



Toxic and drug-induced peripheral neuropathies: updates on causes, mechanisms and management

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Purpose of review

This review discusses publications highlighting current research on toxic, chemotherapy-induced peripheral neuropathies (CIPNs), and drug-induced peripheral neuropathies (DIPNs).

Recent findings

The emphasis in clinical studies is on the early detection and grading of peripheral neuropathies, whereas recent studies in animal models have given insights into molecular mechanisms, with the discovery of novel neuronal, axonal, and Schwann cell targets. Some substances trigger inflammatory changes in the peripheral nerves. Pharmacogenetic techniques are underway to identify genes that may help to predict individuals at higher risk of developing DIPNs. Several papers have been published on chemoprotectants; however, to date, this approach has not been shown effective in clinical trials.

Summary

Both length and nonlength-dependent neuropathies are encountered, including small-fiber involvement. The introduction of new diagnostic techniques, such as excitability studies, skin laser Doppler flowmetry, and pharmacogenetics, holds promise for early detection and to elucidate underlying mechanisms. New approaches to improve functions and quality of life in CIPN patients are discussed. Apart from developing less neurotoxic anticancer therapies, there is still hope to identify chemoprotective agents (erythropoietin and substances involved in the endocannabinoid system are promising) able to prevent or correct painful CIPNs.

Keywords

chemotherapy, drug-induced peripheral neuropathies, toxic neuropathies

INTRODUCTION

Drug-induced peripheral neuropathies (DIPNs) are uncommon, but with the number of new drugs increasing, unusual side effects may not become apparent until after widespread usage. Chemotherapy-induced peripheral neuropathies (CIPNs) are major and dose-limiting side effects of many anticancer treatments, and their characteristics are often related to both the choice of anticancer drugs and the cumulative doses [1]. Toxic, DIPNs, and CIPNs may appear as length or nonlength-dependent neuropathies, with or without small-fiber involvement, and discussions about grading the severity and early detection of neuropathies are still open. Recent publications have revealed new insights into the description and understanding of the pathophysiology and individual susceptibility factors, paving the way for the development of new prophylactic and therapeutic measures.

CLINICAL MANIFESTATIONS AND ASSESSMENT

As the most frequently encountered neuropathic mechanisms target neurons or their axons (see Table 1 and Fig. 1), toxic, DIPNs, and CIPNs are mainly most often characterized by the development of a subacute or chronic, length-dependent, distal, symmetrical polyneuropathy with a predominant sensory involvement, with or without associated dysautonomia. This corresponds to the

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KEY POINTS

- For toxic neuropathies, no real therapeutic breakthroughs but some interesting new insights in pathophysiology are available.
- Adequate animal models and pharmacogenetic data are important for future advances in toxic neuropathies.
- Functional assessment for early detection is necessary when using potentially neurotoxic therapy.

so-called 'dying back axonal degeneration' affecting distal segments of the peripheral nerves. Interestingly, most chemotherapeutic drugs poorly penetrate through the blood–brain barrier, but readily pass through the blood–nerve barrier, probably explaining the clinical observation of toxic damage preferentially affecting the sensory neurons of the dorsal root ganglia (DRG). These induced sensory neuronopathies are now more easily recognized by newly proposed diagnostic strategies [48]. Chronic alcoholic neuropathy, vitamin-related neuropathies, and CIPNs (platin compounds, vinka alkaloids, taxanes, bortezomib, and thalidomide) are classical examples of substance-induced neuropathies, and have been recently extensively reviewed [33²²,49,50²²,51,52²²]. CIPN is one of the main reasons for patients to prematurely terminate antineoplastic treatment. This is now well recognized [53–55], but as the number of long-term cancer survivors increases, new methods of rehabilitation are discussed to improve the patients' functions and quality of life [50²²,56]. Other recently recognized DIPNs include those from long-term triazole antifungal therapies [57] – ixabepilone for metastatic breast cancer [58], bendamustine for lymphomas [59], and stavudine in children receiving antiretroviral treatment [60]. Less toxic and potentially superior alternatives are now reported for the management of nonsmall cell lung cancer [61] and for the front-line treatment of advanced gastric or gastroesophageal adenocarcinoma [62].

More rarely, a nonlength-dependent or multifocal neuropathy may be encountered, either resembling chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) or Lewis Sumner syndrome in DIPN associated with underlying inflammatory or dysimmune mechanisms [11,63]. A nonlength-dependent small-fiber neuropathy may also be observed [64], such as in nitrofurantoin toxicity [65].

Assessment and grading of peripheral neuropathies remain subject to discussions [66], as most of the frequently used scales and grading systems

rely on subjective evaluation either by the patient or the examiner. This is well illustrated in CIPN, where use of one of the classical grading systems, the National Cancer Institute Common Toxicity Criteria (NCI-CTC), tends to overestimate motor neuropathies compared to a composite scale designed to grade impairment in neuropathy patients [Total Neuropathy Score (TNS)] [67], despite both grading systems having good inter and intra-observer reproducibility [52²²]. The newly developed Chemotherapy-Induced Neurotoxicity Questionnaire (CINQ) and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity (FACT/GOG-Ntx) questionnaire acknowledge a considerable negative impact of neuropathy symptoms on daily activities in cancer patients treated with chemotherapy [68]. Quantification or early detection is a persistent matter of debate, but new noninvasive tools for diagnosis are emerging, such as nerve excitability studies utilizing threshold tracking techniques [69], or laser Doppler flowmetry quantifying the small-fiber impairment by the reduced axon-reflex flare areas [70].

WHAT HAVE WE LEARNED FROM ANIMAL MODELS?

Several animal models have been generated over the past years with the aim of understanding the pathophysiology of CIPN and DIPN, and importantly to design specific chemoprotective agents and analgesic drugs for neuropathic pain [71]. A mouse model study has confirmed that the presence of neuropathy before treatment with an antitumoral agent such as bortezomib results in a more marked involvement of peripheral nerves [72], which may be one of the factors rendering some individuals more vulnerable to neurotoxic medications.

Evidence from animal models of CIPN indicates that neuropathy may occur via a common mechanism having a toxic effect on the mitochondria in primary afferent sensory neurons. This has been shown in a model of bortezomib-induced painful peripheral neuropathy in the rat, where mitotoxicity is the core pathological finding (see 'Update on the molecular mechanisms' section below); interestingly, prophylactic treatment with acetyl-L-carnitine completely blocked bortezomib's effects on mitochondria and the development of pain [22]. Mitochondrial dysfunction resulting in the production of neuropathic pain is also suggested from another study on paclitaxel and oxaliplatin-induced neuropathy in rats [14]. A cisplatin-induced hyperalgesia model in mice was used to study the anti-hyperalgesic effects of anandamide and URB597, an

Table 1. Neurotoxic drugs, putative mechanisms, and potential management

Neurotoxicity mechanisms (numbers refer to Fig. 1)		Drugs	Reported potential molecules for management
DRG cytotoxic inflammatory changes (1)		Thalidomide [2]	
		Bortezomib [3,4]	
		Cisplatin [5]	N-acetylcysteine [6], melatonin [7], amifostine, glutathione, vitamin E, pregabalin, and gabapentin [8]
		NRTIs [9] Tacrolimus [11]	Etanercept [10]
Mitotoxicity and oxidative stress (2)		Paclitaxel [12–14]	Glutamine [15], vitamin E [16,17], AV411 (ibudilast) [18], EPO, [19], olesoxime and acetyl-L-carnitine [20], minocycline [21 [■]], melatonin [7]
		Bortezomib [22]	Acetyl-L-carnitine [22]
		Platinum compounds [23 [■]]	Silibinin [23 [■]], olesoxime, and acetyl-L-carnitine [24]
		NRTIs [25] Anti-VEGF compounds [26,27 [■]]	
		Vincaalcaloids	NSAIDs [28], propentofylline [29]
Voltage-gated ion channel dysfunction (4)	Sodium channels	Paclitaxel [12] Epothilones [30]	
		Oxaliplatin [31]	Lidocaine [32], pregabalin and gabapentin [8], glutathione, glutamine and oxcarbazepine [33 [■]], calcium or magnesium salts [34]
	Potassium channels	Cisplatin [35] Oxaliplatin [37,38]	Retigabine [36]
	Calcium channels	Cisplatin [35]	Nimodipine and calmodulin inhibitors [39], calcium or magnesium salts [8]
Dysfunction of TRP family of ion channels (5)	Ankyrin 1 (TRPA1)	Paclitaxel [40]	HC0300031 [41] ^a
	Vanilloid 1 (TRPV1)	Oxaliplatin [42] Cisplatin [43]	Capsazepine and SB366791 [41] ^a
	Vanilloid 4 (TRPV4)	Paclitaxel [6]	RN1734 [41] ^a
DRG neuronal apoptosis (6)		Cisplatin [44]	
Demyelination (7)	Decreased myelin sheath methylation	Bortezomib [4] Nitrous oxide [45]	Vitamin B12 [45]
	Immune-based demyelination	Etanercept, infliximab, adalimumab [46] Oxaliplatin [47]	IVIg [47] IVIg [47]
		Bevacizumab [27 [■]]	
Reduction of VEGF neuroprotective effect (8)	?	Sorafenib [27 [■]] Sunitinib [27 [■]]	

N.B.: most of the substances listed here have been evaluated in preclinical settings. DRG, dorsal root ganglion; EPO, erythropoietin; IVIG, intravenous immunoglobulin; NRTIs, nucleoside analog reverse-transcriptase inhibitors; TRP, transient receptor potential; VEGF, vascular endothelial growth factor. ^aHC0300031, RN1734, capsazepine, and SB366791 are antagonists of TRPA1, TRPV1, and TRPV4, respectively.

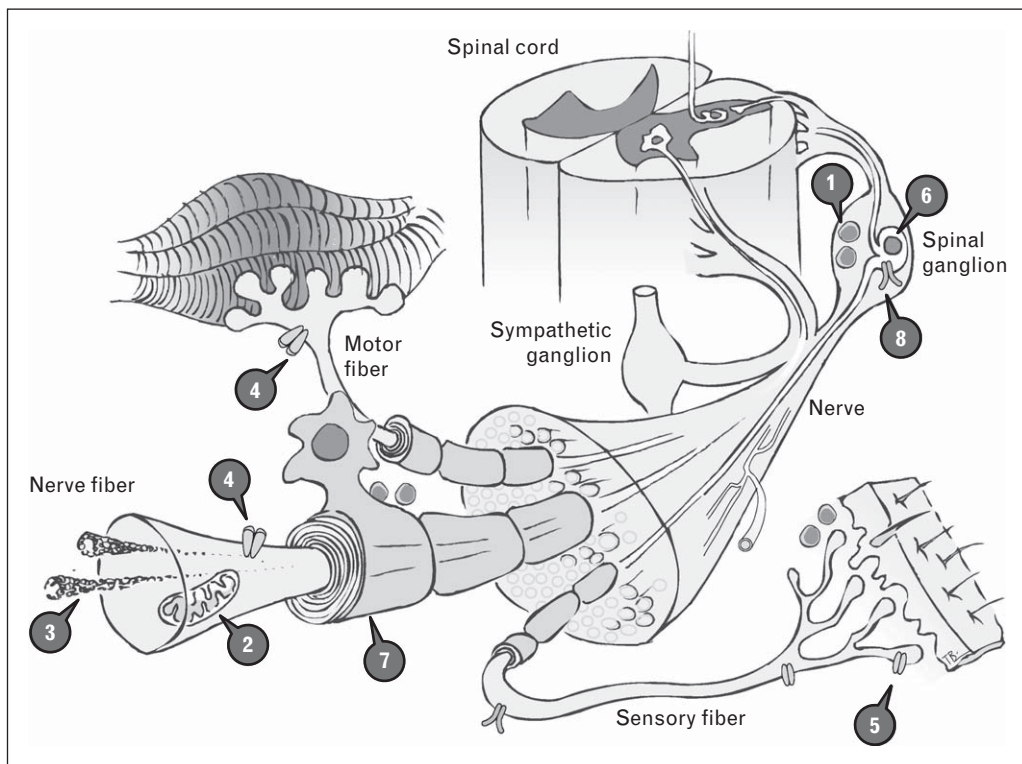


FIGURE 1. Neuronal targets of drug-induced peripheral neuropathy (numbers refer to Table 1).

inhibitor of anandamide hydrolysis implicated in the endocannabinoid system. Although the mechanisms by which anandamide reduces neurotoxicity and prevents development of neuropathy remain to be resolved, this study underscores the potential utility of stimulating the endocannabinoid system for the management of neuropathic pain produced by chemotherapy [73].

Another recent finding is the identification of a molecular self-destruction cascade in axonal degeneration. A model of toxic neuropathy in *Drosophila* has been designed and shares some molecular execution mechanisms with vertebrates [74]. This new model could be used to identify evolutionarily conserved genes involved in axonal degeneration, which could represent potential targets for therapy.

A direct neurotrophic role for vascular endothelial growth factor (VEGF) has recently been demonstrated. Systemic VEGF inhibition (using bevacizumab, a neutralizing VEGF antibody, and sorafenib and sunitinib, VEGF receptor inhibitors), in combination with chemotherapy, improves the outcome of patients with metastatic cancer. Peripheral sensory neuropathies occurring in patients receiving both drugs were traditionally attributed to the chemotherapy drug(s) alone. Using transgenic mice with altered neuronal VEGF receptor expression, systemic inhibition of VEGF receptors was

shown to interfere with the endogenous neuroprotective action of VEGF on sensory neurons, thus providing unprecedented evidence that VEGF receptor inhibitors may themselves trigger a painful neuropathy and aggravate paclitaxel-induced neuropathies [27^{*}].

The role of neurographic in-vivo molecular imaging has also been addressed. Imaging changes were observed in a model of oxaliplatin-induced neuropathy, implying impaired retrograde neural transport, thought to be important in the pathophysiology of this neuropathy [75].

UPDATE ON THE MOLECULAR MECHANISMS

Molecular causes of DIPN have been addressed in several studies. Specific neuronal and non-neuronal dysfunctions leading to disruption of common pathways have been postulated and are summarized in Table 1 and Fig. 1; these include DRG cytotoxic inflammatory changes, mitotoxicity and enhanced oxidative stress, microtubular function disruption, voltage-gated ion channel (VGIC) dysfunction, functional impairment of ion channels of the transient receptor potential (TRP) family, induction of neuronal apoptosis in DRG, demyelination, and reduction of VEGF neuroprotective action.

Inflammation

Endoneurial macrophage infiltration and subsequent secretion of pro-inflammatory cytokines [tumor necrosis factor alpha (TNF α), interleukin 1 beta (IL-1 β), IL-6, and IL-8, and chemokines C-C motif ligand 2 (CCL2), CXC family], growth factors, and inflammatory mediators such as bradykinin, prostaglandins, serotonin, and nitric oxide have been correlated with acute and chronic neuropathic pain in human CIPN or in patients receiving highly active antiretroviral therapy (HAART) agents [9,21[■]]. In animal models, overexpression of matrix metalloproteinases mediating myelin turnover and phenotypic remodeling of glial and neuronal cells, as well as secondary activation of inflammatory cascades, have been recently reviewed [21[■]].

In some DIPNs, medication-induced immune perturbation presumably triggers a dysimmune attack directed at unidentified peripheral nerve myelin epitopes; true peripheral nerve toxicity (i.e. dependent on accumulative dose or serum level) plays no identified role. TNF α blocking molecules and other immunomodulatory, immunosuppressive, or antineoplastic agents, widely used to treat several forms of inflammatory diseases, have been associated with dysimmune conditions, including various forms of demyelinating neuropathies [11,46,63,76].

Mitochondrial toxicity and oxidative stress

The recently discovered mechanisms of mitotoxicity include a link between abnormal opening of the mitochondrial permeability transition pore (mPTP), a mitochondrial calcium leak, and a secondary organelle swelling leading to neuronal hyperexcitability [21[■]]; disruption of the mitochondrial electron transport chain (mETC) in inflammatory-induced neuropathic pain, with the demonstration that inhibition of the mETC complexes can counteract dideoxycytidine and TNF α -induced neuropathic pain [9]; and enhanced oxidative stress, with impairment in the mediated respiration complexes following the administration of paclitaxel, docetaxel vincristine, oxaliplatin, and bortezomib, causing secondary production of pro-inflammatory cytokines [13,14,22,24]. Oxidative stress may be particularly important, based on the significant correlation between the glutathione-S-transferase P1 (GSTP1) genotype and the development of more severe or earlier-onset CIPN following docetaxel administration [77].

Ion channels

Dysfunction of the peripheral nerve VGICs has been advocated as a potential cause of DIPN.

Sodium

Oxaliplatin-induced neuropathy has been suggested from human ex-vivo and animal models to be hyperexcitability secondary to an altered state of the voltage-gated sodium channel, in particular the channel Na $_v$ 1.6 [31]. These results have led to the experimental use of sodium channel blockers in animal disease models [78,79[■]].

Potassium

Other authors, using a cellular model of oxaliplatin-induced neuropathy, have noted that dysfunction of the voltage-gated potassium channel may also be associated with nerve hyperexcitability [38,80].

Calcium

Alterations in voltage-gated calcium channel currents in the rat DRG interfering with calcium homeostasis have been associated with CIPN, especially with platinum compounds and taxanes [40,81].

Transient receptor potential ion channels

TRP channels are a group of ion channels widely expressed in neuronal (e.g. sensory DRG and trigeminal ganglia neurons) and in non-neuronal cells, located mainly on the plasma membrane. They are rather nonselectively permeable to sodium, calcium, and magnesium, and mainly involved in the transduction of a variety of painful or thermal stimuli [82[■],83]. Several members of this family of receptors have been linked to DIPN, mainly secondary to oxaliplatin and paclitaxel, through a mechanism of oxidative stress generation; these include TRP vanilloid 1 (TRPV1, capsaicin receptor), 2, 3, 4, and 8 (menthol receptor), and ankyrin 1 (TRPA1) [6,41,42].

Microtubules

Perturbation of axonal transport secondary to inhibition of microtubule dynamics or excessive tubulin polymerization has been well described in toxic and CIPN, and has been recently extensively reviewed [1,33[■]].

Apoptosis

A painful sensory neuropathy has been associated with VEGF-neutralizing antibodies (bevacizumab) or VEGF receptor inhibitors (sorafenib, sunitinib; see 'What have we learned from animal models?' section above), which are usually administered in combined chemotherapy regimens. This involves disruption of the neuroprotective effect of VEGF,

leading to neuronal stress and apoptosis through a mechanism involving VEGF receptor-2-mediated expression of the antiapoptotic protein Bcl2 [27,33,50].

In another setting, mefloquine, an efficient therapeutic option for drug-resistant *Plasmodium falciparum* malaria, is associated with a clinically well described, but pathophysiologically poorly understood, neurotoxicity [84]. A recent study linked mefloquine to a down-regulation of a non-receptor tyrosine kinase, Pyk2, involved in ion channel regulation through activation of the MAP kinase signaling pathway, ultimately leading to oxidative injury and apoptosis [85].

PHARMACOGENETIC SUSCEPTIBILITY

Pharmacogenetic variations in absorption, distribution, metabolism, elimination, and DNA repair mechanisms have been postulated to explain differences in the observed neurotoxicity of various molecules. For instance, polymorphisms of the gene encoding ABCB1/P-glycoprotein, one of the transporters involved in the elimination of numerous xenobiotic substances, have been suggested to partially explain the variability of taxane-induced DIPN [86,87]. Similarly, genetic variants of proteins involved in the metabolism of xenobiotics, for example, cytochrome 3A5, have been linked to increased risk of DIPN in children receiving vincristine [88].

Likewise, increased susceptibility to peripheral neurotoxicity after exposure to offending agents has been associated with polymorphisms in genes involved in the following pathways: chemotherapy-induced DNA adducts repair [89], immune function (*CTLA4*, *CTSS*), reflexive coupling within Schwann cells (*GJE1*), drug binding (*PSMB1*), and neuron function (*TCF4*, *DYNC111*) [90], apoptosis [4], mitochondrial dysfunction, inflammation [2], and oxidative stress scavengers such as glutathione S-transferase 1 (*GST1*) [91].

TREATMENT

There are no real breakthroughs for the treatment of CIPN. Data from an experimental animal model completed by a randomized controlled trial in patients with nonsmall cell lung cancer treated with cisplatin showed that activators of retinoid receptors stimulate nerve growth factor and may improve nerve conduction [92]. Prophylactic dosing with two drugs, acetyl-L-carnitine and olesoxime, known to protect mitochondria, has been shown to significantly reduce the development of pain hypersensitivity to bortezomib in animal models [92].

In another model of oxaliplatin-induced painful neuropathy, improvement in oxidative alterations and pain relief was established with natural antioxidant compounds such as α -tocopherol and silibinin [23].

The 2011 Cochrane review concluded that the data in human patients are insufficient to conclude that any of the purported chemoprotective agents (acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, glutathione, Org 2766, oxycarbazepine, or vitamin E) prevent or limit the neurotoxicity of platinum compounds [93]. A randomized phase III clinical trial has recently confirmed that vitamin E did not reduce the incidence of sensory neuropathy [17]. During a validation study of the French FACT/GOG-Ntx questionnaire for assessing CIPN, the study raised the possibility that erythropoietin might play a neuroprotective role when administered with paclitaxel [94]. The successful treatment with vitamin B12 injections in cobalamin deficiency and subacute combined degeneration after nitrous oxide anesthesia is again underscored [45]. Several substances have been studied in the past for treating inflammatory causes of DIPN, and recently melatonin [7] and kinin receptor antagonists [95] have been tested in pre-clinical models, showing some positive effects.

The outcome of DIPN as a neurological complication associated with immune modulators (TNF α blockers and alike) has been reported to be favorable in most cases. Although there are no clear-cut recommendations so far on the management of these secondary DIPNs, it is probably advisable to stop the treatment when complications occur, or to treat with steroids or intravenous immunoglobulins.

CONCLUSION

Promising progresses have been made over the past couple of years in understanding both the pathophysiological mechanisms and potential therapeutic options of DIPN. Such advances have required the use of adequate animal models and sufficiently powered clinical studies. Future steps should include pursuing these efforts, trying to link together all the information mentioned above regarding these pathophysiological mechanisms, as well as combining in well designed studies reliable efficacy and toxicity outcome measures, pharmacogenetic data, offending drug dose adaptation, and mechanism-based treatment.

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 588).

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