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REVIEW ARTICLE

Toxic peripheral neuropathy associated with commonly used chemotherapeutic agents

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Summary

Peripheral neuropathy ranks among the most common non-haematological adverse effects of a number of effective chemotherapeutic agents, including platinum compounds, taxanes and vinca alkaloids. Newer agents, such as bortezomib, thalidomide and lenalidomide, frequently exert similar neurotoxic effects on peripheral nerves.

Chemotherapy-induced peripheral neuropathy (CIPN) may result from a variety of mechanisms and may be related to causal factors, such as single dose per course, cumulative dose and risk factors including treatment schedule, prior or concomitant administration of other neurotoxic agents, age and pre-existing peripheral neuropathy of other causes.

The symptoms usually begin during chemotherapy and they may even worsen after cessation of treatment. In most of the cases, patients experience positive (pain, paresthesias) or negative (numbness) sensory symptoms in distal extremities in a stocking-and-glove distribution with less prominent motor and autonomic involvement.

To date, several neuroprotective agents including thiols, neurotrophic factors, anticonvulsants and antioxidants have been tested in preclinical models and clinical open label or randomized controlled trials for their ability to prevent or treat symptoms of CIPN. Although several of these agents hold promise as possible neuroprotective factors, clinical data are still controversial and none have as yet robustly been proven effective against CIPN.

This review critically looks at the pathogenesis, incidence, risk factors, diagnosis, characteristics and management of peripheral neuropathy associated with commonly used chemotherapeutic agents. We also highlight areas of future research to pursue.

Key words: chemotherapy, diagnosis, incidence, peripheral neuropathy, toxicities, treatment

Introduction

Peripheral neuropathy ranks among the most common non-haematological side effects of a number of effective chemotherapeutic agents, including platinum compounds, taxanes and vinca alkaloids. The use of newer agents, such as bortezomib, thalidomide and lenalidomide, is frequently associated with the development of similar neurotoxic effects to peripheral nerves [1,2].

CIPN usually results in dose modification, changes in the treatment plan and can potentially lead to severe disability obviously deteriorating the quality of life (QoL) of patients with cancer [3,4]. Commonly used chemotherapeutic agents in oncology/haematology practice, causing peripheral neuropathy are summarized in Table 1.

Table 1. Categories of commonly used chemotherapeutic agents causing peripheral neuropathy

Categories of chemotherapeutic agents	*Compounds*
Platinum agents	Cisplatin / Oxaliplatin
Taxanes	Paclitaxel / Docetaxel
Proteasome inhibitors	Bortezomib
Immunomodulatory agents	Thalidomide / Lenalidomide
Vinca alkaloids)	Vincristine
Polysulfonated naphthylureas	Suramin

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Overall, CIPN remains a very challenging area in clinical oncology. This review critically looks at the pathogenesis, incidence, risk factors, diagnosis, characteristics and management of peripheral neuropathy associated with commonly used chemotherapeutic agents. We also highlight areas of future research to pursue.

Pathogenesis of peripheral neuropathy

Neurotoxic chemotherapeutic agents can mostly induce a distal axonal sensory neuropathy (axonopathy) causing a "dying back" axonal degeneration, thus affecting all sensory neurons, with a preference to thick myelinated nerve fibers, conducting vibration sensation and proprioception. Primary sensory neurons contained in dorsal root ganglia (DRG) are particularly susceptible to significant cellular changes because of the structure of their capillaries, which have fenestrated walls that allow free passage of molecules between the circulation and the extracellular fluid. The blood-nerve barrier is relative more permeable in the dorsal root sensory ganglia than elsewhere [5,6], and this could be the reason for the selective sensory toxicity as compared to motor neurons in the anterior horn of the spinal cord.

Neurotoxic agents targeting the increased mitochondrial activity of cancer cells and those acting by disrupting microtubules of the mitotic spindle are able to interfere with axonal transport, thus affecting the ganglion soma cells and peripheral neuraxon at least at the functional level. In any case, individual categories of chemotherapeutic agents have specific pathogenetic mechanisms contributing to CIPN genesis. Table 2 describes CIPN by sites of involvement and by type of neuropathy.

Platinum compounds (Cisplatin / Oxaliplatin)

Damage of the sensory neurons in the DRG with concomitant induction of axonal changes secondary to cell body damage is the most widely accepted type of cisplatin neurotoxicity [7]. Histological examination of cisplatin-induced neuropathy reveals axonal loss with secondary atrophy of the dorsal root, whilst reactive gliosis of the dorsal column is evident in case of severe neuropathy [8].

Oxaliplatin induces two clinically distinct forms of neuropathy; namely, the acute, transient within hours or days syndrome, and the chronic form that is a pure sensory, axonal neuropathy closely resembling the cisplatin-induced peripheral neuropathy. The acute neurotoxicity of oxaliplatin has not been observed in patients receiving cisplatin [9].

Oxaliplatin interacts with ion channels located in the cellular membrane, particularly the voltage-gated sodium channels. There is evidence to suggest that the acute oxaliplatin-induced peripheral neuropathy (OXLIPN) may be linked to the rapid chelation of calcium by oxaliplatin -induced oxalate, whereas oxaliplatin is capable of altering the voltage-gated sodium channels through a pathway involving calcium ions [10-12].

On the other hand, the chronic, sensory OXLIPN is considered to be induced by the morphologic and functional changes in the DRG cells resulting from the local deposition and accumulation of oxaliplatin [13]. In addition to the decreased cellular metabolism and axoplasmatic transport in the DRG cells, the prolonged activation of voltage-gated sodium channels could induce cellular stress, thereby further affecting the sensory nerve cells. Oxaliplatin targets the increased mitochondrial activity of cancer cells and this has also been proposed as another potential mechanism of OXLIPN induction [9].

Table 2. Common sites of involvement and specific type of chemotherapy-induced peripheral neuropathy

Agent	*Sites of peripheral nerve damage*	*Type of neuropathy*
Cisplatin	Dorsal root ganglion	Sensory
Oxaliplatin	Dorsal root ganglion; ion channels	Chronic sensory; acute transient neuropathy
Paclitaxel	Dorsal root ganglion; microtubules; nerve terminals	Sensory; occasionally sensorimotor
Docetaxel	Dorsal root ganglion; microtubules; mitochondria; nerve terminals	Sensory; occasionally sensorimotor
Bortezomib	Microtubules; mitochondrial and endoplasmic reticulum; dysregulation of neurotrophins	Painful sensory
Thalidomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins	Sensory
Lenalidomide	Dorsal root ganglion; nerve blood supply; dysregulation of neurotrophins	Sensory
Vincristine	Dorsal root ganglion; microtubules; nerve terminals	Sensorimotor; autonomic; cranial nerves
Suramin	Inhibition of growth factors in dorsal root ganglion	Sensorimotor

Other genetic and molecular factors may contribute to the pathogenesis of OXLIPN. Research on this topic has been initiated and is still ongoing [14,15]. However, further study is warranted before definite conclusions can be drawn.

Taxanes (Paclitaxel / Docetaxel)

Interference with microtubule-based axonal transport and a "dying back" process starting from distal nerve endings followed by effects on Schwann cells, neuronal body or disturbed axonal transport changes in the affected neurons are the most widely accepted mechanisms of taxanes-induced peripheral neuropathy (TIPN) [16,17].

In addition, several cellular changes affecting signal transduction occur after the administration of taxanes, mainly consisting of injury of sensory neurons and their supporting cells in the peripheral nervous system, macrophage activation in both the DRG and peripheral nerve and microglial activation within the spinal cord [18].

Bortezomib

The pathogenesis of bortezomib-induced peripheral neuropathy (BIPN) and the affected anatomical structures are not clearly defined. Mitochondrial and endoplasmic reticulum damage seems to significantly contribute to the genesis of BIPN, since bortezomib is able to activate the mitochondrial-based apoptotic pathway [19]. Dysregulation of neurotrophins has also been proposed as another important mechanism of BIPN genesis, since the main action of bortezomib is the inhibition of NFkB activation, thereby blocking the transcription of nerve growth factor-mediated neuron survival [20]. Results from recently published experimental studies show that bortezomib exerts significant neuronal dysfunction characterized by interference with transcription, nuclear processing and transport, and cytoplasmic translation of mRNAs in DRG neurons associated with mitochondrial and endoplasmic reticulum damage [21,22].

Thalidomide and Lenalidomide

The mechanisms underlying thalidomide and lenalidomide-induced neurotoxicity are also vaguely defined. Reduction in nerve blood supply due to the antiangiogenic properties of these agents, direct toxic effects on sensory neurons in DRG and dysregulation of neurotrophins activity through reduction in TNF-alpha, and secondary inhibition of NFkB, are the most widely accepted mechanisms of neurotoxicity secondary to the administration of this class of immunomodulatory agents [23]. Neuropathological studies show that these agents may cause degeneration of neural cell bodies and alterations in posterior columns, suggesting a degeneration of central projections because of DRG damage [24].

Vincristine

Vinca alkaloids act by binding on intracellular tubulin, thereby interfering with axonal transport. Vincristine hardly crosses the blood-brain barrier [25]; however, painful peripheral nerve damage at the level of the cell body, secondary to its use, is frequently encountered as a result of alterations in the cellular micro-tubuli structure. This kind of damage leads to inflammation and oedema of the fast and slow conducting fibers [26]. In a recent study, it has been shown that inflammatory mediators, such as IL-6 and TNF-alpha, are involved in neuropathic pain caused by vincristine by the induction of macrophage infiltration [27].

Suramin

Suramin is being used either alone or in combination regimens against hormone-refractory or metastatic prostate cancer. Peripheral neuropathy is a common toxicity secondary to suramin administration. Suramin is considered to induce axonal degeneration in DRG, axon atrophy, and accumulation of glycolipid lysosomal inclusions as a result of its ability to antagonize the binding of a number of polypeptide growth factor ligands, such as platelet-derived growth factor, basic fibroblast growth factor, transforming growth factor-fj, and epidermal growth factor, with their receptors [28].

Diagnosis

Different approaches comprehended in several clinical grading scales have mostly been used thus far to assess CIPN. Table 3 outlines the historically available, clinically based scales used in oncologic studies. Recent studies have also employed the use of either the newer version of NCI-CTC-3 or the 11-item neurotoxicity subscale (FACT/GOG-Ntx) that was developed by the Gynecologic Oncology Group (GOG) [29,30].

Recently, the Total Neuropathy Score (TNS), a composite measure that includes symptoms, signs, ability aspects and electrophysiological measures, has demonstrated good validity and higher sensitivity to CIPN changes compared to the widely used clinical

Table 3. Grading scales for chemotherapy-induced peripheral neuropathy

Scale	*Grade 0*	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
NCIC-CTC					
Sensory neuropathy	None	Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Objective sensory loss or paresthesia, interfering with function, but not interfering with activities of daily living (ADL)	Sensory loss or paresthesia interfering with ADL	Permanent sensory loss that interferes with function
Motor neuropathy	None	Subjective weakness but no objective findings	Objective mild weakness, interfering with function but not interfering with ADL	Moderate objective abnormality, severe functional abnormality	Paralysis
Ajani					
Sensory neuropathy	None	Paresthesia and decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paresthesia, moderate objective, severe functional abnormality	Complete sensory loss, loss of function
Motor neuropathy	None	Mild transient muscle weakness	Persistent moderate weakness, but ambulatory	Unable to ambulate	Complete paralysis
WHO toxicity criteria	None	Paresthesias and/or decreased deep tendon reflexes	Severe paresthesias and/or mild weakness	Intolerable paresthesias and/or motor loss	Paralysis
ECOG PS	None	Decreased deep tendon reflexes Mild paresthesias Mild constipation	Absent deep tendon reflexes Severe constipation Mild weakness	Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction secondary to weakness, obstipation requiring surgery, paralysis confining patient to bed or wheelchair

scales, summarized in Table 3 [31,32]. TNSc, a shorter and more easily applied clinical version of the formal TNS, has been recently adopted to assess the severity of CIPN in routine clinical practice [33]. Other modifications of the TNS have been previously used by several groups, including ours, to assess the neurotoxicity secondary to paclitaxel, cisplatin, oxaliplatin, suramin and thalidomide treatment [34-36]. Table 4 describes the components making up both the TNS and TNSc.

To our opinion, the use of a grading scale, such as the TNS that employs both clinical and electrophysiological evaluation, may be the optimal method to objectively evaluate CIPN [37]. However, we acknowledge that TNSc may be the most suitable scale to be broadly applied in routine practice.

In any case, since the need for an easily, widely usable and effective grading system is clear, further systematic clinimetric studies are warranted to accurately detect and grade CIPN. Towards this view, a large international multicentre collaboration study between USA and European centres is running the CIPN outcome measures standardisation study (CI-Perinoms). The results of this study [38] are awaited so as to define the best available methods to accurately assess and monitor CIPN.

Incidence, severity and risk factors

Platinum compounds (Cisplatin / Oxaliplatin)

For cisplatin, the development of neuropathy is closely related to the total cumulative drug dose as the majority of patients receiving more than 400-500 mg/m^2 of cisplatin, are highly likely to experience grade 2-3 peripheral neurotoxicity [39,40]. However, evidence of peripheral nerve damage has been reported even after a cumulative dose of 225 mg/m^2 [41].

In a large series of patients (n=292) treated with cisplatin for ovarian cancer, it has been reported that the overall incidence of cisplatin-induced clinical sensory neurotoxicity was 50% at a dose of 500 mg/m^2, but only 4% of patients experienced grade 3-4 neurotoxicity [42]. The combination of cisplatin/paclitaxel may exhibit significant clinical beneficial effects over monotherapy in treating patients with various malignancies;

Table 4. Summary of Total Neuropathy Score (TNS). Items making up the TNS clinical version (TNSc) are highlighted in grey

	Total Neuropathy Score				
	0	*1*	*2*	*3*	*4*
Sensory symptoms	None	Limited to fingers or toes	Extend to ankle or wrist	Extend to knee or elbow	Above knees/elbows
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Disabled
Autonomic symptoms (n)	0	1	2	3	4 or 5
Pin sensation	Normal	Reduced in fingers or toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Vibration sensibility	Normal	Reduced in fingers or toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon Reflexes	Normal	Ankle reflex (AR) reduced	Ankle reflex absent	AR absent and others reduced	All reflexes absent
QST Vibration sensation	Normal to 125% ULN	126-150% ULN	151-200% ULN	201-300% ULN	>300% ULN
Sural a-SAP	Normal or reduced <5%	76-95% of LLN value	51-75% of LLN value	26-50% of LLN value	0-25% of LLN value
Peroneal a-CMAP	Normal or reduced <5%	76-95% of LLN value	51-75% of LLN value	26-50% of LLN value	0-25% of LLN value

Sural: short saphenous nerve, a-SAP: amplitude of sensory action potentials, a-CMAP: compound muscle action potential, LLN: lower limit of normal, ULN: upper limit of normal, QST: quantitative sensory testing

however, it also has additive effects in producing neuropathy at high rates [35,43].

As for oxaliplatin, data from large studies show that the acute OXLIPN affects the vast majority of patients treated with various oxaliplatin-based regimens at a dose ranging from 85-130 mg/m^2 with incidence rates from 65-98% [44,45]. Cold temperature and the time of oxaliplatin infusion are the main risk factors of acute OXLIPN [46].

On the other hand, the incidence of chronic OXLIPN is usually related to various risk factors, including treatment schedule, single dose per course, cumulative dose, time of infusion and pre-existing peripheral neuropathy [47]. Cumulative dose ranks among the most important risk factors of chronic OXLIPN genesis and this was documented in the de Gramont et al. trial [44], where the estimated incidence of grade 2-3 neuropathy, significantly increased after cumulative doses of 750-850 mg/m^2 and affected 50% of patients after a total dose of 1170 mg/m^2 [47].

In addition, available data from large studies concerning the incidence of OXLIPN in patients with metastatic colorectal cancer show that grade 3-4 overall neuropathy is evident in 6-20% of patients assigned to be treated on either the FOLFOX4 or FOLFOX6 regimen, while the overall rate of neurosensory symptoms can range from 60 to 95% [9,45]. Our experience [34] concurs with available data as in a study conducted by our group, the reported rate of patients manifesting OXLIPN after the administration of the formal FOLFOX4 regimen was 64%.

Taxanes (Paclitaxel / Docetaxel)

Dose, either single or cumulative, represents the most important triggering factor of taxanes-induced neurotoxicity. Current evidence shows that cumulative doses of paclitaxel and docetaxel that exceed the 1000 mg/m^2 and 371 mg/m^2 respectively, are strongly associated with occurrence of severe neurotoxicity [48]. In any case, paclitaxel is more neurotoxic than docetaxel. Grade 3-4 sensory neuropathy can occur in 33% of patients receiving paclitaxel at a high dose of 250 mg/m^2, in 19% of patients receiving paclitaxel at 210 mg/m^2 and in 7% of patients receiving paclitaxel at 175 mg/m^2, as opposed to 5% of patients receiving docetaxel at 100 mg/m^2 [48,49].

Other risk factors are prior or concomitant administration of platinum compounds and pre-existing peripheral neuropathy due to various medical conditions. The risk appears to be also related to treatment schedules for paclitaxel (weekly vs. every three weeks treatment schedule) and duration of infusion (1 to 3-hour infusion vs. 24-hour infusion) [16]. Opposite to previous

reports suggesting that age is a risk factor that increases the incidence of neurotoxicity in elderly people [50], our experience showed that elderly cancer patients do not appear with a greater risk of neurotoxicity and that advanced age is not associated with worst severity of neurotoxicity [51].

Bortezomib

The results of the SUMMIT and CREST phase II trials accurately provide data about the incidence of severity and risk factors of bortezomib-induced peripheral neuropathy (BIPN) [52,53]. Grade 1-2 BIPN can occur in up to 75% and 33% of patients with recurrent or newly diagnosed disease under bortezomib therapy, respectively, while grade 3-4 neurotoxicity may affect up to 30% of patients with recurrent disease and up to 18% of patients with newly diagnosed disease [20,52,53].

Several studies have consistently associated pre-existing neuropathy, comorbidities associated with peripheral nerve damage and cumulative dose with increased incidence of BIPN. However, BIPN typically occurs within the first 5 cycles of bortezomib administration and is rare thereafter, thereby pointing towards a dose threshold rather than a classic cumulative dose effect of bortezomib. The disease itself has also been reported as another contributing factor to BIPN genesis [20].

Thalidomide

The overall incidence of PN can range up to 83%, with a rate of early treatment discontinuation of about 15% [54,55]. Pooled safety analysis on thalidomide monotherapy in multiple myeloma patients revealed an incidence rate for severe neurotoxicity (grade 3-4) of about 6% [56].

There is evidence to suggest a causal relationship between neurotoxicity, age, duration of exposure, dose-intensity and cumulative dose of thalidomide [57]. However, the issue of risk factors for thalidomide-induced neurotoxicity remains controversial, as some authors have found that the relative risk of developing neurotoxicity was not influenced by these factors [56].

Lenalidomide

Lenalidomide, a thalidomide-analogue, is less neurotoxic as the overall incidence of neurotoxicity was 10%, with only 3% of grade 3 after its administration at a dose of 30 mg/day in relapsed/refractory multiple myeloma patients [58,59]. Factors such as age, duration of exposure, dose intensity and cumulative doses, have been reported to influence the incidence of neurological toxicity [23].

Vincristine

Up to 60% of patients treated with vincristine may develop a primarily sensory neuropathy, which is considered to be dose-dependent, as a cumulative dose between 30-50 mg represents the main risk factor of vincristine-induced peripheral neuropathy [60].

Suramin

Likewise to vincristine, suramin-induced neuropathy is dose-dependent. About 50% of patients with suramin plasma peak levels higher than 350 μg/ml will develop a grade 1-2 sensorimotor neuropathy and, therefore, monitoring of plasma levels is strongly advised so as to avoid severe grade 3-4 peripheral nerve damage with flaccid quadriparesis [36].

Clinical and electrophysiological characteristics

Platinum compounds (Cisplatin / Oxaliplatin)

Cisplatin-induced peripheral neuropathy (CisIPN) is clinically manifested with sensory symptoms in a stocking-and-glove distribution, decreased vibration and proprioception and suppression or loss of deep tendon reflexes (DTRs). Sensory nerve conduction studies show a decrease or abolishment of sensory action potentials with preserved sensory conduction velocities, in keeping with an axonal sensory peripheral neuropathy [4,35].

As a clinical hallmark of hyperexcitability syndrome, signs and symptoms of acute OXLIPN may begin during the infusion or within 1-2 days of oxaliplatin administration and include cold-induced and perioral paresthesias, shortness of breath or difficulty in swallowing, cramps, jaw stiffness, visible fasciculations, voice changes, ptosis, and visual field changes [4]. From the electrophysiological point of view, findings of excessive nerve excitability are evident in nerve conduction and needle EMG study, consisting of repetitive compound action potentials, high-frequency discharges of motor unit multiplets and bursts of muscle fibre action potentials [9].

Chronic OXLIPN are clinically characterized by distal sensory loss with positive and negative sensory symptoms, suppression of DTRs and changes in proprioception. From the electrophysiological point of

view, nerve conduction study is consistent with a distal, sensory, axonal neuronopathy without motor involvement [9].

Symptoms of chronic CisIPN and OXLIPN usually completely resolve after 6-8 months after the discontinuation of treatment [1]. However, further progression of neurotoxicity was reported 6 months after the discontinuation of chemotherapy. This event should be attributed to the "coasting" phenomenon, that is characteristic of platinum compounds-based therapy and results from their capacity to accumulate in DRG for a long time [61].

Taxanes (Paclitaxel / Docetaxel)

Predominant clinical symptoms secondary to taxanes-based therapy include paresthesia, numbness and/or pain in a stocking-and-glove distribution, initially affecting the distal lower extremities. Decreased vibration perception and sense of position, loss of pain and temperature sensation and suppression or loss of DTRs are frequently found in patients receiving taxanes therapy [48].

Electrophysiological abnormalities, mainly involving the decrease or abolishment of sensory responses in keeping with an axonal sensory neuropathy, are characteristic of taxanes-induced peripheral neuropathy (TIPN). Motor involvement with reduction of compound muscle action potential responses and myopathy with proximal weakness is less frequently seen [16].

Symptoms usually improve or resolve soon after discontinuation of treatment, whereas severe symptoms may persist for a long time [16]. Our experience shows that TIPN is partially reversible 3 months after discontinuation of chemotherapy, while there is no evidence of further worsening of neurotoxicity after cessation of treatment [62].

Bortezomib

Symptoms and signs of BIPN are clinically characterized by evidence of neuropathic pain, distal sensory loss to all modalities in the lower more than in the upper limbs, suppression or loss of DTRs and changes in proprioception. These clinical findings are in keeping with a painful neuropathy due to dysfunction in all 3 major fiber (Aβ, Aδ, and C) types of sensory nerves [63].

From the electrophysiological point of view, nerve conduction study predominantly reveals low amplitude of sensory action potentials, in keeping with a distal, sensory, axonal neuropathy. Motor involvement is less frequently disclosed. Symptoms of BIPN usually improve or completely resolve after a median interval of 3 months following discontinuation of bortezomib treatment [20].

Thalidomide and Lenalidomide

The clinical and electrophysiological characteristics of thalidomide and lenalidomide-induced peripheral neuropathy resemble those of BIPN. In brief, symptoms are rather sensory and affect small and large diameter fibers with less common motor impairment or autonomic involvement. Trembling in maintaining posture is commonly seen in the affected patients. From the electrophysiological perspective, both drugs mostly induce a length-dependent axonal sensory neuropathy [23,64].

Vincristine

At the initial stage, the clinical manifestations include bilateral and symmetrical sensory disorders, including stinging distal paresthesia and hyperesthesia, distally attenuated. At the advanced stage, affectation of deep vibratory sensitivity and proprioception is commonly seen. Autonomic dysfunction with manifestation of orthostatic hypotension, constipation and erectile impotence is evident in up to 40% of the affected patients. Nerve conduction study usually reveals decreased sensory action potentials with vincristine therapy, in keeping with a length-dependent axonal sensory peripheral neuropathy. Clinical symptoms are reversible after discontinuation of treatment [60].

Suramin

In most patients, neurotoxicity is clinically manifested with distal paresthesias and/or weakness in distal muscles of the lower limbs. Examination reveals reduction of pin sensibility, elevation of vibratory threshold and reduced or absent DRTs. Nerve conduction study shows reduction in sensory and motor amplitudes with relative preservation of latencies and conduction velocities, consistent with a length-dependent, axonal, sensorimotor polyneuropathy. Few cases with subacute demyelinating and inflammatory polyneuropathy secondary to suramin therapy have also been reported [36].

Options for neuroprotection

The ideal candidate for neuroprotection against CIPN should be effective, safe, well-tolerated, but

mostly it should not interfere with the cytotoxic activity of chemotherapy. Table 5 outlines the pharmaceutical interventions for the symptomatic treatment and/or prevention of CIPN.

Platinum compounds (Cisplatin / Oxaliplatin)

A variety of prophylactic compounds, including thiols (amifostine), vitamin E, and glutathione, have been tested thus far and appear in preliminary studies to prevent or treat the CisIPN [65]. However, a recent Cochrane review concluded that there was insufficient evidence to recommend the use of any of these therapies for the prevention of the platinum compounds-induced peripheral neuropathy [66].

Amifostine (WR-2721) is an organic thiophosphate used as cytoprotective adjuvant in cancer chemotherapy mainly because of its ability of scavenging free radicals. Amifostine was found ineffective against the neurotoxic combination comprised of cisplatin/paclitaxel or cisplatin/cyclophosphamide [65]. However, results from a pilot small-sized study in patients treated with an oxaliplatin (130 mg/m^2)-based regimen, demonstrated that amifostine 500 mg given as s.c. injection 20 min before oxaliplatin administration was able to prevent OXLIPN [67].

The results from clinical trials on the efficacy of glutathione (GSH) for prophylaxis against both CisIPN and OXLIPN are very promising. A randomized, double-blind, placebo-controlled trial (RCT) provided evidence that GSH is effective in preventing CisIPN, as the incidence of neurotoxicity was significantly decreased in patients receiving GSH vs. placebo [68]. Another RCT from the same group demonstrated the same beneficial effect of GSH in preventing OXLIPN [69].

Small pilot RCTs favor the use of oral glutamine and a-lipoic acid for prophylaxis against OXLIPN [9,70]. Oxalate chelators, such as calcium-magnesium (Ca/Mg) infusions might be able to delay cumulative neuropathy, especially in 85 mg/m^2 oxaliplatin dosage [71]. However, Ca/Mg i.v. supplementation strategy may not be advisable in combination with the FOLFOX regimen since a large phase III trial was early terminated because patients receiving FOLFOX plus Ca/Mg had significantly decreased response rates compared to patients treated with FOLFOX alone [72].

In a large RCT (Xenox study), 649 chemotherapy-naïve patients with metastatic colorectal cancer were randomly treated with FOLFOX4 plus xaliproden 1 mg p.o. qd or FOLFOX4 plus placebo. The results showed a 39% reduction in the risk of occurrence of grade 3 neurotoxicity in the xaliproden arm without any affectation in overall survival rates, thereby supporting the neuroprotective effects of xaliproden against OXLIPN [73].

Among modern antiepileptic drugs, oxcarbazepine (OXC) may be another suitable preventive measure against OXLIPN. Our experience favors its use since in a RCT conducted by our group the incidence of OXLIPN was strikingly decreased in patients receiving OXC (31.2 vs. 75%), while OXC was well tolerated [74].

Non-pharmacological treatment strategies against OXLIPN are primarily based on the "Stop-and-Go" concept, which uses the predictability and reversibility of neurological symptoms, with the aim at delivering higher cumulative oxaliplatin doses as long as the therapy is still effective. Successful use of the "Stop-and-Go" concept has been previously reported in several studies [9,75].

Taxanes (Paclitaxel / Docetaxel)

For symptomatic management of TIPN, amitriptyline, glutamine, low-dose oral prednisone and gabapentin have been used with some measure of success

Table 5. Medications for prevention and symptomatic relief of chemotherapy-induced peripheral neuropathy (CIPN)

Interventions against CIPN	
Opioids	oxycodone, hydrocodone, morphine, fentanyl
Tricyclic antidepressants	amitriptyline, nortriptyline, desipramine
Anticonvulsants	gapabentin, carbamazepine, oxcarbazepine, pregabalin
SNRIs	duloxetine, venlafaxine
NSAIDs	celecoxib, rofecoxib, ibuprofen, acetaminophen
Vitamins	vitamin E, vitamin B6, vitamin C
Nutritional supplements	a-lipoic acid, glutamine, L-carnitine
Thiols	amifostine
Antioxidants	glutathione
Oxalate chelators	calcium-magnesium (Ca/Mg) infusions
Non-peptidic 5-HT1A receptor agonist	xaliproden

SNRIs: serotonin-norepinephrine reuptake inhibitors, NSAIDs: non-steroidal anti-inflammatory drugs

Table 6. Dose modification guidelines for bortezomib-induced peripheral neuropathy (BIPN)

Severity of BIPN	*Action*
Grade 1 (paresthesias or areflexia without pain or loss of function)	Continuation as scheduled
Grade 1 with pain or grade 2 (interferes with function but not with daily living activities)	Dose reduction to 1.0 mg/m^2
Grade 2 with pain or grade 3 (interferes with daily living activities)	Withhold bortezomib treatment until BIPN resolves and then reinitiating at a dose of 0.7 mg/m^2 once weekly
Grade 4 (sensorimotor neuropathy significantly interfering with daily living activities)	Therapy discontinuation

for reducing pain, myalgia and arthralgia. Overall, data about symptomatic treatment of TIPN are limited and therefore further prospective studies are warranted [16].

Concerning prophylactic treatment, several neuroprotective agents including thiols, neurotrophic factors and antioxidants hold promise as possible neuroprotective factors, clinical data are still controversial [65].

Briefly, the clinical efficacy of amifostine (WR-2721) has been conflictingly addressed in several RCTs [65,76]. In a large double-blind randomized controlled trial of 117 patients with various types of solid tumors, recombinant human leukemia inhibitory factor (AM424) at a dose of 4 μg/kg failed to demonstrate efficacy in preventing neurotoxicity caused by carboplatin/paclitaxel [77].

Glutamine, a neutral gluconeogenic nonessential amino acid, demonstrated that is capable in preventing high dose paclitaxel-induced peripheral neuropathy in a phase II clinical trial. In this setting, patients who received glutamine developed significantly less neurosensory symptoms than controls [78].

Acetyl-l-carnitine (ALC) showed that is capable of significantly reducing paclitaxel-induced peripheral neuropathy in a large phase II clinical trial. In this study, at least one WHO grade improvement in the severity of peripheral neuropathy was disclosed in 19 of 26 (73%) patients after administration of 1 g/day i.v. infusion of ALC [79].

Our experience shows that vitamin E at a daily dose of 600 mg bid exhibits neuroprotective effects in patients either treated with paclitaxel-based regimens alone [80] or with paclitaxel/cisplatin regimens [81]. Our results demonstrated that the relative risk of developing peripheral neuropathy was significantly higher in controls than in vitamin E group patients [80,81].

Bortezomib

To date, several pharmacological agents, including various opioids, tricyclic antidepressants, anticonvulsants, serotonin-norepinephrine reuptake inhibitors, non-steroidal anti-inflammatory agents, vitamins and nutritional supplements, have been tested to symptomatically treat the painful, sensory BIPN [20].

Among non-pharmacological approaches, the dose and treatment schedule modification is the cornerstone of treating BIPN [20]. Therefore, strict adherence to these dose modification guidelines, as outlined in Table 6, is recommended to allow the continuation and intensification of treatment [82].

Thalidomide and Lenalidomide

The symptomatic treatment of painful peripheral neuropathy secondary to these agents does not differ from that of BIPN (23].

Vincristine

The administration of glutamic acid has decreased vincristine-induced neurotoxicity without any attendant adverse effect in a RCT, in which 42 patients were randomly assigned to receive vincristine 1.0 mg/m^2 weekly for 6 doses and 42 patients were assigned to receive glutamic acid 500 mg orally 3 times daily plus vincristine [83]. In any case, there is insufficient evidence to recommend the use of glutamic acid in clinical practice more broadly against vincristine-induced neurotoxicity.

Future research perspectives

Peripheral neuropathy is the major non-haematological adverse effect of commonly used chemotherapeutic agents, adversely affecting the QoL of patients with cancer. CIPN is still not reliably assessed, as a widely accepted grading scale of neurotoxicity is lacking. Therefore, validation of a grading instrument demonstrating high sensitivity and reduced interobserver and intraobserver variability is definitely warranted and, to our knowledge, is ongoing.

Susceptibility between individuals receiving the same regimen differs and therefore well-designed phar-

macogenetic studies should be performed to provide evidence to identify patients at high risk for developing CIPN. Improved understanding of the pathophysiological mechanism of CIPN in the preclinical setting would facilitate the identification of effective and safe neuroprotective agents.

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