of this patient group, are steroid-induced myopathy, critical illness myopathy, and myopathies related to electrolyte abnormalities; these need to be considered in the appropriate settings because the adjustment of corticosteroid dose, early mobilization, and electrolyte correction may result in improved patient's strength without requiring modification of more specific cancer treatments. CPIs and bone marrow transplantation complicated with cGVHD may both cause myositis; within the first three months of therapy in the former and after three months from transplantation in the latter; in both cases, optimal treatment for myositis is required. Radiation may cause a myopathy years after completion of radiotherapy that unfortunately does not yet have a specific treatment. Lastly, chemotherapeutic agents are very rarely a cause of myopathy and other etiologies should be considered in the differential diagnosis prior to discontinuation of chemotherapeutic agents.

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CHAPTER 2.7

THE CANCER CACHEXIA SYNDROME

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Abstract

Cancer associated cachexia is defined as “a multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.” It is commonly observed in patients with incurable neoplasms and is associated with increased morbidity and mortality; however, it may pass clinically undetected in overweight/obese patients. The pathophysiology involves the production of tumor- and host-derived mediators that cause anorexia, alterations of energy balance, excess catabolism and systemic inflammation leading to involuntary weight loss, which is the principal clinical feature. The syndrome is considered as a continuum of three distinct stages: pre-cachexia, cachexia and refractory cachexia. Diagnosis is based on weight loss history with cutoffs that vary in relation to the patient’s body mass index and muscle mass. However, neither laboratory biomarkers, nor the gradual demographic shift in cancer patients toward obesity have been taken into account in this perception, and efforts to improve this current definition are in progress. Screening for early signs of cachexia is of vital importance, as it is believed that timely initiation of any treatment modality is a key component for an effective management. Other confounding factors such as age, comorbidities, uncontrolled symptoms, and/or toxicity of antineoplastic therapies that might potentially impair the process of food intake and/or directly affect body stature should be recognized and treated at this point. Considering the absence of a validated clinical tool in this field, some other nutritional screening questionnaires, originally developed for different clinical entities that still cover some of the main domains of the syndrome, could be used. Targeted

patients should be referred for an in-depth assessment, through which the multidimensional nature of cancer cachexia should be appraised. Protein-caloric balance, body composition analysis, physical activity and systemic inflammation, should be assessed—ideally on an individualized basis—as well as other, broader aspects of cachexia such as psychosocial status and quality of life. All these parameters combined with clinical data (stage of the disease, potential response to therapy) will aid the development of a nutritional care plan. Currently, no standard guidelines for the treatment of cancer cachexia exist. Still, nutritional support is believed to be the basis of any intervention and the patient's daily nutritional deficits should be restored. However, by definition, this cannot be enough given the complexity of the syndrome. Exercise has a good rationale as a therapeutic modality because it combines an anti-inflammatory effect together with a potent anabolic stimulus on musculature, and it seems to be safe. However, data from clinical trials are lacking and the level of evidence is currently low. Lastly, up to now, no pharmacological therapy has ever been approved for the treatment of cancer cachexia. Nevertheless, there are some older drugs with a reasonable mechanism of action, such as orexigenic and prokinetic agents, that are being used in clinical practice. Based on the recent progress in understanding the pathophysiology of the syndrome, newer drugs have been developed and are now being tested in modern designed, robust clinical trials.

Keywords: Cancer, cachexia, malnutrition, sarcopenia, muscle wasting, sarcopenic obesity, lipolysis, inflammation, energy balance, body composition, malnutrition, anorexia, nutritional screening, nutritional assessment, quality of life, nutritional support, physical performance, exercise, nutraceuticals, anabolic agents, survival

Introduction

1.1. Definition

Cachexia is a syndrome of deterioration that always occurs in association with an underlying disease and is related to involuntary loss of body weight, alterations of body composition and loss of homeostatic control of energy-protein balance. Cancer cachexia, specifically, has been recently defined by an international consensus as "a multifactorial syndrome characterized by ongoing loss of muscle mass (with or without loss of fat) that cannot be completely reversed by conventional nutritional support and eventually leads to progressive functional impairments."[1]

1.2. Frequency

The frequency of the syndrome varies in relation to the primary site: patients with pancreatic, gastro-esophageal or head and neck tumors are more prone to develop cachexia due to anatomical reasons (i.e., obstruction of the gastrointestinal tract) and/or specific pathophysiological characteristics (i.e., overproduction of cytokines and other pro-inflammatory mediators). In these cases, the prevalence of cachexia may range between 55–70% while for other primaries (e.g., prostate or breast cancer) it does not exceed 15–25% even in end-of-life stages. Other particular features such as metastatic stage at diagnosis, advanced age, female gender and the presence of other comorbidities may contribute further to the severity of the syndrome and may link cachexia with adverse clinical outcomes.[2]

1.3. Stages of cachexia

According to the international consensus cachexia exists through a range of three stages of progressive severity:[1]

1. In an original "pre-cachectic stage" there are some minor symptoms and signs such as anorexia and/or impaired glucose tolerance but no significant involuntary weight loss.
2. An established "cachectic stage" follows and is characterized by reduced food intake and signs of systemic inflammation and patients report weight loss of >5 % over the past six months, or >2% if body mass index (BMI) is <20 kg/m^2 or sarcopenia is present.
3. The refractory cachectic stage usually accompanies the final stage of cancer and signifies a highly catabolic state. It is defined by a low performance status (World Health Organization [WHO] score 3 or 4) and a life expectancy of less than three months.

From a therapeutic standpoint, it is believed that as cachexia progresses, the odds for effective intervention are restricting and in the final stage of refractory cachexia, when patients are bedridden, the reversal of functionality is practically impossible. The incorporation of the aforementioned stages of cachexia into the disease's trajectory is shown in Figure 2-7-1.

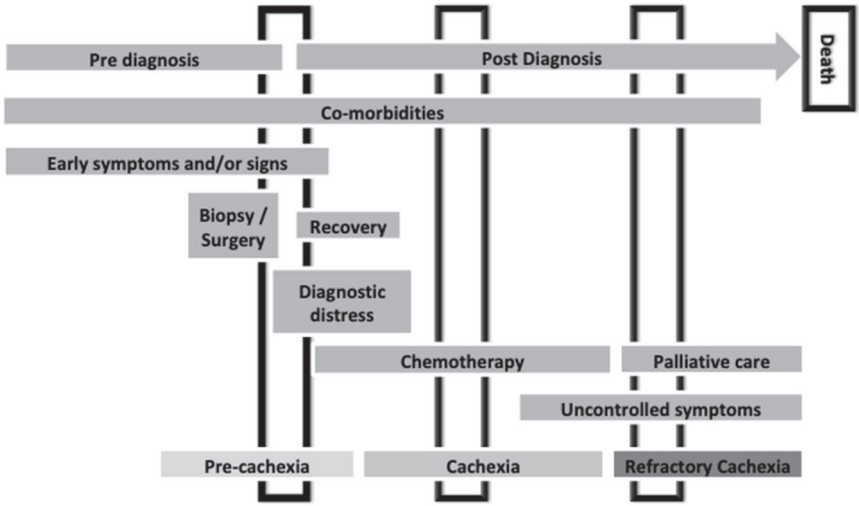

Figure 2-7-1. A proposed model of integration of the cachexia stages into cancer trajectory.

1.4. The impact of obesity

The cancer cachexia syndrome might be under-recognized in the context of epidemic obesity. Indeed, as the prevalence of excess body weight has been rising worldwide and obesity is causally related with carcinogenesis, the percentage of overweight/obese cancer patients is elevated; it may exceed 40% even in primary tumors that are associated with a particularly high incidence of cachexia (e.g., metastatic pancreatic cancer).[3]

In practice, this means that the syndrome may be evolving clinically undetected for two reasons: firstly, loss of some of the "spare weight" may be erroneously considered as a "desirable event" by patients and/or health care providers; however, in the presence of cachexia not only extra fat mass but also muscle mass is usually reduced. Secondly, muscle wasting takes place under a thick layer of (subcutaneous) fat and, in that sense, actual alterations of body composition are masked.

Body

2.1. Pathophysiology

Any patient represents a closed thermodynamic system and the balance between food intake and energy expenditure [the sum of resting energy expenditure (REE), activity-related energy expenditure (AEE) and the thermic effect of food (TEF)] determines changes of body weight.[2] The basis of the pathophysiology of the cachexia syndrome is a disruption of this energy balance; it had been estimated that cachectic patients might lose up to 1200 kcals per day.[4]

This homeostatic imbalance is caused by overproduction of inflammatory cytokines and altered hormonal signals both of which resulted from a cross-talk between tumor cells and the host. Moreover, it had been shown that tumors secrete various catabolic factors.[2] These key mediators act on the central nervous system (CNS) as well as on various peripheral organs, such as skeletal muscles, and are responsible for the main signs and symptoms associated with cachexia.

2.1.1. CNS

Existing evidence supports the view that the cause of anorexia—the main symptom responsible for reduced energy intake—is hypothalamic inflammation caused by cytokines such as interleukin (IL) -1β and Tumor Necrosis Factor (TNF).[5] These cytokines can generate an imbalance between orexigenic and anorexigenic signaling pathways at the level of the second-order neuronal populations - namely the pro-opiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) neurons - thus after peripheral signals reach CNS.[6] Therefore, due to the hyperactivity of the melanocortin system, the hypothalamus is incapable of exerting a physiological——orexigenic—effect as a response to energy deficiency.

In addition, animal studies suggest that IL-1β may induce muscle atrophy through a mechanism independent of the substantial peripheral inflammation, via activation of the hypothalamic-pituitary-adrenal axis.[7]

2.1.2. Effects on the periphery

2.1.2.1. Acute phase response (APR) and futile biochemical cycles.

Certain pro-inflammatory cytokines, such as IL-6, IL-1, TNF and interferon (IFN)-γ, are responsible for the induction of the APR. A central event in this otherwise physiological reaction to stress and trauma is the

re-ordering of hepatic protein synthesis, resulting in increased production of the positive acute phase proteins (APP) (i.e., C-reactive protein (CRP) and fibrinogen).[8] Furthermore, plasma levels of negative APP (i.e., albumin, pre-albumin and transferrin) are reduced due to transcapillary escape secondary to increased microvascular permeability while their hepatic synthesis remains unaltered.[8]

As these patients may also suffer from anorexia, a daily negative energy-protein balance is usually detected. These increased energetic demands are consequently met from the breakdown of the adipose tissue. During this process, which is called lipolysis, triacylglycerols are breaking down to glycerol and to free fatty acids. Glycerol is subsequently taken up by the liver and, through the process of gluconeogenesis, is used for the generation of glucose.[9]

Furthermore, a synergistic action of APP (i.e., serum amyloid A) and cytokines (i.e., IL-6) may cause muscle wasting by enhancing protein degradation. This process is called proteolysis and drives the release of large amounts of amino acids (namely alanine and glutamine) from skeletal muscle into the circulation. The liver then uses alanine, for both gluconeogenesis and protein synthesis, while glutamine can be taken up by tumor cells to sustain their energy and nitrogen demands.[9,10]

Finally, tumors consume predominantly glucose and produce increased amounts of lactate—via the process of glycolysis—even in the presence of oxygen (this phenomenon is also known as the "Warburg effect"). This overload of lactate is then converted back to glucose (this process is called gluconeogenesis) in the liver by the Cori cycle, a demanding biochemical route that may contribute up to 40% of the increase in energy expenditure in a metastatic cancer patient.[11]

2.1.2.2 Adipose tissue

In cachexia, as well as in other syndromes of deterioration, mobilization of fat stores is one of the most effective ways to replenish the energy requirements. In the case of cancer cachexia, however, an even more profound loss of white adipose tissue (WAT) is observed owing to factors produced by tumors (i.e., adrenomedulin) and systemic inflammatory cytokines (e.g., TNF) that function mainly by promoting lipolysis and—to a lesser degree—by inhibiting lipogenesis.[2,11] As mentioned, triglycerides are hydrolyzed to glycerol and free fatty acids (FFAs) and through these processes adipocytes may subsequently lose up to 95% of their initial volume.[11]

In addition, under the effect of parathyroid-related peptide produced by tumors, as well as the presence of IL-6 and β-adrenergic stimulation, white

adipocytes are converted into beige adipocytes.[12] These cells are characterized by high mitochondrial content and increased expression of the uncoupling proteins (UCPs) -1 which are responsible for disengaging the use of the mitochondrial electron transport chain from ATP synthesis toward heat production.[12] This process is known as "adipose tissue browning" and contributes further to hypermetabolism and increasing REE in these patients. Moreover, it explains a low-grade fever (part of b-symptoms) that is usually experienced by cachectic patients in the afternoon hours when the anti-inflammatory effect of the endogenous cortisone released in the morning (in the context of the circadian rhythm) is lost.

2.1.2.3 Skeletal muscle mass

The most striking event of the cachexia syndrome is muscle wasting. Depletion of muscularity (muscle mass adjusted for stature) under a certain threshold is called sarcopenia and is associated with adverse clinical outcomes such as increased risk of falls, decreased tolerance to chemotherapy, reduced quality of life and, ultimately, diminished survival.[13]

At the cellular level, cytokines act through surface receptors and activate transcription factors which in turn bind to promoters of genes encoding components of the ubiquitin–proteasome and autophagy systems.[2] Intriguingly, while there are at least four such signaling pathways [the TNF, the TNF-related weak inducer of apoptosis (TWEAK), the IL-6/leukemia inhibitory factor (LIF) and the myostatin/activin/transforming growth factor (TGF)-β], there is only one competitor (the insulin growth factor (IGF)-1), which inhibits the transcription factors forkhead box protein (FOX)O1 and FOXO3 by preventing their nuclear translocation and thus completing the transcription of autophagy genes.[2]

In addition, recent studies have revealed a cross-talk between lipolysis and muscle wasting. Das et al. have demonstrated that in mice bearing the IL-6 producing (C26) tumor, when adipose triglyceride lipase (one of the key enzymes responsible for the hydrolyzation of fatty acids) is genetically ablated, not only excessive lipolysis was prevented but—unexpectedly—skeletal muscle mass could also be preserved.[14] A proposed mechanism involves the aforementioned increased release of FFAs from the adipose tissue due to excessive lipolysis. When released in physiological concentrations, FFAs are taken up by muscle cells and produce intramyocellular triacylglycerol or are oxidized in mitochondria. However, when released in excess, they accumulate within myocytes and are

consequently converted to active lipid metabolites, which can then cause alterations of mitochondrial respiration and eventually lead to changes of myocellular redox state.[15]

Scattered data, mostly derived from animal studies, have shown that the cardiac muscle may equally bear atrophy although it was originally assumed that it might be spared from serving as an amino acid supplier under any case of energy depleted state due to its vital role. Nonetheless, the cardiac muscle shares the same catabolic pathways with skeletal muscles and, consequently, various proteolytic and apoptotic signals activated in cachexia may exert their effects triggering cardiac muscle wasting as well.[16]

2.1.2.4. The gut and gut microbioma

Recent studies indicate a possible role of intestinal micro-organisms and intestinal barrier in the development of the cachexia syndrome. It has been proposed that tumor-derived factors may cause enteric inflammation and alter microbial ecology benefiting overgrowth of aerotolerant bacteria. In addition, overproduction of nitrate—a by-product of systemic inflammation—and various stress-related hormones, favor the growth and affect the virulence of Escherichia coli and other Enterobacteriaceae.[17]

Furthermore, although the exact mechanism has not been fully elucidated, it has been hypothesized that high production of cytokines such as TNF and IFN-γ, may increase intracellular permeability allowing penetration of intact microbes or their endotoxins into systemic circulation further enhancing the inflammatory response in cachexic patients.[18]

2.1.2.5. Genetic bases of cachexia

In another approach, it could be the host's genotype that may determine the intensity of cachexia. In that sense, two tumors identical in size and dynamics, in two different individuals, may generate two quite diverse cachectic syndromes in terms of clinical manifestations and severity, according to the particular single-nucleotide polymorphisms (SNPs) that each host bears.[11]

In a larger study of this field, a panel of known SNPs related with various characteristics of cachexia like appetite regulation, immune response, pro- or anti-inflammatory pathways, energy regulation, muscle metabolism, adipose tissue metabolism and corticosteroid signaling were analyzed. Authors were able to identify sixteen SNPs in eleven genes (GCKR, LEPR, SELP, ACVR2B, TLR4, FOXO3, IGF1, CPN1, APOE,

FOXO1, and GHRL) that have shown an association with weight loss and another panel of four SNPs in four different genes (LEPR, ACVR2B, TNF, and ACE) that were related to weight loss and sarcopenia.[19]

These kinds of studies aim to establish a group of SNPs in various genes that could be used to predict which patients will develop cachexia or not irrespective of tumor site and stage.

2.2. Other contributing factors

2.2.1. The direct effect of tumors

In some cases, the anatomical location of certain tumors may cause swallowing problems and dysphagia resulting in restriction of food intake and undernutrition. The most characteristic paradigms are tumors of the head and neck region or esophageal tumors.

It has also been documented that the presence of hepatic metastasis may lead to increased production of hepatic APP. Moreover, evidence suggests that there is a positive linear association between liver mass and REE. In colorectal cancer patients with visceral metastasis for example, a cumulative REE of over 17,500 kcals within a period of three months had been calculated.

Finally, the direct energy consumption by the tumor can be of clinical importance for a patient when the net weight of the overall tumor mass exceeds 0.75 kg.[13]

2.2.2. Age and comorbidities

In everyday practice there are many other conditions and clinical entities which are associated with malnutrition, chronic inflammation and/or sarcopenia that might precede diagnosis. As an example, the median age of cancer patients is around 66 years; the nutritional status for many of them may already be affected from the process of normal aging. Age is associated with a variety of factors that may impact food intake, such as oral problems, sensory impairments (i.e., decreased sense of taste or smell) and a range of psychosocial problems (e.g., depression, isolation, financial issues). More importantly, aging may gradually cause sarcopenia, but with different pathophysiological mechanisms than those described in cancer cachexia (i.e., reduction of systemic levels of anabolic hormones, presence of oxidative stress and increased apoptotic signals in myocytes and mitochondrial dysfunction and deformation).[20]

Furthermore, age is usually associated with the presence of comorbidities, such as chronic obstructive pulmonary disease, chronic renal failure, chronic heart failure, rheumatoid arthritis, etc. These are in turn related to the presence of chronic inflammation and could lead to increased morbidity due to periods of bed rest, and consequently further impair physical function.[20]

2.2.3. Antineoplastic therapy

The armamentarium of antineoplastic agents is evolving and new drugs are tested each year in preclinical and clinical settings with a few of them receiving permission for use in everyday practice by regulatory authorities. All these approved drugs must have shown convincing evidence of clinical and/or survival benefit, however, some of them may cause side effects that could impair energy intake or directly provoke loss of muscle mass and therefore adversely impact the patient's quality of life.

The typical toxicity profile of the classical chemotherapeutic agents, for example, antimetabolites and tubulin inhibitors, includes symptoms and signs from the CNS (anorexia, nausea and fatigue) and the gastrointestinal tract (taste alterations, stomatitis, mucositis, diarrhea, constipation); all of which may adversely affect food intake.

Moreover, certain drugs that are commonly prescribed in oncologic patients may directly damage myocytes. A characteristic example is the use of steroids that are commonly used in certain clinical scenarios, such as in the case of irradiated brain metastasis. Prolonged use of high doses of dexamethasone may cause muscle atrophy by inducing muscle catabolism, increasing muscle protein breakdown and by inhibiting protein synthesis. This effect is more prominent in the proximal muscles of the lower limbs (proximal myopathy).[21] In addition, the classical chemotherapeutic drugs may also provoke muscle wasting by distinct metabolic derangements (i.e., mitochondrial dysfunctions as well as alterations of oxidative phosphorylation within the Kreb's cycle, fatty acid metabolism, and calcium transportation signaling).[22]

Furthermore, many tumors bear hormone-dependent clones and thus anti-hormonal therapies, such as androgen deprivation therapy (ADT), are frequently recommended. These therapeutic manipulations are generally considered to have a more favorable toxicity profile than classical cytotoxic chemotherapeutic agents. However, in the case of prostate cancer—the most frequent cancer type in men—ADT is related to the development of sarcopenic obesity due to the simultaneous loss of lean body mass in association with a progressive increase of fat mass.[23] The

main mechanism involves the depletion of androgens, which are major determinants of muscle mass in men. It has been estimated that in men under ADT, lean body mass decreases on average by 1.0% after 12 months and by 2.4% after 36 months.[23]

In addition, even the so-called "targeted agents," such as certain inhibitors of tyrosine kinase may have an unfavorable effect on muscle mass as the same signaling pathways (like the PI3K-AKT-mTOR pathway and the RAF-MEK-MAPK/ERK) are present and regulate proteinosynthetic and survival signals in both cancer cells and myocytes. Sorafenib for example, which is a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGF-TKI), prolongs progression-free survival and had been approved for the treatment of pretreated patients with advanced renal cell carcinoma. However, the muscle loss of these patients was estimated to be equivalent to 2.1 kg per year of therapy and that was irrespective of the disease's response.[24] Unsurprisingly, some of the most common side effects of the drug are weight loss, fatigue and weakness.

Finally, a novel class of drugs known as immune checkpoint inhibitors (ICIs) had been developed and received approval for the treatment of various tumors, including melanoma, renal cell carcinoma and non-small cell lung cancer (NSCLC). These agents act indirectly, by inhibiting some of the most important negative regulatory components of the immune response, such as the cytotoxic T lymphocytes-associated antigen 4 (CTLA-4) and the programmed cell death protein-1 (PD-1) and its ligand (PD-L1) and, thus, leading T-cells to attack against the cancer cells. Fatigue is the most frequent side effect (reported in up to 40% of patients treated with an anti-CTLA-4 antibody and in up to 24% of those treated with an anti-PD-1/anti-PDL-1 antibody).[27] Fatigue is usually mild if it is not a part of other adverse effects, for example, endocrinopathy; still, it may potentially have an indirect adverse impact on the patient's nutritional status. Gastrointestinal toxicity (namely diarrhea and colitis) is reported in up to 40% of patients treated with an anti-CTLA-4 regimen. However, severe grade III/IV diarrhea is observed in 10%, and in 1–2% of patients treated with an anti-PD-1 or an anti-PDL-1 monotherapy, respectively.[27] Other frequent adverse reactions include dermatological manifestations, endocrinopathies, pneumonitis and hepatotoxicity and, in addition, there is a wide range of rare events that includes—but is not limited to—manifestations from the nervous, hematopoietic and urinary systems. Apparently, when ICIs therapies are combined, the expected incidence of severe adverse events might be even higher (i.e., up to 55% when ipilimumab (an anti-CTLA-4 agent) is combined with nivolumab (an anti-

PD-1 agent)) while when ICIs are combined with chemotherapeutic agents, the reported toxicity rates varies.[27]

Notably, the treatment of choice for most of the side effects is temporary immunosuppression with glucocorticoids in variable dose and duration depending on the severity of the event.[27]

2.2.4. Uncontrolled symptoms

Cancer patients frequently experience multiple symptoms during the course of the disease. These symptoms are grouped in clusters i.e., gastrointestinal (nausea, vomiting, lack of appetite, constipation, etc.), psychoneurological (pain, fatigue, insomnia, anxiety, depression, etc.) and respiratory (cough, breathlessness, fatigue). Particular symptoms among these clusters can adversely affect nutritional status as they may interact with the process of food intake.[25] In the context of a nutritional care plan, these symptoms should be recognized and managed effectively prior to any nutritional intervention.[13]

2.3. Diagnosis of cachexia

Based on the recent progress that had been achieved in elucidating the pathophysiology of the syndrome, many experts and groups of health care professionals aimed to establish diagnostic criteria for cancer cachexia. However, cachexia is a multifactorial syndrome, with variable symptoms and clinical signs that are evolving and variate in severity in relation to the progress of the underlying cancer and, thus, no constant conclusions could be made.

The most widely accepted criteria were published in 2011 by an international expert panel, under the auspices of the European Palliative Care Research Collaborative.[1] The basic effort of this framework was to provide a formal definition and classification of cancer cachexia after a consensus process, including focus groups and two Delphi rounds. According to them, any cancer patient with involuntary weight loss of over 5% during the past six months or with weight loss of over 2% and BMI less than 20 and/or sarcopenia is defined as “cachectic.” Moreover, two additional stages, an early “pre-cachectic stage” and a “refractory cachectic stage,” were identified. The aforementioned diagnostic criteria and stages of cancer cachexia represent our current conception about this “ancient” syndrome; the term “cachexia” was originally introduced by Hippocrates from the Greek words kakos (=bad) and hexis (=condition).

Nevertheless, this is still an outcome of a "consensus statement" and, as authors acknowledge, it could be used for clinical trial design, development of practice guidelines and routine clinical management only after validation.[1] One other important issue is that, up to now, there are no established treatment options for cancer cachexia and the philosophy that lies behind the development of these diagnostic criteria is largely based on the general impression that the earlier the initiation of a therapeutic intervention, the better for the patients. Even so, systemic inflammation (assessed in practice by blood CRP levels), a major determinant of cancer survival, was not included as a diagnostic factor due to the lack of contemporary datasets in cancer cachectic patients.

A limited number of subsequent studies aimed to evaluate the proposed diagnostic and classification criteria of cancer cachexia and compare them with other existing criteria with contradictive results that could be attributed on one hand to the heterogeneity of sample sizes, and on the other to certain methodological drawbacks in comparing data across different sets of criteria.[26] In addition, while some studies confirmed the association between the pre-cachectic status and better treatment response, some others failed to demonstrate any survival difference between pre-cachectic and non-cachectic patients.[26] Thus, a robust risk assessment method of cancer cachexia is still necessitated.

More recently, an international multicenter study aimed to develop a prognostic score based on involuntary weight loss (the major clinical sign of cachexia) and the patient's BMI, taking into account the current demographic shift in cancer patients toward obesity.[27] The proposed grading score (depicted in Table 2-7-1), was adapted from the latest "ESPEN guidelines on nutrition in cancer patients" released in 2017.[28,1]

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[i] In 2019, the Global Leadership Initiative on Malnutrition (GLIM) proposed a consensus scheme for diagnosing malnutrition in adults in clinical settings on a global scale. The top ranked diagnostic criteria were weight loss, low BMI, reduced muscle mass, reduced food intake or assimilation and disease burden/inflammation. It was recognized, however, that due to some distinct features of the cachexia syndrome, the GLIM consensus criteria for malnutrition should be used in parallel with established concepts and nomenclature.
Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats AJS, Crivelli AN, Evans DC, Gramlich L, Fuchs-Tarlovsky V, Keller H, Llido L, Malone A, Mogensen KM, Morley JE, Muscaritoli M, Nyulasi I, Pirlich M, Pisprasert V, de van der Schueren MAE, Siltharm S, Singer P, Tappenden K, Velasco N, Waitzberg D, Yamwong P, Yu J, Van Gossum A, Compher C; GLIM Core Leadership Committee, GLIM Working Group. GLIM criteria for the diagnosis of

Table 2-7-1. A prognostic grading system based on weight loss history and BMI.

	BMI kg/m^2				
Weight loss (%)	28	25	22	20	
2,5	0	0	1	1	3
6	1	2	2	2	3
11	2	3	3	3	4
15	3	3	3	4	4
	3	4	4	4	4

2.4. Assessment of cancer cachexia

The main goal of "assessing a syndrome" is to determine its important components in order to provide a treatment that could potentially prevent worsening or even improve some or any of the components. In that sense, assessment of cancer cachexia is a complex issue as it is a multidimensional syndrome, with—up to now—no clear benefit from any treatment and its progression is largely determined by the course of the underlying disease. Nevertheless, it is believed that assessment of cancer cachexia should include four major domains:[2,13,26]

malnutrition - A consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle. 2019 Feb;10(1):207-217.

2.4.1. Nutritional screening and assessment

Periodical nutritional screening and assessment of nutritional status is vital for all cancer patients. Dietary intake may be affected directly by cachexia (via anorexia) or in association with cancer treatment, the tumor's anatomical location and/or by the presence of various psychosocial conditions. Due to cost and time issues, in-depth assessment by registered dieticians for all patients is impractical; instead, some nutritional screening tools have been proposed. These tools have been originally developed for different populations and can be completed either by patients or by any healthcare provider within a few minutes; nevertheless, they include certain fields that may cover some of the most important cachexia domains and have been adapted/validated in cancer patients as well (Table 2-7-2).[26,29]

2.4.2. Assessment of muscle mass and strength

Quantification of muscle mass and its alterations is essential. Anthropometry of the mid-upper-arm muscle area may provide a gross estimation of muscle mass. The Dual Energy X-ray Absorptiometry (DEXA) represents the gold standard method of body composition analysis and patients are exposed to a limited amount of radiation. The Bioelectrical Impedance Analysis (BIA) is a less complex and costly method but is also less accurate than DEXA. Recently, the opportunistic analysis of regular Computer Tomography (CT) images or Magnetic Resonance Imaging (MRI) had been proposed.[30] Aside from practicality, these methods are more reliable in obese patients and may additionally estimate muscle quality by measuring myosteatosis (the accumulation of intra-/intermuscular fat).

Other methods, such as handgrip strength measurement and the Short Physical Performance Battery (SPPB) test, may be used for an objective assessment of muscle strength and physical performance. Aside from their proven prognostic value, they have recently been utilized as endpoints in randomized clinical trials.[31]

Table 2-7-2. Nutritional screening tool used in cancer cachexia. *HCP - Health care provider.

Nutritional screening tool	Completed by	Validated in cancer patients	Domain of Assessment				
			Caloric intake	Nutritional status/energy stores	Body composition	Rate of depletion	Functional Status
Patient-Generated Subjective Global Assessment (PG-SGA)	Patient/HCP*	+	+	+	+	+	+
Mini-Nutritional Assessment (MNA)	HCP		+	+	+	+	+
Malnutrition Screening Tool (MST)	Patient		+	+		+	
Malnutrition Universal Screening Tool (MUST)	HCP		+	+		+	
Nutritional Risk Screening-2002 (NRS-2002)	HCP		+	+		+	

2.4.3. Biomarkers

Any substance that can be easily measured in daily practice and can be used for the early identification and/or the classification of a syndrome may be used as a biomarker. In the case of cancer cachexia, markers of systemic inflammation, muscle wasting, lipolysis, etc. might be used. Although some of these have already been tested in clinical trials, no one can be considered validated and established.[26] The most widely studied is the Glasgow Prognostic Score (GPS) that co-variates albumin and CRP (i.e., nutritional status and systemic inflammation).[32]

2.4.4 Quality of life

Cancer cachexia is associated with reduced survival, but it also has a major effect on the quality of life. Indeed, symptoms and signs such as anorexia and weight loss may alter patients' self-perception and cause restriction or cessation of many expressions of their everyday life (e.g., hobbies, social interactions). Any alterations in eating habits and the non-participation in household meals may be crucial for both patients (it may lead them to isolation and depression) and the family (creation of a sense of failure).[26] In obese patients, though, weight loss may be erroneously well appraised as it may lead to improvement of self-imaging. Still, in the context of cancer cachexia, this "loss" is attributed not only due to lipolysis but also due to muscle wasting and this misconception of "well-being" may interfere with the compliance of the proposed nutritional care plan.

There are numerous questionnaires, visual analog scales and tools that could be used to assess symptoms like anorexia and fatigue or to evaluate a patient's functionality, mood disturbances, sense of well-being, level of independence and quality of life, and some of them have been used in the clinical setting as well.

2.5. Treatment of Cachexia

By definition, the best way to treat cachexia is to treat the underlying disease. However, a "proof in principle" exists that cachexia could be disconnected mechanistically from cancer. Still, up to now, no standard therapy or any relevant international guidelines are available. Based on the current knowledge, it is strongly believed that an effective therapeutic approach should be multimodal - thus, coping with the multifactorial nature of the syndrome, and should be initiated in a timely manner—that is

before the syndrome becomes irreversible. According to the recent ESPEN guidelines, these actions should be incorporated in a nutritional care plan.[1,13,26,28,29,32,34]

Step 1 - Nutritional screening

The first step of this plan is a "nutritional screening process" that should be performed with every cancer patient at diagnosis in order to evaluate weight alterations and nutritional intake and to identify patients in an early, pre-cachectic, stage. This process should include the proposed grading system for weight loss—BMI and/or any of the accessible nutritional screening tools; these can be carried out even by non-nutrition centered trained health care providers. This screening process should be repeated regularly and patients with abnormal scores should be referred for further assessment.

Step 2 - Nutritional assessment

In-depth nutritional assessment is the next step of the nutritional care plan; this should be carried out by a registered dietician. The main goal is the detailed and quantitative assessment of nutritional intake, nutritional impact symptoms, body composition, systemic inflammation and physical performance.

Although the level of evidence is low—or moderate at best—the targeted energy intake should be between 25 and 30 kcals/kg/day and the recommended protein intake should be above 1 g/kg/day and—if possible—up to 1.5 g/kg/day. In addition, assessment of micronutrient status (trace elements and minerals) should be performed. If possible, the aforementioned requirements should be estimated on an individual basis, using food frequency questionnaires or keeping a three-day food intake record and covariating other important parameters such as body composition, systemic inflammation and physical activity.

Finally, it is important that nutritional assessment should be part of a more general interdisciplinary care process involving nurses, family doctors, oncologists, palliative care physicians, etc.

Step 3 - Nutritional support

It is believed that although normalization of energy intake is not enough per se, it remains the cornerstone of any effective treatment of cancer cachexia. Firstly, any symptom that may hamper volitional feeding should be identified and treated. In addition, dietary advice should be provided in order to optimize proteino-caloric intake via normal food. When this is not possible food enrichment and/or oral nutritional

supplements should be offered. In general, subscription of specifically formulated amino acid mixtures is not required and up to now there is no convincing evidence that supplementation with branched-chain amino acids is beneficial. In weight-losing patients with insulin resistance and possibly in those with systemic inflammation, a high-fat diet is preferred.

In patients with impaired oral intake for any reason (e.g., radiation stomatitis, esophageal tumors) artificial nutritional support should be considered.[2]

If intestinal function is sufficient, enteral feeding is preferred either via nasogastric tubes (when the estimated period will be relatively short) or via percutaneous gastrostomies. In patients with severe intestinal deficiency (e.g., peritoneal carcinomatosis) and with a prognosis of over two months, total parenteral nutrition should be considered. In this setting, however, medical, bioethical and financial issues should be discussed with patients and their families.

Step 4 - Physical exercise

It had been estimated that cachectic patients take about 4,000 steps/day (less than 50% compared with healthy individuals) and they spend less than three hours a day standing or walking. In this setting, enhancement of daily physical activity should be proposed in order to avoid the detrimental effects of sedentariness (e.g., motivating patients to take short walks). Moreover, an aerobic training program may increase cardiovascular capacity, reduce the production of pro-inflammatory cytokines and increase lipids oxidation in skeletal muscles. On the other hand, resistance training increases oxidation of carbohydrates in skeletal muscles and acts as a strong anabolic stimulus. Although the overall level of evidence is low, available data indicate that physical exercise is safe even in advanced-stage cancer patients and it is associated with maintenance or improvement of aerobic capacity, muscle strength and quality of life.

Patients are usually advised to follow a supervised or home-based training program of moderate intensity, for ten- to sixty-minute sessions, three sessions/week but those with multiple comorbidities would probably benefit from individualized exercise programs supervised by trained experts. It should be noted, however, that any form of exercise will further increase energy expenditure and these additional calories should also be counted in estimating the overall daily nutritional requirements.

[2] According to ESPEN guidelines, “impaired oral energy intake” is defined when patients are expected to receive less than 500 kcals/day for several days or less than 75% of requirements for more than 1–2 weeks.

Step 5 - Pharmaconutrients

"Pharmaconutrients" are substances normally found in free diet that, when supplied in pharmacological doses can modulate immune and metabolic functions. The most thoroughly studied pharmaconutrients in cancer cachexia are the N-3 fatty acids. Although the level of evidence is low, supplementation with 1 to 2 g/day of N-3 fatty acids is recommended to improve appetite, energy intake and lean body mass. Other pharmaconutrients such as amino acids and phytocannabinoids have also been tested in cachectic patients due to their potential role to increase FFM and appetite, respectively; however, up to now, available data from clinical trials are inconclusive.

Step 6 - Pharmacologic treatment

Although many agents have been tested for the treatment of cancer cachexia no approved drug is available. It is believed that this "lack of evidence" can be partly attributed to the complexity of the underlying pathophysiological mechanisms but also due to the absence of well-designed randomized clinical trials.

Still, there are some drugs approved for other indications that are recommended in this setting:

Progestins are orexigenic drugs that may increase appetite and body weight. Megestrol acetate has been approved by the FDA for the treatment of (AIDS-associated) cachexia. Nevertheless, progestins do not improve FFM and they are associated with some serious adverse events such as thromboembolic events, thus, they should be used with caution in the setting of cancer cachexia.

Corticosteroids may also improve appetite as well as the sense of well-being. However due to their known side effects (such as muscle wasting and insulin resistance) they should be not be used for more than two to three weeks.

Prokinetic agents such as metoclopramide and domperidone can stimulate gastric emptying and improve early satiety, chronic nausea and dyspepsia. Both drugs are relatively safe.

Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the release of cytokines and, thus, suppress systemic inflammation. Some of them, like Cox-2 inhibitors have been tested in controlled clinical trials with promising results with regards to muscle mass, physical activity and functionality.

Management of refractory cachexia

Close to the end of life, as disease progresses and becomes unresponsive to antineoplastic therapy, cancer cachexia may enter a refractory—to treatment—stage. At this point more emphasis should be given to psychological support rather than on aggressive nutritional supplementation (i.e., artificial nutrition) that may be associated with even more side effects and extra costs.[2] Ideally, these kinds of decisions should be discussed in a timely way with patients and their families and should be incorporated in a general plan of terminal care.[35]

Future perspectives

Based on preclinical research, our understanding of the pathophysiology of cancer cachexia is evolving, new biomarkers have been proposed and novel therapeutic agents are being developed. In the clinical setting, newer and more sophisticated diagnostic criteria have been proposed that are currently validated. Moreover, two drugs have already been tested in randomized clinical trials with promising results.[2]

1. Anamorelin is a ghrelin analog that can release growth hormones from the pituitary gland. In two phase III trials, it was given for twelve weeks in patients with advanced NSCLC and resulted in significant improvement of appetite, body weight and lean body mass; still, there was no significant effect on muscle strength (measured by the handgrip strength).

2. Enobosarm is a selective androgen receptor modulator (SARM) that acts via stimulation of the skeletal muscle androgen receptor. It was tested in two phase 2b trial clinical trials in newly diagnosed patients with NSCLC and preliminary results showed an improvement of lean body mass as well as an increase in power and speed on a stair-climbing test (in one of the two trials).

Currently, at least six phase III randomized clinical trials testing dietary advice, nutraceuticals, and monoclonal antibodies are underway. Another trial—the MENAC trial—tests a multimodal approach that combines dietary intervention and treatment of nutritional symptoms, oral nutritional supplements, together with administration of N-3 fatty acids, a home-based exercise program and a non-steroidal anti-inflammatory medication, in patients with lung or pancreatic cancer receiving anti-cancer treatment.[2]

Discussion

Cancer cachexia is a complex syndrome with multifactorial etiology that may adversely affect patients' quality and quantity of life. Its frequency varies according to the tumor site and stage of the disease. Overall, it is estimated that 50–80% of cancer patients will develop the syndrome.

The major pathophysiological mechanisms involve alterations of hormonal signals as well as overproduction of cytokines resulting from a cross-talk between the tumor and the host's immune system. Anorexia, increased resting energy expenditure, presence of systemic inflammation, activation of unprofitable biochemical circles, and insulin resistance are all important features of the syndrome leading to weight loss and changes in body composition.

In this context disproportionate lipolysis may occur, however, the most striking event of cancer cachexia is excessive muscle wasting that ultimately leads to sarcopenia—defined as muscular depletion under a certain cutoff—which is associated with decreased tolerance to antineoplastic therapy and increased morbidity and mortality. Obese patients may also be sarcopenic—this condition is called sarcopenic obesity—and is an independent prognostic factor across diverse tumor types and stages. More importantly, these patients may erroneously be spared from routine nutritional screening/assessment, as sarcopenia lies undetected under a thick layer of subcutaneous fat.

Other factors, such as normal aging and various comorbidities, may have contributed to the development of sarcopenia already at diagnosis. In addition, obstruction of the GI tract and classic side effects of chemotherapy (such as anorexia, nausea, mucositis, etc.) could further restrict food intake. On top of that, most types of common antineoplastic therapies, i.e., corticosteroids, systemic chemotherapy, hormonal therapy, targeted therapy and possibly immunotherapy, may act directly on muscle cells, affecting proteinosynthetic and survival pathways. In a sense, any proven survival benefit may cost the patients' quality of life, unless the muscularity can be supported and retained.

With regards to diagnosis of the cancer cachexia syndrome, several criteria had been proposed, given the heterogeneity in the clinical presentation. Although a single unifying definition does not exist, the most widely accepted diagnostic criteria and classification system had been proposed by an international consensus panel, in 2011. Three stages of the syndrome had been recognized: a pre-cachectic, a cachectic and a refractory (to treatment) stage. According to them, weight loss, which is

the most striking clinical sign of cachexia, is considered as a rather late event. Therefore, nutritional support should be initiated at the pre-cachectic stage—that is, before weight loss becomes clinically apparent. In this line, clinical symptoms such as anorexia and metabolic signs like impaired glucose tolerance could be used for the classification of cancer patients in this early stage. However, aside from the fact that they had never been validated, they cannot predict which patient and when they will enter into the cachectic stage. In that sense, the development of biomarkers that could be used for the early identification and/or prediction of the syndrome's trajectory would be of great value.

In 2015, a grading system based on weight loss history and BMI was developed and validated in a total cohort of over 10,500 cancer patients in Europe and Canada. Methodologically this was a well-designed clinical study that classified patients into mortality risk groups. According to this model, obese patients seem to have a survival advantage irrespective of the percentage of weight loss, denoting that the "obesity paradox" may also occur in the setting of cancer. Still, this prognostic model is based on simply two clinical factors. Adding more clinico-laboratory variables, such as GPS and PS may further enhance the prognostic power of the model and the better categorization of those patients. Relevant studies are in progress.

In addition, nutritional screening tools may be utilized for the early identification of patients at risk, ideally before weight loss becomes clinically apparent. There are at least twenty-two tools available in the literature; at present, however, none can be considered as the gold standard. In any case, regular screening should be part of a nutritional care plan, so symptoms and signs of the syndrome are promptly recognized, and all secondary causes of malnutrition should be identified and treated. If needed, advance evaluation of cachexia domains should be performed. Ideally, this should incorporate an in-depth nutritional assessment, quantification of muscle mass and strength, assessment of physical function and aspects of quality of life.

Nutritional support is the basis of any intervention. Mechanistically it is not possible to improve the syndrome if the daily proteino-caloric balance remains negative. A parallel step is to support the patient's physical activity in order to prevent muscle loss and to maintain or—if possible—to improve physical function. Furthermore, although data from clinical trials are not conclusive, N-3 fatty acids could be used given their potent effects on appetite, and lean body mass.

In terms of pharmacological treatment, there are some drugs that are currently being used in clinical practice, for example, the orexigenic

progestins and corticosteroids and the prokinetics metoclopramide and domperidone. However, due to safety concerns and mostly because their efficacy remains unproven, the overall level of evidence remains low or moderate at best. In addition, a number of agents (like anti-inflammatory drugs) with relevant rational have been tested in clinical trials with disappointing results. It is believed, however, that it would be rather unfair to indict this failure exclusively to ineffectiveness in their mechanism of action. Indeed, until recently, studies had quite different designs and some key issues for a successive anti-cachectic therapy were not taken into consideration. As an example, accrued patients came from the palliative setting (once active oncological care was terminated) so they belonged to a mixture of "cachectic" and/or "refractory cachectic" stages. In this line, "weight loss of over 5%" was a representative inclusion criterion. Notably, the refractory stage denotes that patients are close to death and, according to the recent definition, their life expectance should be less than three months and, thus, any effort to reverse the syndrome might be not only futile but could also raise ethical considerations. As such, the odds of success were minimum and, unsurprisingly, most of these trials were negative.

Moreover, with some exceptions, there is a lack of data regarding the efficacy of multimodal approaches for the treatment of cancer cachexia. Up to now, while numerous single agents or solitary nutritional interventions have been tested for the treatment of cancer cachexia, a striking response to any of them cannot be realistically expected due to the multifactorial nature of the syndrome. It is, for example, questionable as to whether an anabolic agent, given as monotherapy, will be effective if the daily protein-caloric demands were not fulfilled or when systemic inflammation is present.[36]

Finally, the classical endpoints used in oncologic clinical trials i.e., response to antineoplastic therapy or overall survival, seem to have no place in the field of cachexia clinical research. The concept that an effective nutritional intervention may be able to alter the course of the underlying disease (incurable cancer) with a usual predicted life expectancy of some months represents a rather over-optimistic outlook. Modern trials are now focusing on improving features of body composition (musculature) and symptoms like anorexia and fatigue. In addition, they incorporate other significant endpoints such as physical performance (measured by handgrip test, stair-climbing test, etc.) and domains of patient's quality of life.

In conclusion, a lot of progress has been made during the last decade in understanding the pathophysiology of cancer cachexia. In addition, a new

clinical definition and diagnostic criteria of the syndrome have been proposed and three distinct phases have been recognized: pre-cachexia, cachexia and refractory cachexia. Clinical research is also underway in order to improve the existing grading system and to target patients timely for therapeutic interventions. Finally, current clinical studies have a better design and refined outcomes, and novel drug therapies have emerged. All these recent advances have created some optimism for effective management of this syndrome that is frequently observed in patients with incurable cancers.

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