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REVIEW ARTICLE

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Selected neurological complications of oncological treatment — literature overview

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ABSTRACT

Treatment in oncology may lead to several adverse side effects, including those affecting the nervous system. These side effects may reduce the quality of life of patients, both during and after treatment, and may necessitate changes in the treatment regimen or reduction of drug doses, thus reducing the effectiveness of therapy. The knowledge of therapy-induced side effects is essential for their early recognition and differentiation from symptoms resulting from the progression of neoplastic disease, metabolic disorders, or infections, requiring prompt initiation of causal treatment. This article presents the current state of knowledge regarding central and peripheral neurotoxicity of treatment in oncology. Adverse effects described after chemo- and radiotherapy are better known but still limit the potential possibilities of the applied treatment. Neurotoxicities of targeted therapy and immunotherapy, which are of increasing importance in the era of personalization of treatment, are presented.
Key words: neurotoxicity, chemotherapy-induced peripheral polyneuropathy, acute polyneuropathy, chemobrain, ototoxicity, plexopathy

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Introduction

Neurotoxicity of systemic treatment in oncology is the second dose-limiting effect of chemotherapy, after myelotoxicity. Toxicity affects both the central and peripheral nervous systems: it can occur already during treatment and many years after its completion. The probability of its occurrence depends on the dose of the drug, the rhythm of treatment, concomitant use of other drugs and neurotoxic substances, comorbidities of the nervous system, and individual predisposition [1, 2]. Non-selective damage of cellular DNA by chemotherapy, excessive response of the immune system against normal cells induced by immunotherapy, and in the case of radiotherapy, direct or indirect damage of nerve cells, endocrine disorders, or fibrosis of neuronal structures contribute to the development of neurotoxicity [2]. In this article, we present a review of neurological complications of treatment applied in oncology concerning the peripheral and central nervous systems.

Adverse side effects of the peripheral nervous system

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common nervous adverse system side effects associated with oncological treat-

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ment. It is estimated that this problem affects 30–40% of patients undergoing chemotherapy [3]. It is most commonly induced by platinum derivatives, taxanes, vinca alkaloids, bortezomib, or thalidomide. CIPN can occur after a single dose of a drug or after exceeding a cumulative dose [3, 4]. Chemotherapy-induced peripheral polyneuropathy most often appears in the first two months of treatment and increases in the course of its duration [5]. There is a phenomenon of "the coasting effect" of chemotherapy-induced peripheral polyneuropathy after treatment with platinum derivatives [6, 7]. The predisposing factors of CIPN are older age, pre-existing polyneuropathy, chronic renal failure, current or past smoking, concomitant use of other neurotoxic substances, genetic predisposition [single nucleotide polymorphisms (SNPs) associated with a higher risk of CIPN] [4, 5]. CIPN manifests itself in many ways. Nerve fibers with a small cross-sectional area (C fibers) are mainly damaged, resulting in burning pain, hypersensitivity, and then loss of pain and temperature sensation. Initially, the disorder involves fingers and toes, then spreads proximally and involves larger areas of the extremities (the so-called glove and sock symptom). Patients report numbness, tingling, paresthesia, dysesthesia, and sensory disturbances. These symptoms may be accompanied by pain, lack of deep sensation, balance problems, gait impairment, and loss of ability to perform fine movements. The occurrence of peripheral polyneuropathy during chemotherapy often leads to a reduction of drug doses and sometimes to discontinuation of treatment. Both during and after treatment, peripheral polyneuropathy can significantly reduce quality of life (QoL) and have a negative impact on health status, increasing the risk of falls, inducing sleep disturbances, and contributing to psychiatric disorders (Tab. 1) [3, 6, 8]. The only drug whose efficacy

Table 1. Chemotherapy-induced peripheral polyneuropathy of the most commonly used chemotherapeutics: pathomechanism and clinical presentation [4, 6–8]

Drug group	Mechanism of CIPN	CIPN Symptoms
Platinum derivatives • Cisplatin • Oxaliplatin • Carboplatin	• mitochondrial DNA damage • atrophy of dorsal root ganglion cells • dysfunction of ion channels • impairment of intracellular signaling • increased levels of proinflammatory cytokines	Oxaliplatin is a drug that can induce both chronic peripheral and acute neuropathy Oxaliplatin-induced peripheral polyneuropathy is purely sensory with glove and sock distribution and occurs in 50–70% of those undergoing treatment Cisplatin causes chronic polyneuropathy after 12 months in 5–20% of treated Neurotoxicity resulting mainly from damage to large-diameter fibers is manifested by disturbances of vibration and position sensation Carboplatin has the lowest neurotoxicity in this group. Polyneuropathy is experienced by 13–42% of those treated
Taxanes • Paclitaxel • Docetaxel • Cabasitaxel • Nab-paclitaxel	• influence on pore permeability within mitochondria and endoplasmic reticulum • increased synthesis of proinflammatory cytokines (TNF alpha and IL-1 beta), decreased synthesis of anti-inflammatory cytokines (IL-4 and IL-10) • altered expression and function of ion channels leading to morphological and biochemical changes in the dorsal roots of spinal nerves • direct damage to sensory neurons through degeneration of nerve fibers and their demyelination	Taxanes primarily cause damage to small-diameter fibers manifesting as paresthesias, dysesthesias, or numbness in the stocking-and-glove distribution, loss of proprioception, and impairment of fine motor movements Motor neuron function and autonomic nervous system function may be impaired Paclitaxel induces sensory neuropathy of severe severity (G3 and G4) in 20–35% of patients receiving 250 mg/m^2 of chemotherapeutic agent every 3 weeks, and in 5–12% of patients treated with < 200 mg/m^2 administered every 3 weeks
Vinca alkaloids • Vincristine • Vinorelbine • Vindesine • Vinblastine	• impaired axonal transport inducing distal axonopathy • changes in axons and dorsal root ganglion neurons leading to primary axonal degeneration called Waller's degeneration • changes in the activity of ion channels and hyperactivity of peripheral nervous system neurons • increased levels of proinflammatory cytokines	Symptoms of polyneuropathy involve both sensory and autonomic nerves. Patients most commonly report numbness, tingling, and neuropathic pain in the extremities Distribution of glove- and sock-like symptoms in 35–45% of those treated The substance with the highest neuropathic potential in this group of cytostatics is vincristine. Severe polyradiculopathies resembling Guillain-Barré syndrome have been reported. Autonomic nervous system disorders after the use of vinca alkaloids are manifested by constipation, urinary retention, and sometimes orthostatic hypotension

CIPN — Chemotherapy-induced peripheral neuropathy

in relieving the symptoms of chemotherapy-induced peripheral polyneuropathy has been confirmed in phase III clinical trials is duloxetine [9, 10]. Last January the results of a prospective study were published to evaluate the efficacy and safety of duloxetine in a group of 100 patients who developed peripheral polyneuropathy during cancer treatment. The response to treatment was evaluated using the PGIC (Patient Global Impression of Change) scale, in which 1 represented no response and 7 represented an excellent response. In this analysis, higher scores, and thus higher treatment efficacy, were obtained in the group of women and those displaying CIPN symptoms for a shorter period. Fifty-seven percent of patients discontinued taking duloxetine early due to adverse effects (37%) and lack of treatment efficacy (20%); men predominated in this subgroup of patients [11].

Plexopathy

Treatments used in oncology can induce plexopathy, i.e. damage to nerve plexuses. It mainly affects the brachial and lumbosacral plexuses. Symptoms are muscle weakness, sensory disturbances, and impaired deep reflexes which may be accompanied by pain [2]. The injury of the plexus is mainly induced by radiotherapy to the thoracic region. The symptoms of plexopathy usually appear with a delay, from 6 months to even 30 years after the end of radiotherapy [2, 12]. In differentiating between plexus cancer infiltration and radiation damage, the etiology secondary to treatment is indicated by mild pain, involvement of the upper part of the plexus, and accompanying lymphedema of the limb. Magnetic resonance imaging and electromyography may be helpful in the diagnosis. Lumbosacral plexopathy is usually associated with radiotherapy to the pelvic region. The predominant symptoms are paresis of the lower extremities, and, less frequently, sensory disturbances [12]. Symptoms of plexus injury, although much less frequent, may occur after treatment with cytarabine, IL-2, or INF-alpha [2].

Acute polyneuropathy

Paclitaxel is a widely used chemotherapeutic agent in oncology that, in addition to causing chronic polyneuropathy, can induce paclitaxel-acute pain syndrome (P-APS). Up to 58% of patients treated with paclitaxel may experience P-APS, and 20% of these patients report pain ranging from 5 to 10 on the 10-point Visual Analogue Scales (VAS) pain scale. The muscle and joint pain experienced by patients most commonly affects the lower extremities, hips, and lower back. Pain experienced after the first infusion does not always correlate with complaints reported with subsequent infusions. The sensory neuropathy accompanying the disorder, including numbness and tingling, is more strongly expressed than autonomic or motor neuropathy [13, 14]. Importantly, patients reporting more severe pain are more likely to develop chronic polyneuropathy. Typically, symptoms appear up to 3 days after drug application and resolve spontaneously within a week. Both the mechanism of onset and prevention are unknown. Treatment is exclusively symptomatic and consists of non-steroidal anti-inflammatory drugs (NSAIDs) to relieve pain [3, 13]. Oxaliplatin is another chemotherapeutic agent that can cause acute neuropathy in addition to chronic neuropathy. Symptoms usually appear during the infusion or within hours after its completion and resolve spontaneously within hours or days. It is estimated that up to 96% of patients experience hand dysesthesia provoked by low temperature. Other manifestations of neuropathy include hand and foot paresthesia, cold-induced dysesthesia of the feet, mouth and throat, hand and forearm muscle spasms, trismus, eye pain, and tongue numbness [14, 15]. The incidence of grade 3–4 laryngeal dysesthesia according to the Common Terminology Criteria for Adverse Events (CTCAE) is estimated at 1–2% of patients receiving oxaliplatin for advanced colorectal cancer [15].

Ototoxicity

Cisplatin is the chemotherapeutic agent with the highest ototoxic potential, leading to irreversible bilateral conductive and sensorineural hearing impairment in 20–75% of those treated. Risk factors include younger age, high cumulative dose, duration of treatment, as well as pre-existing hearing loss, noise exposure, intake of other ototoxic substances, malnutrition, renal insufficiency, genetic predisposition, and radiotherapy to the cranial region [5, 16–18]. Initially, hearing impairment involves high-frequency sounds, and once the cumulative dose of cisplatin (100 mg/m^2) is exceeded, it also involves mid-frequency sounds [17]. In addition, most patients report experiencing tinnitus, which can persist after treatment in up to 40% of those treated. This is another complication whose occurrence can reduce QoL by generating anxiety and insomnia, leading to the development of depression [19]. Other less ototoxic substances are carboplatin, vinca alkaloids, and oxaliplatin (Tab. 2) [5].

Peripheral polyneuropathy induced by targeted drugs and immunotherapy

Neurological complications following immune checkpoint inhibitors (ICIs) in the form of anti-CTLA-4, anti-PD1, and anti-PD-L1 antibodies are rare, relatively understudied, but clinically relevant. Severe forms in

Table 2. Selected symptoms of cranial nerve damage along with the factor potentially inducing the disorder [1, 2]

Symptom of cranial nerve damage	Type of treatment used
Loss or deterioration of smell, taste	Radiotherapy Each type of chemotherapy
Eyesight impairment	Cisplatin Oxaliplatin Tamoxifen Bevacizumab Vincristine Radiotherapy
Hearing loss/deterioration	Cisplatin Vincristine Oxaliplatin Radiotherapy
Oculomotor nerve dysfunction	Cytarabine Vincristine Interferon alpha
Ptosis	Vincristine Oxaliplatin

grades 3–4, according to CTCAE v.4.0, affect < 1% of treated patients. Most of these are peripheral nerve dysfunction with clinical features of Guillain-Barré syndrome, peripheral polyneuropathy, meningoradiculitis, or myasthenia gravis. The mean time to onset of immune-related adverse event (irAE) is 6 weeks, except for myasthenia gravis, which may appear as early as after 3 weeks, more often with concomitant myositis and myocarditis, which increases the death rate (~20%) [20–28]. Guillain-Barré syndrome with progressive, symmetric ascending flaccid paresis of the lower limb muscles, weakness or abolition of deep reflexes, hemiparesis of the oculomotor muscles, autonomic disturbances (cardiac arrhythmias, arterial pressure fluctuations), and eventually respiratory failure, is a dose-independent, potentially life-threatening adverse effect of both platinum derivatives and ICIs [20]. These compounds can also cause damage to neuromuscular junctions, manifested by excessive muscle fatigue, drooping eyelids, double vision, slurred speech, impaired chewing and swallowing of food, and, in the end-stage of the disease, dyspnea due to respiratory muscle weakness [2, 3]. Trastuzumab emtansine (T-DM1, trastuzumab emtansine) is an antibody-drug conjugate that contains trastuzumab, a humanized monoclonal antibody bound to a microtubule inhibitor: emtansine (DM1). This drug can lead to clinically significant sensory polyneuropathy [29, 30].

Central nervous system adverse side effects

Headaches

Isolated headaches are a common side effect of oncological treatment and the most common neurologic adverse effect of any pharmacotherapy. Risk factors for headache include a history of headache, blood-brain barrier-penetrating chemotherapy, and intrathecal administration of the drug. Headaches have been reported in 26% of patients receiving cetuximab for advanced colorectal cancer. Other drugs that promote headache include asparaginase, etoposide, fludarabine, methotrexate, rituximab, trastuzumab, tamoxifen, and temozolomide [1–3]. Headache may be a symptom of other neurological complications of systemic treatment, such as aseptic meningitis, posterior reversible leukoencephalopathy syndrome (PRES), idiopathic pseudotumor cerebri, or blood-brain barrier damage induced by radiotherapy [2].

Convulsions

Many drugs lower the seizure threshold, resulting in seizures. These include cisplatin, gemcitabine, 5-fluorouracil, etoposide, paclitaxel, or vincristine [1, 2]. Busulfan is a drug that is associated with a high risk of seizure induction. The risk of seizure occurrence is increased by intrathecal administration of drugs, especially cytarabine or methotrexate. Seizures may be an isolated adverse event or one of the manifestations of other treatment-induced conditions such as encephalopathy or PRES [1, 5].

Chemotherapy-related cognitive impairment

Chemotherapy-related cognitive impairment (CRCI), commonly referred to as "chemobrain", was first described in 1980. It is estimated to occur in 17% to 75% of patients receiving cancer treatment. Potential mechanisms that may contribute to the development of the disorder include direct neurotoxicity from chemotherapy, decreased levels of neurotransmitters, damage to cellular DNA, and hormonal and immune dysregulation. Cognitive disorders are usually of mild to moderate severity, manifested by deterioration of attention, memory, executive functions, prolonged information processing and reaction time, and limited vocabulary [31–33]. They lead to a reduced QoL; they make it difficult to return to work, reduce self-confidence, and impair social relationships [33, 34]. Subjectively, difficulties are greater than indicated by objective test results. CRCI is reported by more than 50% of patients receiving chemotherapy for breast cancer, which translates into objective test scores in 15–25% of them. The decline in cognitive function in

the study occurred shortly after the start of treatment, with partial return of ability one year after the end of treatment. Observation of patients undergoing hormone therapy alone for breast cancer has shown that the use of anastrozole or tamoxifen may be associated with cognitive decline [33]. Among patients undergoing chemotherapy for colorectal cancer, cognitive impairment after 6 months was reported in 32%, i.e. twice as often as in patients not receiving chemotherapy; at 12 months after the end of treatment the relationship was no longer so clear. No difference in the severity of cognitive impairment has been observed between patients with disseminated and limited forms of colorectal cancer [33, 35] The use of androgen deprivation therapy (ADT) in patients with prostate cancer may impair cognitive abilities to a small extent, with eye-hand coordination being impaired more frequently [33]. Observation of patients with metastatic renal cell carcinoma undergoing targeted therapy with antiangiogenic drugs confirmed that this type of therapy causes cognitive deterioration in 31% of those treated [36]. Importantly, cognitive impairment is also reported by cancer patients who are not receiving chemotherapy. Thus, the phenomenon of "chemobrain" is difficult to assess objectively. It should be kept in mind that comorbid metabolic and endocrine disorders, anemia, fatigue, insomnia, or depression are all directly related to cancer, and oncological treatment itself may overlap with the CRCI picture [32].

Neurological complications of immunological treatment

Nervous system side effects occur in 6.1% of patients taking anti-PD-1 antibodies, 3.8% of anti-CTLA-4 antibodies, and 12% of those treated with a combination of both drugs (Tab. 3). The most common manifestation described is headache. Adverse effects induced by immunotherapy may appear already at the beginning of treatment, but also after its completion. The occurrence of pathological symptoms of the central nervous system requires high vigilance and quick differential diagnosis to exclude metabolic disorders, central nervous system metastases, neoplastic invasion of the cerebrospinal meninges or their inflammation and take action appropriate to the diagnosis [37–40]. Other central nervous system side effects induced by immunotherapy include aseptic meningitis, PRES, transverse myelitis, or encephalopathy (Tab. 4) [37, 39].

General principles of treatment of neurological complications induced by immunotherapy

In the case of **mild severity (G1)**, immunotherapy can be continued with the implementation of simultaneous differential diagnosis excluding infectious and metabolic etiology, as well as disease progression [38–40].

In neurological disorders of **moderate severity (G2),** it is recommended to temporarily hold the treatment with simultaneous implementation of differential diagnostics and consideration of oral steroid therapy, i.e. prednisone 0.5–1 mg/kg body weight. After a reduction in the severity of symptoms, a gradual reduction in the steroid dose over at least 4 weeks to a maximum of 10 mg of prednisone daily is indicated. If the effect does not reappear after the reduction of the steroid dose, treatment can be resumed, but discontinuation of treatment is recommended in case of recurrent side effects of moderate severity [38–40].

In neurological side effects of **high and very high severity (G3 and G4),** immunotherapy should be discontinued without fail and intravenous steroid therapy should be instituted in the hospital setting, and if ineffective, immunosuppressive treatment should be instituted (Tab. 5) [38–40].

Table 3. The frequency of nervous system adverse side effects induced by antibodies used in systemic cancer treatment [45]

	anti-CTL4	anti-EGFR	anti-HER2	anti-PD1/PDL-1	anti-VEGF
Headache	12%	25%	16%	3%	25%
Neuropathy	1.5%	16%	33%	0.9%	1.3–2.2%
Encephalopathy	5.1%	2–6%	2%	1%	2–4%
Stroke/TIA	2%	< 1%	0.1%	0.9–1.7%	2%
Other	Myasthenia gravis 1% Aseptic meningitis 0.2% Intracerebral hemorrhage: 5% of patients with secondary CNS lesions receiving radiotherapy	Sleep disorders 15%	Convulsions 0.2%	Myasthenia gravis 1% Walking difficulties 1% Sleep disorders 1.2–1.5% Convulsions 0.4%	Sleep disturbance 1.2% Intracranial hemorrhage of at least CTC3 severity < 1% In patients with secondary CNS lesions, seizures were observed in 7–13%, intracerebral hemorrhage in 4%, radionecrosis in 5%

CNS — central nervous system

Table 4. Selected neurological complications induced by oncological treatment

Complication	Manifestation and characteristics
Encephalopathy	Confusion, impaired consciousness, apathy, lethargy, impaired attention, hallucinations, agitation, and seizures [2, 3]
	Acute encephalopathy has been described in 10–25% of patients after ifosfamide treatment. Other substances that may induce encephalopathy include cisplatin, etoposide, mitomycin, fludarabine, and tamoxifen [2]
	Risk factors for encephalopathy include the dose of the drug and its ability to penetrate the blood-brain barrier, concomitant use of CYP2B6 inhibitors, renal failure, and hypoalbuminemia [5]
Cerebellar syndrome	Ataxia, gait disturbances, balance disorders, nystagmus, and scanning speech [2]
	It may occur after molecularly targeted drugs such as trastuzumab or rituximab, as well as after classical chemotherapeutics such as cytarabine [2, 5]
	Risk factors are hepatic and renal failure, age > 40 years, and high doses of drugs used [5]
Aseptic meningitis	Fever, headache, meningeal symptoms, and photophobia [37, 40]
	Symptoms are associated with intrathecal administration of chemotherapeutics and result from irritation of the meninges. They usually appear 2–4 hours after drug application and symptoms resolve by 72 h [5]
	Ipilimumab through abnormal activation of the immune system can induce aseptic meningitis [2]
Posterior reversible leukoencephalopathy syndrome (PRES)	High blood pressure values, headache, dizziness, visual disturbances, disorders of consciousness, and seizures [2, 5]
	The hypertensive crisis that may occur after the use of monoclonal antibodies that bind to vascular endothelial growth factor receptors may lead to the development of PRES. The occurrence of PRES has also been described after cyclosporin, cyclophosphamide, or sunitinib [2]
	The risk factors include pre-treatment hypertension, autoimmune disease, renal failure, high doses of anticancer drugs, organ transplant status, and immunosuppression [5]
Transverse myelitis	Symptoms of sensory and motor nerve damage, back and limb pain, paraplegia, and sphincter dysfunction [5, 40]
	It may occur after intrathecal administration of methotrexate, cytarine, cisplatin, or thiotepa [5]
	Risk factors are concurrent radiotherapy to the craniospinal region, and frequent intrathecal injections [5]
Stroke	Focal neurological symptoms, hemiparesis, speech impairment, facial asymmetry, dizziness, and impaired consciousness [3]
	An increased risk of thromboembolism and thus of ischemic stroke is associated with the use of cisplatin, 5-fluorouracil, gemcitabine, and bleomycin [5]. The use of angiogenesis inhibitors also increases the risk of stroke [2]
	The occurrence of hemorrhagic or ischemic stroke related to the use of chemotherapy is rare. The risk of stroke in the oncology patient population is similar to that in the general population [3]
Major depressive disorders	Anhedonia, apathy, abulia, insomnia, tearfulness, lack of or excessive appetite
	Mood disorders often accompany the diagnosis of cancer. However, there are groups of drugs whose use is associated with an increased risk of depressive disorders. These include procarbazine, carmustine, vinca alkaloids, pemetrexed, fludarabine, taxoids, cetuximab, imatinib, sorafenib, or sunitinib [3]

PRES — posterior reversible leukoencephalopathy syndrome

Central nervous system adverse side effects induced by radiotherapy

Central nervous system (CNS) adverse side effects are divided into early ones, occurring up to 6 months after radiotherapy, and late ones, occurring after 6 months. Early adverse reactions are usually reversible and of low intensity [41, 42]. The most common in this group is fatigue syndrome, which occurs during or shortly after treatment. Other side effects include focal neurological symptoms, cognitive decline, or seizures. PRES induced by systemic therapy may also be a consequence of central nervous system radiotherapy. It appears already after 3 weeks of treatment and is caused by damage to the blood-brain barrier [2, 41, 42]. Leukoencephalopathy, which may manifest as slowly progressing cognitive disorders, personality changes, and even epileptic seizures, usually appears 1–2 years after whole-brain radiotherapy [41]. Another central nervous system side effect after radiotherapy is pseudoprogression of focal lesions, which occurs in 12–64% of patients undergoing radiotherapy. It consists of an increase in the size of focal lesions on magnetic resonance imaging and an increase in central nervous system symptoms. It usually resolves within 6 months after irradiation. It is recognized that up to 30% of early tumor progression on imaging studies is pseudoprogression, and distinguishing between these two clinical situations is essential in

Table 5. Guidelines for diagnostic and therapeutic management of nervous system adverse side effects induced by immunotherapy based on NCCN 01.2022 [37, 44–46]

	Frequency of side effects incidence after administering ICI*	Diagnostics	Management
Myasthenia Gravis	0.12–1.16%	Neurological consultation Laboratory tests: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), aldolase, phosphocreatine kinase (CPK), acetylcholine receptor antibodies (AChR-Ab; present in 60% of cases of ICI-induced MG), striated muscle antibodies (i.e. anti-titin, anti-RyR, anti-RAP-SN), tyrosine kinase antibodies (anti-MuSK). Electrophysiological examinations to exclude myositis or neuropathy, i.e. electromyography (EMG), nerve conduction study (NCS) Respiratory function tests Additional tests: • in the case of suspected myocarditis: electrocardiography (ECG), transthoracic ultrasound (TTE), determination of troponins levels • in the case of suspected neoplasm invasion in the central nervous system or other potential causes of symptoms magnetic resonance imaging (MRI)	**Management of symptoms of moderate severity (G2):** **Definitive discontinuation of immunotherapy** Inpatient use of pyridostigmine initially at a dose of 30 mg 3 times daily, with gradual escalation to a maximum of 120 mg up to 4 times daily Consider inclusion of prednisone initially at a dose of 20 mg daily, with gradual dose escalation to 1 mg/kg per day (do not exceed 100 mg daily) **Management of symptoms of high severity (G3–G4):** **Definitive discontinuation of immunotherapy** Inpatient use of pharmacotherapy: methylprednisolone 1–2 mg/kg The use of plasmapheresis or intravenous preparations of immunoglobulin, and in the absence of their effectiveness, consider the addition of rituximab Medications that may exacerbate symptoms of myasthenia gravis (i.e. ciprofloxacin, aminoglycosides, or beta-blockers) should be avoided, the respiratory system should be assessed and the patient's neurological status should be monitored
Guillain-Barré Syndrome (GBS)	0.1–0.2%	• Neurological consultation • MRI of the spinal cord • Lumbar puncture (a general examination of the CSF should be performed and potentially infectious agents such as HSV or other viruses should be excluded depending on the clinical picture; CSF pressure should be measured) • Respiratory function tests • Electrophysiological examinations, i.e. electromyography (EMG), electroneurography (NCS) • Additional investigations: determination of specific serum anti-ganglioside antibodies (anti-GQ1b)	**Management of moderate to severe symptoms (G2–G4)** **Definitive discontinuation of immunotherapy.** In-hospital administration of intravenous immunoglobulin or plasmapheresis with pulses of methylprednisolone at a dose of 1 gram daily for 5 days followed by gradual dose reduction over 4 weeks. Steroid therapy is not recommended for idiopathic GBS The patient should be evaluated neurologically, for respiratory distress and autonomic dysfunction. 15–30% of patients with idiopathic GBS require assisted ventilation In case of pain, the following are used: gabapentin, pregabalin, and duloxetine
Aseptic meningitis	0.36%	• Neurological consultation should be considered • Lumbar puncture (general examination of cerebrospinal fluid, tests to rule out viral infections including HSV) • MRI of the brain to exclude brain or meningeal metastases	**Management of symptoms of moderate severity (G2):** Hold immunotherapy Until a result is obtained to rule out HSV infection, it is recommended that acyclovir be considered for inclusion After excluding a viral or bacterial etiology, consider starting steroid therapy i.e. prednisone 0.5–1 mg/kg per day or methylprednisolone 1–2 mg/kg per day

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Table 5 cont. Guidelines for diagnostic and therapeutic management of nervous system adverse side effects induced by immunotherapy based on NCCN 01.2022 [37, 44–46]

	Frequency of side effects incidence after administering ICI*	Diagnostics	Management
			Management of symptoms of high severity (G3–G4) **Consider definitive discontinuation of immunotherapy** Hospitalization of the patient Consider inclusion of acyclovir pending PCR result for HSV Once an infectious etiology of the complaint has been ruled out, consider starting steroid therapy i.e. prednisone 0.5–1 mg/kg per day or methylprednisolone 1–2 mg/kg per day
Transverse myelitis	< 0.06%	• Neurological consultation • MRI of the brain and spinal cord • Lumbar puncture (general examination of cerebrospinal fluid, tests to exclude viral infections, onconeuronal antibodies, oligoclonal bands). • Determination of vitamin B12 level, antinuclear antibodies ANA, anti-Ro, anti-La, anti-aquaporin 4 (AQP4-IgG) antibodies, anti-myelin glycoprotein oligodendrocytes antibodies level, paraneoplastic antibodies determination (anti-Hu, anti-CRMP5, anti-CV2), ruling out HIV infection • Evaluation of the presence of constipation and urinary stasis based on bladder imaging	**Definitive discontinuation of immunotherapy.** In-hospital initiation of methylprednisolone 1 g per day for 3–5 days, consideration of plasmapheresis or intravenous immunoglobulin preparations
Encephalitis (often with a limbic encephalitis phenotype, less commonly cerebellitis)	0.84%	• Neurological consultation • MRI of the brain • Lumbar puncture (general examination of cerebrospinal fluid, tests to exclude viral infections, i.e. HSV, paraneoplastic antibodies, oligoclonal bands, antineuronal autoantibodies; assessment of cerebrospinal fluid pressure) • Electroencephalography (EEG) • Laboratory tests: blood count, ESR, glucose, ionogram, total protein, albumin, aminotransferases, alkaline phosphatase, bilirubin, urea, CRP, anti-neutrophil cytoplasmic antibodies (ANCA), TSH, fT3, fT4, TPO, thyroglobulin, paraneoplastic antibodies	**Management of symptoms of moderate severity (G2):** **Definitive discontinuation of immunotherapy** Consider intravenous acyclovir until PCR results are available to rule out HSV 1 and 2 infections Initiate methylprednisolone at 1–2 mg/kg per day. Continue use for up to 4 weeks after resolution of symptoms **Management of symptoms of high severity (G3–G4)** **Definitive discontinuation of immunotherapy** Hospitalization of the patient Methylprednisolone 1g i.v. for 3–5 days in combination with intravenous immunoglobulin preparations or plasmapheresis. This form of steroid therapy should also be considered in patients with observed progression of symptoms within 24 h or with the presence of oligoclonal bands in the CSF In selected cases i.e. autoimmune encephalopathy or no improvement after 7–14 days consider rituximab

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Table 5 cont. Guidelines for diagnostic and therapeutic management of nervous system adverse side effects induced by immunotherapy based on NCCN 01.2022 [37, 44–46]

	Frequency of side effects incidence after administering ICI*	Diagnostics	Management
Peripheral polyneuropathy	1.3%	Factors that may induce polyneuropathy should be excluded, i.e. drugs, infections, metabolic or endocrine disorders, autoimmune diseases, and vascular diseases Consider imaging the cerebrospinal axis In CTCAE grade G2, consider neurological consultation and additional tests such as EMG or NCS Diagnostic procedure for CTCAE grades G3–G4 according to the Guillain-Barré guidelines	For mild symptoms (G1), consider withholding immunotherapy, and evaluate the severity of complaints after one week In the case of moderate symptoms (G2), stop immunotherapy and consider starting prednisone 0.5–1 mg/kg orally. If symptoms progress, include methylprednisolone at 2–4 mg/kg/day Consider including medications to alleviate pain associated with peripheral polyneuropathy such as gabapentin, pregabalin, or duloxetine Treatment of severe cases (G3-G4) is the same as in Guillain-Barré syndrome

*ICI — Immune checkpoint inhibitors

making therapeutic decisions regarding the continuation of treatment in patients taking thalidomide [41, 42]. The late and most serious consequence of radiotherapy to the central nervous system area is radiation necrosis. In the literature, its incidence is estimated at up to 24% of patients undergoing radiotherapy, usually 1 to 3 years after the end of treatment, and the most vulnerable areas are the frontal and temporal lobes. The formation of necrosis results from perivascular inflammation, leading to white matter edema. Like in pseudoprogression, one risk factor for occurrence is concurrent chemotherapy. This complication may be asymptomatic or cause drowsiness, headaches, or neurological symptoms, whose picture depends on the location of necrotic lesions [41, 43]. Radiotherapy to the central nervous system and head and neck region increases the risk of stroke through the development of vasculopathy and acceleration of atherosclerosis. Radiotherapy-induced cavernous angiomas develop one to 26 years after irradiation and have a higher risk of bleeding and may cause seizures. Other vascular changes associated with radiation therapy include telangiectasias within the spinal cord vessels, which can be a source of bleeding. SMART (Stroke-like Migraine Attacks after Radiation Therapy) may manifest with episodes of focal neurologic symptoms or seizures and is another late radiation reaction occurring one to 30 years after the end of treatment. It is prevented with medications recommended for migraine prophylaxis [2, 42].

Summary

Systemic therapy used in oncology may generate numerous adverse effects on the nervous system. Neurotoxicity is a cause of drug dose reduction and treatment discontinuation; it may also be directly life-threatening. Although the majority of side effects are mild, they may diminish QoL, stigmatize the patient, and make it difficult to return to work or social activity after treatment.

Conflict of interest

Authors declare no conflict of interest.

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