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Neurological complications of systemic tumor therapy

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Summary The treatment of malignant tumors has considerably improved in recent years, and also the number of "long term cancer survivors" is increasing. The spectrum of anti-tumoral agents is increasing at a fast pace and in addition to conventional therapies such as surgery, radiotherapy, and chemotherapy, new drugs with entirely new mechanisms are appearing. Side effects of old and new drugs can affect the central and peripheral nervous system, the neuromuscular junction, and muscle. These side effects often have to be distinguished from other causes and need neurological expertise. Although the majority of patients still receive conventional therapies, several new strategies such as immune therapies are being implemented. These drugs have also drug specific side effects, which do not always follow the classical principles of "toxicity."
This review focuses on the well-known and described side effects of conventional cancer therapies and adds new observations on new drugs.

Keywords Oncology · Radiation therapy · Chemotherapy · Immune therapy · Central nervous system · Peripheral nervous system · Side effects · New drugs

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Neurologische Komplikationen der systemischen Tumortherapie

Zusammenfassung Die Behandlung maligner Tumoren hat sich in den letzten Jahren beträchtlich verbessert. Auch die Zahl der Langzeitüberlebenden nach Tumorerkrankung steigt.
Das Spektrum der Wirkstoffe gegen Krebs nimmt rasant zu. Neben konventionellen Therapien, wie operativen Eingriffen, Radiotherapie und Chemotherapie, werden neue Substanzen mit vollkommen neuen Wirkmechanismen eingeführt. Nebenwirkungen alter und neuer Medikamente können das zentrale und periphere Nervensystem, die motorische Endplatte und den Muskel betreffen. Diese Nebenwirkungen müssen häufig von anderen Ursachen abgegrenzt werden und erfordern neurologisches Fachwissen. Auch wenn die Mehrzahl der Patienten immer noch konventionelle Therapien erhält, werden aktuell verschiedene neue Strategien wie Immuntherapien etabliert. Entsprechende Medikamente haben auch spezifische Nebenwirkungen, die nicht immer den klassischen Grundsätzen der „Toxizität" folgen.
Der Fokus der vorliegenden Übersicht liegt auf bekannten und gut charakterisierten Nebenwirkungen konventioneller Tumortherapien. Darüber hinaus werden Beobachtungen zu neuen Medikamenten beschrieben.

Schlüsselwörter Onkologie · Strahlentherapie · Chemotherapie · Immuntherapie · Zentrales Nervensystem · Peripheres Nervensystem · Nebenwirkungen · Neue Substanzen

Introduction

Side effects of tumor therapies are common and can involve the central and peripheral nervous system. In

Table 1 Table 1 shows a selection of recent drugs, which are classified into "inhibitors," antibody therapies, and immunotherapies. They have different modes of action and targets. With the exception of immune conjugates, their toxicity does not follow the classical principle of dose-related toxicity. Drugs are appearing at a fast pace and the list may be incomplete

Small molecule kinase inhibitors
Anaplastic lymphoma kinase (ALK) inhibitors
BRAF kinase inhibitors
Breakpoint cluster region-Abelson murine leukemia kinase inhibitors
Cyclin dependent kinase inhibitors
Epidermal growth receptor inhibitors
MEK inhibitors
Multiple receptor tyrosine kinase inhibitors
Other inhibitors
B-cell lymphoma 2 inhibitor
Hedgehog inhibitors
Histone deacetylase inhibitors
Mechanistic TOR Kinase inhibitors
PARP inhibitor protein synthesis inhibitors
Proteasome inhibitors
Antibody therapies
Various types: with various targets; also use of "immune conjugates"
Immunotherapies
Immune checkpoint inhibitors (mono therapies or combinations)

addition to the classical triad of surgery, radiotherapy, and chemotherapy/hormonal therapy, increasingly new treatments such as antibodies, immune therapies, targeted therapies are added, which can also have neurological side effects.

Surgery can cause direct nerve damage or result in scarring causing nerve lesions. At times, also nerve tissue needs to be deliberately sacrificed.

The toxicity of radiotherapy is well described and much effort has been put into the prevention. Side effects of chemotherapy and hormonal therapy are well known and supported by large observational studies. Whereas the classical therapy side effects are often related to toxicity, new drugs such as immune therapies have different mechanisms to conventional toxic effects. To date, the frequency of their appearance is not clear and is solely based on case reports and small observational studies.

Contrary to the past, where neurologists were asked for the explanation of symptoms and often for suggestions for localization of damage by cancer, neurologists are increasingly incorporated into tumor boards, and in addition to metastasis, direct tumor effects, paraneoplastic, and metabolic syndromes, also the neurological aspects of therapy side effects, are included. These often complex and difficult discriminations have a strong influence on the chosen therapeutic tools.

This short review aims to describe side effects on the central and peripheral nervous system, describing

the classical spectrum and adding new drugs when feasible.

Cancer can interact in several ways with the nervous system. Most frequently, direct tumor effects such as tumor spread, metastasis, or diffuse dissemination in the cerebrospinal fluid (CSF) are observed. Depending on the tumor type, metastasis can be the presenting or early event, or appear after a long latency. For most tumor types, a "natural course" of the disease has been observed. For an increasing number of tumors, dramatic and significant progress in tumor treatments have been made, which has increased survival.

This has an effect on the pattern of metastases, but also endocrine, metabolic, and paraneoplastic effects occur. Increased survival also increases the appearance of late toxicities.

Tumor treatment aims to eliminate or reduce tumor mass. The conventional triad is surgery, radiotherapy, and chemotherapy/hormonal therapy. Therapy-induced neurological dysfunction can appear as acute or chronic, and also in the case of chemotherapy induced neuropathy (CIPN), often remain as persisting late effects. Side effects, in particular due to chemotherapy, can be dose limiting.

Drug treatment is based on a variety of alkylating, antimitotic, spindle inhibitor, antimetabolite and other therapies, usually with a well-described spectrum of side effects. Also, in "conventional therapies," new application types, e.g., in vinca alkaloids, new antimetabolites (pralatrexate), DNA damaging drugs (trabectin), and new antiandrogenic drugs (abiterone, enzalutamide) were introduced [1]. Table 1 is an attempt to describe the emerging new categories of drugs.

New drugs

For this review, we have classified the side effects into lesions of the central nervous system and the peripheral nervous system. Most data concern conventional therapies. The frequency of side effects of new drugs, immune therapies and inhibitors is not clear, as systematic inverstigations are lacking, and evidence is based on individual observations or small studies.

Complications of therapies

Central nervous system (CNS)

Radiation therapy
Conventionally, the side effects of radiation therapy (RT) are classified into "early, delayed, and late" complications [2]. The impression is that RT has been much improved and side effects are fewer.

Late effects depend on the site and volume of radiation. Whole-brain RT is used in some cancers, even as a prophylactic treatment [3]. Late effects are a concern in long-term survivors with regard to cognition

[4]. Hippocampal sparing techniques are increasingly used [5] to avoid this. Rarely also movement disorders have been observed [6].

The simultaneous application of drugs as MTX and RT needs to be avoided [7], as side effects may increase.

In addition, RT-induced necrosis [8] is a concern and sometimes difficult to discriminate from recurrence [9]. Of concern are extra- and intracranial vessels. Enhanced arteriosclerosis of the carotid arteries has been described [10], and also dramatic changes such as the carotid "blow out" syndrome [11]. Noteworthily, cerebrovascular effects have also been described in platinum therapies, but are based on observational reports [12, 13].

Effects of other treatments on the brain

The term "encephalopathy" is usually somehow unfocused and vague, and describes mainly cognitive dysfunctions. Some drugs as ifosfamide [14] and interferons [15] seem to have these effects. Also, headache, fatigue, and seizures have been reported in several drugs and need to be distinguished from neuropsychological or focal symptoms. Several other drugs used in cancer treatment also have a variety of CNS effects [16].

Increasingly, the term "chemobrain" is used, describing mainly an uncharacteristic cognitive dysfunction following chemotherapy [17, 18] and electrophysiological observations have also been made [19]. The mechanisms of chemotherapy on the brain are not clear, and do not seem to be restricted by the passage of the agent through the blood–brain barrier [20]. Fatigue, depression, and neuropsychological changes are attributed to chemobrain, but need to be differentiated from other causes.

"Posterior reversible encephalopathies" (PRES) have been observed with several conventional chemotherapies and in bevacizumab treatment [21], after intrathecal therapy with MTX [22] and several targeted therapies, multiple tyrosinkinase inhibitors [23], calcineurin Inhibitors, und rapalogenes [24].

The appearance of progressive multifocal leukoencephalopathy has been observed in several immune therapies [25], such as alemtuzumab, bevacizumab, cetuximab, ibrutinib, rituximab, and others.

Hypophysitis has been described as a CNS effect of immune checkpoint inhibitor therapies [26–28] as well as EGRF inhibitors.

Cerebrovascular effects of therapies other than coagulation disorders and endocarditis have been considered in VEGF, VEGFR, EGFR, mTor inhibitors, Alk inhibitors, BRAF, BTK, BCR-ABL, and omacetaxine among others—the clinical relevance is presently not certain. Platinum drugs were mentioned above.

Spinal cord

As is the brain, the spinal cord (SC) is also sensitive to RT. Early effects are rare, but the appearance of transient Lhermitte phenomena as a delayed effect has been observed [29, 30]. Also, platinum therapies can induce the Lhermitte's phenomenon [31], which can be quite disabling.

Late effects on the SC such as radiation necrosis have been determined controversially [32], and depend on the site and dose. Radiation of the lumbar spinal cord can result in "lower motor neuron syndrome" [33], resembling neuropathy. Also, intrathecal drug treatment can cause myelopathies [34] and polyradiculopathies.

Rarely, long-duration steroid treatment can cause spinal lipomatosis [35], which may cause radicular lesion and severe myelopathies.

The peripheral nervous system (PNS)

Side effects on the peripheral nervous system were subject to reviews [36, 37] and due to new drug and therapy developments need constant updating.

Surgical interventions can damage nerve roots, the nerve plexus, and peripheral nerves. The painful lesion of the intercostobrachial nerve after axillary surgery is a typical example [38, 39]. Mis- or erroneous reinnervations, for instance of the latissimus dorsi flap (reconstruction) used for plastic surgery after breast surgery, can cause unwanted involuntary movements [40], term the "jumping breast." Painful neuroma formation can cause neuropathic pain after surgical interventions.

At times, nerves have to be sacrificed to allow tumor surgery [41, 42], which may result in weakness, sensory loss, phantom sensations, neuroma formation, and neuropathic pain.

Surgical interventions in ear, nose, and throat (ENT) tumors, such as neck dissection, and RT following ENT tumors can cause damage of the accessory nerves and the cervical plexus and its branches. Characteristic changes were found after "mantle field" RT treating Hodgkin's disease. These RT effects can be associated with muscle atrophy and fibrosis, and were often seen after RT. The sparing of the pectoral muscle is typical in mantle field radiation, due to the radiation field.

However, RT damage is not only confined to neural tissue, other tissues and structures are also involved. This has been described as "radiofibrosis syndrome" [43].

In addition to neoplastic causes, the brachial plexus can be damaged by RT, and the distinction was for a long time dependent on electrophysiology. Increasingly, imaging techniques such as ultrasound and MRI can differentiate with more accuracy. RT techniques have improved, and brachial plexus lesions caused by RT are infrequent using modern techniques [44].

The lumbar plexus is rarely damaged by local tumors; however, local infections and hematomas can cause a lumbar plexus lesion. Also, an iliac syndrome has to be distinguished [45].

Table 2 Chemotherapy-induced neuropathy (CIPN)

Chemotherapy-induced neuropathy	Acute effects	Chronic cumulative	"Coasting"	"Late effects"	Neuropathies due to other mechanisms
Frequent	Oxaliplatin	Platinum Taxane Vinka Alkaloids Eribulin Ixaepilone Bortezomib[a] Thalidomid[b]	Platinum	All. Persisting neuropathic symptoms: sensory, neuropathic pain, Raynaud phenomenon	–
Rare	Taxane	Various single case observations	Possibly vinka alkaloids	–	–
Incidence unknown:	–	–	–	–	–
New drugs	–	–	–	–	Vasculitis, CIDP[c]

[a]Bortezomib: proteasome inhibitor
[b]Thalidomide: α-phthalimidoglutarimid, is a hypnotic drug
[c]The references are based on case reports (e.g.: [55–58]).

For the sacral plexus, local tumors and tumor recurrences need to be distinguished. The clinical features include pain and the absence of sweat secretion in the affected foot.

The clinical distinction between root, plexus, and nerve lesions is difficult due to the proximity of the structures [46]. Also, imaging techniques are best suited for this diagnosis, whereas electrophysiology can only identify indirect and collateral damage. In addition to focal metastasis, also spread of tumors along nerves has been described [47].

RT-induced damage of the sacral plexus results in anhydrosis ("the warm and dry foot"; [48]) and typical EMG findings [49]. Individual nerves from the sacral plexus are less frequently affected [50]. Radiation of nerves can also result in the development of malignant peripheral nerve sheath tumors [51].

The most frequent damage of the peripheral nerves is chemotherapy-induced neuropathy (CIPN; [52]), which can be a dose-limiting factor, but also cause late effects. As different drugs are used in cancer treatment, several mechanisms of nerve damage have to be considered. Also, the individual susceptibility varies. Preceding chemotherapies, other toxic neuropathies, and diabetic neuropathy seem to increase the likelihood of CIPN, and for several cases of hereditary neuropathies, dramatic worsening of neuropathy after chemotherapy has been described [53].

In clinical settings, four different situations appear (Table 2): 1) Acute neuropathic syndromes such as pain, cramps, swallowing difficulties have been observed in oxaliplatin treatment. They are usually cold dependent and can appear at the first chemotherapy cycle. 2) Most frequently, chronic cumulative effects appear, typically following the 3rd or 4th cycle. Mainly sensory symptoms, clumsiness, coordination difficulties, and, variably, neuropathic pain appear. 3) After the termination of the last chemotherapy cycle, symptoms may still progress for a variable time. This has been seen mainly in platinum drugs and is referred as "coasting". 4) The increase in long-term survivors, has also shown that CIPN can persist. Sensory symptoms,

neuropathic pain, and the Raynaud syndrome are often noted [54], even years after the chemotherapy in survivors.

The effects of chemotherapy, in particular the impairment and handicap by sensory loss, are often underestimated. Several scales and scores for the detection of CIPN have been proposed [59, 60]. A simple and robust patient self-evaluation tool is lacking and has been proposed in the monitoring of myeloma patients (http://www.velcade.com/Files/PDFs/tools/Neurotoxocity_Assessment_Tool_Resource.pdf) following the common toxicity criteria (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf). This is practically highly relevant, as most toxicity scores are time consuming and complicated. Patient self-assessment it an invaluable tool.

The late effects of CIPN have only been described in recent years, and seem to have a higher prevalence than previously assumed [61], and presently several studies and investigations focus on this field.

Regional therapy

Of interest are also regional or compartmentalized chemotherapies. Most studies have been done in the CSF, where several types of toxicity have been observed with different drugs [62].

An often-neglected compartment is the abdominal cavity, where local chemotherapies are instilled [63] and also peripheral neurotoxicity appeared.

Limb perfusion for local cancer can damage peripheral nerves [64], and is an interesting paradigm of local short-term intervention resulting in peripheral neurotoxicity.

In addition to the conventional chemotherapies, most reports describe side effects of immune checkpoint inhibitors. Less frequently, neuropathies were described following treatment with GD2 antibodies [65], to ALK inhibitors [66], and sunitinib [67]; these reports at the moment do not exceed the observational reporting level, and frequencies and impor-

Table 3 Causes of different pain syndromes in tumor patients

Pain	Causes	Therapy	Possible causes by tumor therapy
Pain caused by tumors (nociceptiv)	Bone metastases Vertebral column metastases "Pancoast tumors"	Local therapies, surgery, RT	–
Tumor-associated visceral pain	Obstruction, perineal pain, peritoneal seeding	Intestinal therapies	Autonomic symptoms in vinka alakloid therapy
Neuropathic pain syndromes	Meningeal seeding Cranial nerve lesions Nerve root lesions Plexopathies Painful neuropathies	Local intervention (surgery, RT) Therapy of neuropathic pain	Possible
Pain syndromes following surgery	Post-mastectomy, and post-thoracotomy: Phantom pain	Therapy of neuropathic pain Phantom pain: complex neuropsychological therapies	Possible
Pain following RT	RT-induced plexopathy, and focal neuropathy Lhermitte following RT, Osteoradionecrosis RT-induced local nerve tumors	Therapy of neuropathic pain Tumors: Intervention and RT Steroids Physiotherapy	Possible
Pain following chemotherapy	Painful neuropathy. Raynaude Myalgia Steroid-induced compression fracture Osteonecrosis following therapy of osteoporosis	Therapy of neuropathic pain Use different drugs Osteoporosis prevention Application (e.g., iv, sc) Physical: avoidance of heat/cold (e.g., oxaliplatin)	Possible

tance have not been defined. Immune-conjugates are a combination of antibody-directed tumor therapy in association with neurotoxic drugs [68, 69].

A permanent and important question are prophylactic therapies intended to prevent neuropathies in chemotherapy. So far, several drugs have been found to be ineffective, and no preventive strategy has been defined. Small improvements can be achieved by changes in the mode of administration, as shown in bortezomib from iv to sc.

Several factors influencing the development of CIPN are discussed. One possible hypothesis for the development of CIPN are inflammation or autoimmunity factors [70, 71], which might be influenced by immune modulation.

The role of preexisting neuropathies is not entirely defined. Preexisting neuropathies can have different etiologies such as diabetes, alcohol, or possibly also prior chemotherapy with different drugs. Several reports on the worsening of some genetic neuropathies following chemotherapy are available [53] and should present a red flag in any patient with known hereditary chemotherapy, who is scheduled to be on chemotherapy.

As CIPN can produce a variety of symptoms, a tailor-made symptomatic therapy is needed. Depending on symptoms as neuropathic pain, itch, or dysesthesia, drug therapies are often based on anticonvulsants. As usually sensory symptoms and coordination issues appear, physiotherapy, balance, and coordination training and also occupational therapy for fine motor tasks are needed. The preservation of mobility and the activities of daily living (ADL) are main goals. In recent years, in addition to neurorehabilitation, also specific onco-rehabilitation was introduced.

Mononeuropathies, in particular carpal tunnel syndrome, have appeared during tamoxifen therapy [74] and as the onset of CIPN is rarely in the hands, mononeuropathies of other causes have to be considered in differential diagnosis.

Neuromuscular junction

Effects of anti-cancer treatment on the neuromuscular junction are less frequent. Worsening of symptoms in preexisting myasthenia gravis (MG) patients due to steroid treatment [75] and some antibiotics are well known [76]. Immune checkpoint inhibitors can induce myasthenia or worsen preexisting MG [77, 78]. Myasthenic syndromes have also been observed in combination with myositis [79].

Muscle

Muscle involvement in cancer patients includes type 2 muscle atrophy, cachexia [80, 81], and rarely also paraneoplastic involvement [82] such as myositis or necrotizing myopathy. The most frequent involvement of muscle though is cachexia, which sometimes precedes or accompanies cancer patients. As cachexia is a prognostic factor, increasingly therapies to prevent cachexia are also appearing [83].

Although muscle tissue was previously considered to be radiation resistant, this is not the case. The resulting weakness is attributed more to damage of muscle cells, resulting in reduced contractibility, then fibrosis.

In addition to the previously mentioned radiation fibrosis syndrome, also similar to skin reactions towards previous chemotherapy, a muscle radiation recall syndrome has been observed [89].

Treatment-related muscle symptoms occur due to steroid treatment, usually dose and time dependent [72]. Proximal weakness and early atrophy of the thighs is characteristic. Creatinin phosphokinase (CK) levels remain normal, as well as EMG studies are normal. High-dose treatment with dexamethasone can result in weakness in 1–2 weeks. Less well characterized are weakness and atrophy due to anti-testosterone therapies [73].

Myalgia can be a treatment effect in taxanes and gemcitabine [84, 85]. In the new spectrum of therapies, myalgia has been described in Hedgehog [86] and CDK4/6 inhibitors.

Inflammatory myopathies have been observed during treatment with checkpoint inhibitors [79, 87], although the frequency of these effects is still unresolved. Also, rhabdomyolysis can be caused by cancer therapy with MEK inhibitors [88].

In addition to paraneoplastic myopathies, also immunologically induced inflammatory myopathies have been observed in "graft versus host disease" (GVhD; [90]) and following bone marrow transplant [91].

Pain syndromes in tumor patients

Pain is one of the most disabling and debilitating symptoms in cancer patients. In addition to nociceptive and visceral pain, neuropathic components can often be detected. Also, the effects of therapies need to be considered. Table 3 demonstrates several causes and types of pain.

Symptomatic treatment and rehabilitation

Although causative therapies are often lacking, symptomatic treatment must always be considered. Neuropathic pain can usually be treated with standard medications such as anticonvulsants, antidepressants, or opioids. The preservation of function, ADL, and quality of life are the goals. Neuro- and onco-rehabilitation are well established in Austria, and contribute essentially towards treatment and rehabilitation of patients with neurological dysfunction of the central and peripheral nervous system, which has been a positive development in the past decades.

CNS symptoms involving cognition, other neuropsychological dysfunctions, fatigue, coordination, and stability dysfunctions are equally important treatment targets and often need multidisciplinary and multiprofessional treatment.

Increasingly, the future planning of "long-term survivors" is important, and varies in different tumor entities [92].

Conclusion

New cancer therapies have changed the fate of many oncological patients. In some tumor entities dramatic changes in response and survival have changed the "natural course" of many tumor diseases. This includes that the therapy concepts are expanded and long-term care needs consideration. In addition to conventional side effects, new drug therapies and these "late effects" provide current and future challenges.

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