REVIEW

Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature

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Abstract: Commonly used chemotherapeutic agents in oncology/hematology practice, causing toxic peripheral neuropathy, include taxanes, platinum compounds, vinca alkaloids, proteasome inhibitors, and antiangiogenic/immunomodulatory agents. This review paper intends to put together and discuss the spectrum of chemotherapy-induced peripheral neuropathy (CIPN) characteristics so as to highlight areas of future research to pursue on the topic. Current knowledge shows that the pathogenesis of CIPN still remains elusive, mostly because there are several sites of involvement in the peripheral nervous system. In any case, it is acknowledged that the dorsal root ganglia of the primary sensory neurons are the most common neural targets of CIPN. Both the incidence and severity of CIPN are clinically under- and misreported, and it has been demonstrated that scoring CIPN with common toxicity scales is associated with significant inter-observer variability. Only a proportion of chemotherapy-treated patients develop treatment-emergent and persistent CIPN, and to date it has been impossible to predict high- and low-risk subjects even within groups who receive the same drug regimen. This issue has recently been investigated in the context of pharmacogenetic analyses, but these studies have not implemented a proper methodological approach and their results are inconsistent and not really clinically relevant. As such, a stringent approach has to be implemented to validate that information. Another open issue is that, at present, there is insufficient evidence to support the use of any of the already tested chemoprotective agents to prevent or limit CIPN. The results of comprehensive interventions, including clinical, neurophysiological, and pharmacogenetic approaches, are expected to produce a consistent advantage for both doctors and patients and thus allow the registration and analysis of reliable data on the true characteristics of CIPN, eventually leading to potential preventive and therapeutic interventions.

Keywords: neurotoxicity, incidence, diagnosis, treatment

Introduction

Chemotherapy drugs used to treat cancer can be neurotoxic by either exerting a direct noxious effect on the brain or the peripheral nerves.[1,2] Nonetheless, chemotherapy-induced peripheral neurotoxicity (CIPN) is considered to be among the most common non-hematological adverse effects of a number of effective chemotherapeutic agents. Depending on its severity, CIPN can be dose limiting and may also significantly diminish the quality of life (QOL) of patients, because it can persist or even intensify long after the completion of chemotherapy.[2] Moreover, the economic cost of neurotoxicity secondary to antineoplastic agents on health systems is significant, as cancer patients with CIPN have significant excess health care costs and resource use.[3]

CIPN can usually affect the dorsal root ganglia (DRG) of the primary sensory neurons, but other sites, ie, the nerve terminals (distal terminations of the branches

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of an axon), may also be involved. Its clinical features vary depending on the type of the offending agent involved and the site of action, ranging from pure sensory or sensory–motor peripheral nerve damage of large myelinated or small unmyelinated fibers. Damage to peripheral nerve systems from chemotherapy can present with or without autonomic impairment. Rarely, cranial nerve involvement occurs.[4]

The diagnosis of CIPN usually relies on traditional clinical grading scales, such as the World Health Organization (WHO), Ajani, and Eastern Cooperative Oncology Group (ECOG) scales.[2,4] Nevertheless, the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) for sensory and motor neuropathy are considered to be the standard method for assessing CIPN. NCI-CTCAE version 3 grades its severity from 1) loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function/subjective weakness with no objective findings, to 4) permanent sensory loss that interferes with function/paralysis. Grade 5 is assigned to death from neurotoxicity. In summary, NCI-CTCAEv3 has been constructed to grade the severity of neurosensory and neuromotor symptoms with particular relevance to their interference with function. However, clinical experience shows that the use of NCI-CTCAEv3 is associated with underestimation of CIPN prevalence and severity.[5] The newer NCI-CTCAEv4 was released in May 2009, and its most important difference when compared with version 3 is that NCI-CTCAEv4 harmonizes with the lowest level terms from the Medical Dictionary for Regulatory Activities (MedDRA), which are listed based on their MedDRA primary system organ class, eg, immune system disorders or nervous system disorders.[6] One would expect that the changes in NCI-CTCAEv4 would impact the prevalence estimates of CIPN. However, this does not seem to be the case, because again, no formal neurological examination is required and grading of CIPN severity remains subjective, solely relying on patients' reported symptoms. Moreover, the use of the same tool of peripheral sensory neuropathy as a separate item and addition of definitions, ie, dysesthesia, paresthesia, or neuralgia as distinct items seems to confuse rather than offer clarity.[7]

Alternatively to NCI-CTCAE, the 11-item neurotoxicity subscale (FACT/GOG-Ntx [Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity]) developed by the Gynecologic Oncology Group has also been used.[8] However, significant inter-observer disagreement occurs in scoring CIPN with these scales and as such,

initiatives have been launched to define the optimal outcome measures of CIPN assessment.[9,10]

Recently, the CI-PeriNoms (chemotherapy-induced peripheral neuropathy) study group reported initial validity and reliability findings for grading scales, such as the NCI-CTCAE, the Total Neuropathy Score clinical version (TNSc©), the modified Inflammatory Neuropathy Cause and Treatment (INCAT) scale, and the group sensory sum score (mISS).[11] The TNSc, a shorter and more easily applied clinical version of the formal TNS, is a composite measure that includes symptoms, signs, and ability aspects, and its use is proposed because it appears superior to NCI-CTCAE in terms of responsiveness.[11–15]

Furthermore, patients have reported a validated scale that has been used to assess CIPN in a more comprehensive and accurate manner: the Rasch-built Overall Disability Scale (CIPN-R-ODS), consisting of 28 items, was able to detect disability in CIPN patients with proper validity and reliability, and to bypass the difficulties with ordinal-based measures.[16] In any case, it seems that clinical and patients' reported outcome measures should always be combined to achieve a comprehensive knowledge of CIPN, including a reliable assessment of both the severity and the quality of CIPN-related sensory impairment.[17]

Commonly used chemotherapeutic agents in oncology/hematology practice causing peripheral neuropathy are taxanes, platinum compounds, vinca alkaloids, proteasome inhibitors, and antiangiogenic/immunomodulatory agents. We will herein review and discuss the spectrum of CIPN characteristics resulting from the administration of chemotherapeutic agents. Tables summarizing the common sites of involvement (Table 1), risk factors of CIPN (Table 2), as well as the type of neuropathy and clinical pattern of CIPN (Table 3) by neurotoxic drug classification are also presented. Additionally, we will highlight areas for future research to pursue.

Taxanes (paclitaxel/docetaxel)
Pathogenesis
Conventionally, the mechanisms underlying the pathogenesis of taxane-induced peripheral neuropathy (TIPN) include interference with microtubule-based axonal transport, macrophage activation in both the DRG and peripheral nerve, as well as microglial activation within the spinal cord.[18] As a result of the problematic signal transduction, there is evidence of a "dying back" process starting from the distal nerve endings followed by effects on Schwann cells and

Table 1 Common sites of involvement by neurotoxic drug classification

Agent	Sites of peripheral nerve damage
Cisplatin	Dorsal root ganglion
Oxaliplatin	Dorsal root ganglion; ion channels
Paclitaxel	Dorsal root ganglion; microtubules; nerve terminals
Docetaxel	Dorsal root ganglion; microtubules; mitochondria; nerve terminals
Epothilones	Dorsal root ganglion; microtubules; nerve terminals
Bortezomib	Microtubules; mitochondrial and endoplasmic reticulum; dysregulation of neurotrophins
Thalidomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins
Lenalidomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins
Pomalodomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins
Vincristine	Dorsal root ganglion; microtubules; nerve terminals
Suramin	Inhibition of growth factors in dorsal root ganglion

neuronal bodies, or disturbed axonal transport changes in the affected neurons.[19,20]

Recent evidence shows that the activation of spinal astrocytes and the inhibition of microtubule-based fast axonal transport may al so be significant contributors to TIPN.[21] The structure of internodal myelin in peripheral nerves remains unaffected in TIPN.[22]

Table 2 Risk factors of CIPN by neurotoxic drug classification

Agent	Risk factors
Cisplatin	Prior or concomitant administration of taxanes, single and cumulative dose level, pre-existing peripheral neuropathy
Oxaliplatin	
Acute form	Cold, duration of infusion (2-hour vs 4- or 6-hour infusion)
Chronic form	Single and cumulative dose level, severity of the acute form of neurotoxicity, time of infusion, pre-existing peripheral neuropathy, treatment duration
Paclitaxel	Single and cumulative dose level, prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy, duration of infusion (1- to 3-hour vs 24-hour infusion)
Docetaxel	Single and cumulative dose level, prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy
Epothilones	Single and cumulative dose level, prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy
Bortezomib	Single and cumulative dose level, pre-existing peripheral neuropathy
Thalidomide	Same as bortezomib
Lenalidomide	Same as bortezomib
Pomalodomide	Same as bortezomib
Vincristine	Single and cumulative dose level, treatment duration
Suramin	Single and cumulative dose level

Abbreviation: CIPN, chemotherapy-induced peripheral neuropathy.

Incidence, severity, and risk factors

Paclitaxel appears to be more neurotoxic than docetaxel with an overall incidence of about 60% and 15% for each agent, respectively.[23,24] Current evidence shows that the most important triggering factor of TIPN is the accumulation of doses over the course of chemotherapy with a neurotoxic threshold of 1,000 mg/m^2 for paclitaxel and 400 mg/m^2 for docetaxel.[25] Grade 3–4 sensory neuropathy is much more common with paclitaxel than with docetaxel.[2,26] The nanoparticle albumin-bound (Nab) form of paclitaxel was formulated to enable lower doses and reduce toxicity, but clinical experience shows that grade $\geq$2 peripheral neuropathy still remains a significant treatment-limiting toxicity.[27,28]

Other risk factors include prior or concomitant administration of platinum compounds, pre-existing peripheral neuropathy due to various medical conditions, and duration of infusion (1- to 3-hour infusion vs 24-hour infusion).[29] The issue relating to the risk of neurotoxicity after the administration of weekly versus every 3 weeks paclitaxel treatment schedules has been conflictingly addressed. There was evidence to suggest that the risk is lower with the weekly paclitaxel schedule, while the opposite was demonstrated in other studies.[30,31] The risk appears to be unrelated to advanced age.[32]

Clinical and electrophysiological characteristics

Usually, patients affected by TIPN complain of paresthesia, numbness, and/or neuropathic pain in a stocking-and-glove distribution. Clinical examination documents loss of proprioception and suppression or loss of deep tendon reflexes (DTRs).[23] Nerve conduction studies reveal the decrease or abolishment of sensory responses in keeping with an axonal sensory neuropathy as a result of axonal loss from sensory nerves.[33] The sural nerve is particularly affected.[34] Motor involvement with reduction of compound muscle action potential responses and myopathy with proximal weakness is less frequently seen.[35] The significance of sympathetic skin response to provide electrophysiological evidence of small fiber neuropathy in taxane-treated patients merits further study.[36]

Course of neurotoxicity

Symptoms usually improve or resolve within 3 months after the discontinuation of treatment, whereas severe symptoms may persist for a longer period.[23,33]

Table 3 Type of neuropathy and clinical pattern of CIPN by neurotoxic drug classification

Agent	Type of neuropathy	Clinical pattern
Cisplatin	Sensory	Paresthesia, numbness in a stocking-and-glove distribution
Oxaliplatin	Chronic sensory; acute transient neuropathy	Paresthesia, numbness and/or neuropathic pain in a stocking-and-glove distribution; neuromyotonia-like symptoms
Paclitaxel	Sensory; occasionally sensorimotor	Paresthesia, numbness and/or neuropathic pain in a stocking-and-glove distribution; myalgia, myopathy
Docetaxel	Sensory; occasionally sensorimotor	Same as paclitaxel
Epothilones	Sensory; occasionally sensorimotor	Same as paclitaxel
Bortezomib	Painful sensory	Neuropathic pain and paresthesias in distal extremities of limbs
Thalidomide	Sensory	Same as bortezomib
Lenalidomide	Sensory	Same as bortezomib
Pomalidomide	Sensory	Same as bortezomib
Vincristine	Sensorimotor; autonomic; cranial nerves	Paresthesia, numbness and/or neuropathic pain in a stocking-and-glove distribution; muscle cramps, mild distal weakness
Suramin	Sensorimotor; subacute demyelinating and inflammatory polyneuropathy	Bilateral and symmetrical painful paresthesia and hyperesthesia, distally attenuated

Abbreviation: CIPN, chemotherapy-induced peripheral neuropathy.

Options for treatment or prevention

Previous evidence in relation to the symptomatic management of painful TIPN shows that amitriptyline, glutamine, low-dose of oral prednisone, and gabapentin may alleviate the patients' pain.[4] Newer drugs, such as duloxetine alone or in combination with pregabalin have provided additional measures of success in reducing pain, myalgia, and arthralgia.[37,38]

Although several neuroprotective agents, including amifostine, glutamine, acetyl-l-carnitine, and vitamin E hold promise as possible neuroprotective factors, clinical data are still controversial and their routine use is currently not recommended in everyday clinical practice.[39–44]

Epothilones (ixabepilone/sagopilone)
Pathogenesis

Epothilones are able to evoke peripheral neuropathy by inducing tubulin polymerization into microtubules, by interfering with the normal process of anterograde and retrograde axonal transport.[45,46] Additionally, it seems that epothilones are able to induce damage to the ganglion soma cells and peripheral neuroaxons through the disruption of microtubules of the mitotic spindle and by interfering with axonal transport and cytoplasmic flow in the affected neurons.[47] Besides axonopathy, DRG changes have been demonstrated in epothilone-treated animal models.[48]

Incidence, severity, and risk factors

The neurotoxicity threshold for ixabepilone is reached at a dose of 40 mg/m^2.[49] Above that dose, a significant percentage of patients exposed to ixabepilone treatment, varying from 40%–88%, exhibit sensory peripheral neuropathy.[50,51] The incidence of treatment-related advanced sensory or motor neurotoxicity can affect up to 24% and 5% of patients, respectively.[50–52]

ZK-EPO (sagopilone), a third-generation epothilone B derivative, has been clinically tested in metastatic breast or platinum-resistant ovarian cancer patients, and safety data show that the incidence and severity of neurotoxicity was comparable to that of taxanes and ixabepilone.[53] Sagopilone-induced peripheral neuropathy occurs in up to 81.5% of patients, usually in the form of a dose-related sensory neuropathy.[54,55] The rates of treatment-emergent neurotoxicity are significant, as up to 16% of patients can experience grade 3 peripheral neuropathy.[55]

Clinical and electrophysiological characteristics

Both ixabepilone and sagopilone have been reported to produce a clinical and electrophysiological spectrum of neurotoxicity, similar to taxanes.[49]

Course of neurotoxicity

Current knowledge shows that recovery from neurotoxicity symptoms is relatively faster than the period required for the recovery from symptoms of taxane-related neuropathy; it usually takes only 4–6 weeks for grade 3–4 symptoms to improve by at least one NCI-CTCAE grade after the finalization of treatment with either ixabepilone or sagopilone.[54,56]

Options for treatment or prevention

To date, the literature has provided only weak evidence to support the use of any prophylactic treatment against ixabepilone-induced neurotoxicity.[49] A quite recent Phase II European multicenter clinical trial failed to support the efficacy

of acetyl-L-carnitine against the neurotoxicity induced by sagopilone, an analog of ixabepilone.[57] Therefore, adherence to dose modification guidelines is clearly warranted.[54,58]

Platinum compounds (cisplatin/carboplatin/oxaliplatin)
Pathogenesis

DRG represent the main structure that is affected by the deposition of platinum compounds, thereby generating neurotoxicity.[59] Two putative mechanisms are primarily involved in platinum-induced neurotoxicity, and DRG neuron apoptosis is the common cornerstone.[60,61]

Firstly, they are able to alter the tertiary structure of DNA by forming intrastrand adducts and interstrand crosslinks.[62] Moreover, it has been documented that the neuronal apoptosis on DRG could be triggered by oxidative stress, mitochondrial dysfunction with a release of the cytochrome-c pathway, independence of Fas receptor activation, or by increased activity of p53, p38, and ERK1/2.[63–66]

The pathogenesis of oxaliplatin-induced neurotoxicity does not share the same characteristics, as this platinum compound induces two clinically distinct forms of neurotoxicity, namely acute and chronic. The chronic, sensory form is considered to be induced by the morphologic and functional changes in the DRG cells, resulting from the local deposition and accumulation of oxaliplatin. On the other hand, the acute form is thought to be caused by a dysfunction of nodal axonal voltage-gated Na^+ channels, likely resulting from the oxalate chelating effect on both Ca^{2+} and Mg^{2+}.[67]

Incidence, severity, and risk factors

For cisplatin, evidence of peripheral nerve damage of any grade has been reported in about 60% of patients receiving a total cumulative drug dose ranging from 225–500 mg/m^2.[2] However, only 10% of them experience treatment-emergent grade 3–4 neurotoxicity.[68,69] The combination of cisplatin/paclitaxel exerts additive effects in producing neuropathy at higher rates than cisplatin monotherapy.[33,70]

Available data show that carboplatin is almost unrelated to peripheral neuropathy when given as monotherapy at an area under the curve of 6 (AUC6), while its administration at an AUC12 is not associated with the occurrence of grade 3–4 neurotoxicity.[71,72] As such, carboplatin is definitely much less neurotoxic than cisplatin or oxaliplatin.[2]

As to the acute form of neurotoxicity induced by oxaliplatin, it is generally acknowledged that the vast majority of patients treated with various oxaliplatin-based regimens at a dose ranging from 85–130 mg/m^2 experience some grade

of neurotoxicity.[4,73,74] Severe acute OXLIPN (oxaliplatin-induced peripheral neuropathy) that requires prolongation of oxaliplatin infusion or treatment discontinuation may occur in up to 22% of treated patients.[75] Cold temperatures and the time of oxaliplatin infusion are the main risk factors of acute OXLIPN.[76]

On the other hand, the overall rate of neurosensory symptoms in the context of chronic oxaliplatin-induced neurotoxicity (OXAIPN) can range from 60%–75% in patients assigned to be treated with oxaliplatin-based regiments, including FOLFOX4, FOLFOX6, or XELOX.[77,78] Data from large studies show that treatment-emergent grade 3–4 neurotoxicity can occur in up to 20% of oxaliplatin-treated patients, but it can be predicted by clinical and neurophysiological information obtained at mid-treatment.[77,79]

The cumulative oxaliplatin dose, time of infusion, and the existence of peripheral neuropathy prior to the initiation of chemotherapy rank among the most important triggers of chronic OXAIPN genesis.[80] In addition to these well-known risk factors, recent evidence from a large homogeneous series of colorectal cancer patients showed that patients who have a more complex combination of acute phenomena related to axonal hyperexcitability are those who eventually develop more severe chronic neurotoxicity.[75] Furthermore, it seems that the chemotherapy regimen may also represent a risk factor of OXAIPN. This view was supported by a recently published study, which documented that XELOX may be the preferable regimen to avoid the more severe neurotoxicity associated with FOLFOX, despite comparable oxaliplatin cumulative dose.[81] Advanced age does not seem to represent a significant risk factor of OXAIPN in patients without any other significant comorbidity.[82]

Clinical and electrophysiological characteristics

The clinical spectrum of cisplatin-induced peripheral neuropathy is comprised of sensory symptoms in a stocking-and-glove distribution, decreased vibration, and proprioception and suppression or loss of DTRs. Neurophysiology is in keeping with an axonal sensory peripheral neuropathy with a decrease or abolishment of sensory action potentials and normal sensory conduction velocities.[4,33]

Signs and symptoms of acute OXLIPN may begin during the infusion or within 1–2 days of oxaliplatin administration and mostly include distal and perioral cold-induced paresthesias and dysesthesias. However, other uncommon symptoms, such as shortness of breath, jaw spasm, fasciculations, cramps, and difficulty swallowing may also be present

at significant rates. Voice and visual changes, ptosis, and pseudo-laryngospasm rarely occur.[83] Recording of repetitive compound action potentials, high-frequency discharges of motor unit multiplets, and bursts of muscle fiber action potentials are evident during nerve conduction study and needle electromyography examination. This pattern is in keeping with neuromyotonia as a result of excessive nerve excitability, distally attenuated.[84] The clinical and neurophysiological characteristics of chronic OXLIPN are generally similar to those of cisplatin.[2]

Long-term outcome

Although there are few specifically designed studies to assess the long-term course of platinum-induced neurotoxicity, it is expected to improve or completely resolve within 1 year after the discontinuation of treatment. However, there have been cases in which CIPN remained persistent or at best, partially reversible, because of the "coasting" phenomenon resulting from the capacity of platinum compounds to accumulate in DRG for a long time.[25]

Options for treatment or prevention

Based on results from randomized controlled trials (RCTs), there are no effective symptomatic treatments, and only duloxetine at a dose of 60 mg per day has been shown in a well-designed RCT to be effective in alleviating oxaliplatin-associated neuropathic pain.[37] As to prophylaxis, there have been insufficient data thus far, to support the use of any candidate chemoprotective agents, such as acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxcarbazepine, or vitamin E to prevent or limit the neurotoxicity of platinum compounds.[85] As such, adherence to the non-pharmacological stop-and-go approach (ie, intermittent oxaliplatin dosing) may be warranted to prevent platinum compound-induced peripheral neuropathy, particularly OXAIPN.[86]

Vinca alkaloids (vincristine)
Pathogenesis

Vincristine detrimentally affects both fast- and slow-conducting peripheral nerve fibers by interfering with axonal transport at the level of the cell body and alterations in the cellular microtubuli structure.[87]

Incidence, severity, and risk factors

Vincristine-induced peripheral neuropathy is dose dependent, as up to 60% of patients may develop a clinically significant (grade 1–2) primarily sensory or sensorimotor neuropathy at vincristine cumulative doses between 30–50 mg.[88]

Clinical and electrophysiological characteristics

At the initial stage, the clinical manifestations of vincristine-induced peripheral neuropathy include bilateral and symmetrical painful paresthesia and hyperesthesia, distally attenuated. Muscle cramps and mild distal weakness are frequently seen. Neurological examination reveals proprioception and DTR abnormalities. Autonomic dysfunction is frequently seen in vincristine-treated patients, with evidence of orthostatic hypotension, constipation, and erectile impotence. Few cases of cranial nerve palsies have been reported while patients were being treated with chemotherapy using vincristine.[89] Nerve conduction abnormalities are in keeping with a length-dependent axonal sensory or sensorimotor peripheral neuropathy.[90]

Long-term outcome

Neurotoxic symptoms of vincristine are reversible after discontinuation of treatment.[88] However, off-therapy worsening of neurotoxic symptoms and signs might unexpectedly occur.[91]

Options for treatment or prevention

To date, there has been insufficient evidence to recommend the use of any neuroprotectant against vincristine-induced peripheral neuropathy in clinical practice.[2]

Binding of growth factor inhibitors (suramin)
Pathogenesis

The cardinal pathogenetic hallmark of suramin neurotoxicity is the axonal degeneration in DRG and the accumulation of glycolipid lysosomal inclusions, probably because of the competition between suramin and nerve growth factor (NGF) at the high-affinity NGF receptor.[92]

Incidence, severity, and risk factors

Suramin-induced peripheral neuropathy is dose dependent, as up to 60% of patients may develop a clinically significant (grade 1–2) primarily sensory or sensorimotor neuropathy at suramin plasma peak levels higher than 350 µg/mL.[93]

Clinical and electrophysiological characteristics

At the initial stage, the clinical manifestations of suramin-induced peripheral neuropathy include bilateral and symmetrical painful paresthesia and hyperesthesia, distally attenuated. Neurological examination reveals proprioception and DTR

abnormalities. Nerve conduction abnormalities are in keeping with a length-dependent axonal sensory or sensorimotor peripheral neuropathy.[93] Single case reports of subacute demyelinating and inflammatory polyneuropathy secondary to suramin therapy have also been occasionally published.[94]

Long-term outcome
Neurotoxic symptoms of suramin are usually reversible after discontinuation of treatment.[93]

Options for treatment or prevention
To date, none of the candidate neuroprotective agents have been proven effective to treat suramin-induced peripheral neuropathy.[2]

Proteasome inhibitors (bortezomib)
Pathogenesis
The pathogenetic hallmark of bortezomib-induced peripheral neuropathy (BIPN) consists of morphological alterations in the spinal cord, DRG, and peripheral nerves with specific functional alterations in Aδ and C peripheral nerve fibers.[95,96] In addition, proteasome inhibition, increased a-tubulin polymerization, mitochondrial and endoplasmic reticulum damage, and dysregulation of neurotrophins through inhibition of NFkB activation may also significantly contribute to BIPN genesis.[97–99]

Incidence, severity, and risk factors
The incidence of clinically significant, ie, grade 1–2 BIPN, can occur in up to 75% patients with multiple myeloma who have relapsed after or were refractory to frontline therapy, while treatment emergent grade 3–4 neurotoxicity may appear in 12% of bortezomib-treated patients.[100,101] BIPN is usually exacerbated in patients with pre-existing neuropathy and comorbidities associated with peripheral nerve damage.[98,102] However, the cumulative dose effect of bortezomib remains the main triggering factor of BIPN, although the severity of neurotoxicity is escalated until the completion of the first five cycles of bortezomib administration and thereafter remains stable.[103]

Bortezomib administered subcutaneously rather than intravenously has an improved safety profile and appears to be ideal for patients with pre-existing neuropathy or at a high risk of developing neurotoxicity. In a large randomized, Phase III, non-inferiority study enrolling 222 patients with relapsed multiple myeloma (148 on subcutaneous versus (vs) 74 patients on intravenous bortezomib), it was documented

that peripheral neuropathy of any grade (38% vs 53%; P=0.044), grade $\geq$2 (24% vs 41%; P=0.012), and grade $\geq$3 (6% vs 16%; P=0.026) was significantly less common with subcutaneous than with intravenous administration.[104]

Clinical and electrophysiological characteristics
The cardinal symptom of BIPN is neuropathic pain and paresthesias in distal extremities of limbs, in keeping with a painful neuropathy due to dysfunction in all three major fiber (Aβ, Aδ, and C) types of sensory nerves, as demonstrated in both clinical and animal models.[95,105] Neurological examination reveals distal sensory loss to all modalities and changes in proprioception, while DTRs are either suppressed or absent. Nerve conduction study usually reveals typical findings of CIPN consistent with a distal, sensory, axonal neuronopathy. Motor involvement is occasionally present. Reversal of BIPN usually occurs after a median interval of 3 months following the discontinuation of bortezomib treatment, but it may persist for up to 2 years or remain indefinitely in some cases.[98,103]

Options for treatment or prevention
Lafutidine, a H2-blocker with gastroprotective activity, may be able to prevent or improve BIPN, based on the results of a recently published small case series of eight patients.[106] However, the protective activity of lafutidine against BIPN needs to be further demonstrated in large RCTs. As such, there is no proven effective prophylactic treatment to prevent the development of BIPN, and medication towards this aspect is merely symptomatic.[98] Therefore, likewise to the case of EIPN, adherence to the dose-modification guidelines is advised.

Antiangiogenic/immunomodulatory agents (thalidomide/lenalidomide/ pomalidomide)
Pathogenesis
Neurotoxicity is considered to be generated by both thalidomide and lenalidomide as either the result of their antiangiogenic properties with a reduction of nerve blood supply or because of functional and metabolic changes in the DRG. Dysregulation of neurotrophin activity may also play a significant role in the pathogenesis of neurotoxicity.[107]

Incidence, severity, and risk factors
Quoting the results of an analysis of clinical trials assessing the efficacy and safety of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma, the overall incidence of PN can range up to 44%, with a rate of early

treatment discontinuation of about 15%.[108] Moreover, another meta-analysis of safety data after thalidomide monotherapy in multiple myeloma patients revealed that the rate of treatment-emergent neurotoxicity (grade 3–4) was 6%, whereas according to the same report, there is no well-established factor to increase the risk of thalidomide-induced neurotoxicity.[109]

Lenalidomide appears to be less neurotoxic and better tolerated than thalidomide at a dose of 30 mg/day in relapsed/refractory multiple myeloma patients, with only 3% of significant grade 3 neurotoxicity after the completion of chemotherapy.[110,111]

Orally administered pomalidomide was recently approved by the US Food and Drug Administration for use in multiple myeloma patients who have received at least two prior therapies, including lenalidomide and bortezomib, and whose disease did not respond to treatment and progressed within 60 days of the last treatment. Grade 1–2 peripheral neurotoxicity can occasionally (up to 9% of patients) be seen but no grade 3–4 peripheral neuropathy was reported in large RCTs testing the efficacy and safety of this agent.[112,113]

Clinical and electrophysiological characteristics

The clinical and neurophysiological characteristics of neurotoxicity secondary to thalidomide, lenalidomide, and pomalidomide are generally similar to those of bortezomib.[107]

Options for treatment or prevention

The symptomatic treatment of painful peripheral neuropathy secondary to these agents does not differ from that of BIPN.[107]

Other drugs less commonly associated with CIPN

Fluorouracil or 5-FU is a pyrimidine analog, and peripheral neuropathy associated with its administration is unusual. Anyhow, the literature contains a small series of two patients experiencing neurotoxicity while they were receiving chemotherapy with 5-FU.[114] Gemcitabine may occasionally evoke peripheral neuropathy with paresthesias and myalgias, whereas neurotoxicity rarely occurs while patients are treated with methotrexate, cytosine arabinoside (Ara-C), or topoisomerase inhibitors, such as irinotecan or topotecan.[25]

Rehabilitation and complementary/alternative therapies against CIPN

CIPN can significantly undermine the daily living activities and QOL of patients. Sensory ataxia is a common clinical phenomenon in the context of neuronopathies and it is associated with unsteady gait and impaired balance and coordination, as well as poor mobility. As a consequence, falls may occur in a significant proportion of cancer survivors. An increased risk of falls was associated with the degree of CIPN, particularly with evidence of sensory ataxia and severe muscle weakness.[115]

A variety of rehabilitative methods, such as balance and gait retraining as well as the use of gait aids and orthotics, have been tested with positive effects to prevent falls in patients with peripheral neuropathies and to assist them in adapting their activities and their environment.[116] Both aerobic and resistance exercise, mindfulness, occupational therapy, and environmental planning are also proposed among effective self-management strategies in reducing the impact of CIPN symptoms.[117]

Acupuncture is the most widely used complementary intervention in CIPN subjects. However, a recently published meta-analysis of clinical studies found that there is no evidence to support the use of acupuncture for treating CIPN, and further studies with robust methodology are needed before one can conclude with confidence about its true usefulness.[118] Supplementation with single medical herbs or herbal combinations might hold promise for its ability to exert neuroprotection or neuroregeneration in CIPN. However, it is similar to acupuncture in that the level of evidence is at present too low to establish a standard practice.[119]

CIPN in the era of pharmacogenetics

Although candidate gene approaches have been launched during the last decade to extract results from single nuclear polymorphisms (SNPs) in genes involved in the pharmacokinetic and pharmacodynamic properties of neurotoxic drugs, no reliable biomarker has thus far been identified to detect patients at high risk of developing CIPN. In the past, several SNPs have been reported to be associated with CIPN. For instance, SNPs in genes involved in the pharmacokinetic, transport, and pharmacodynamic properties of taxanes have been shown to be relevant for TIPN.[120,121] Likewise, increased susceptibility to peripheral neurotoxicity after exposure to oxaliplatin and other platinum compounds has been associated with pharmacogenetic variations in genes encoding for drug transporters, detoxification enzymes, genes involved in DNA repair mechanisms, and *integrin B3* Leu33Pro polymorphism.[122–124]

However, the results of most previous pharmacogenetic studies focused on oxaliplatin were limited, and with several methodological flaws, including small sample size,

retrospective study design, and the implementation of a post-hoc analysis of oncology-based databases of different, not pre-planned sizes. Other major limitations of these studies include the lack of a pre-study hypothesis based on the known role of the investigated targets in the peripheral nervous system and the inappropriate outcome measures for neurological impairment.[122,123,125]

A recently published collaborative international study attempted to overcome all of those limitations, thoroughly investigating a series of SNPs in genes coding for neurologically relevant targets in an adequately powered, prospective cohort of well-characterized patients, such as the voltage-gated sodium channels (SCNA). The results of this study provided evidence to support a causal relationship between *SCN4A* and *SCN10A* polymorphisms and increased incidence and/or severity of oxaliplatin-induced peripheral neuropathy.[78] Further SCNA SNPs, such as the *SCN2A R19K* polymorphism, have been previously investigated with negative results.[126]

Other polymorphisms in genes involved with immune function, reflexive coupling within Schwann cells, drug binding, neuron function, and steroid hormone biosynthesis have been associated with BIPN.[127,128] Table 4 summarizes genetic biomarkers that have been linked with liability to CIPN, by neurotoxic drug classification.

Table 4 Genetic biomarkers linked to CIPN by neurotoxic drug classification

Agent	Relevance to chemotherapeutic agent	SNPs in genes
Paclitaxel	Pharmacokinetic, transport, and pharmacodynamic properties of paclitaxel	*OATP1, CYP3A5, CYP3A4, CYP1B1, CYP2C8, ABCB1, ABCC1, ABCG1*
Cisplatin and oxaliplatin	Drug transporters	*ABCC1* and *ABCG1*
	Detoxification enzymes	*MPO, GSTA1, GSTM1/3, GSTP1* and *GSTT1*
	DNA repair mechanisms	*ERCC2, XPA, XRCC1* and *ERCC1*
Oxaliplatin-specific	Cell adhesion and in cell surface-mediated signaling	*Integrin B3 Leu33Pro*
	Voltage-gated sodium channels	*SCN4A*-rs2302237 and *SCN10A*-rs1263292
Bortezomib	Immune function	*CTLA4, CTSS*
	Reflexive coupling within Schwann cells	*GJE1*
	Drug binding	*PSMB1*
	Neuron function	*TCF4, DYNC1I1*
	Steroid hormone biosynthesis	*rs619824* in *CYP17A1*

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; SNPs, single-nucleotide polymorphisms.

Conclusion and future perspectives for research

CIPN is one of the most severe adverse effects of treatment, with a significant impact on the QOL of affected patients, mostly because the long-term effects of the persistence of symptoms/signs cannot be estimated. In the framework of promoting cancer therapies with fewer adverse effects, there are several open issues to be addressed in the future.

Important clinically relevant questions include: how to measure the incidence of neurotoxicity; how to grade the severity of the peripheral neuropathy; how to estimate its long-term course after the discontinuation of chemotherapy; and how to utilize this information clinically. An additional important issue is to determine reliable biomarkers to allow prompt identification of patients at high risk to develop CIPN. To address these gaps in knowledge, further large systematic prospective collection of data on CIPN is needed, comprising a comprehensive set of reliable clinical assessments and patient-reported outcomes, with the support of focused neurophysiological examinations, skin biopsies, and DNA analysis. Of note, skin biopsy may be a useful tool to examine the clinical applicability and correlation of intraepidermal nerve fiber density in CIPN with other clinical outcome measures, eventually leading to both possible preventive and therapeutic intervention.[129]

The results of such interventions would significantly contribute to improved comfort and QOL of cancer survivors. Proper and well-evaluated approaches would also produce a consistent advantage for both doctors and patients to allow the registration and analysis of reliable data on the incidence, prevalence, risk factors, and long-term impact of CIPN, eventually leading to both potential preventive and therapeutic multidimensional interventions.

Author contributions

Each author jointly contributed in the preparation of this review paper.

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