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

Manuel Diezi[a,b], *Thierry Buclin*[a], *and Thierry Kuntzer*[c]

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

[a]Division of Clinical Pharmacology, [b]Department of Pediatrics, Hemato-Oncology Unit and [c]Department of Clinical Neurosciences, Lausanne University Hospital (CHUV), Lausanne, Switzerland

Correspondence to Dr Thierry Kuntzer, Department of Clinical Neurosciences, Nerve-Muscle Unit, CHUV, Rue du Bugnon 46, 1011 Lausanne, Switzerland. Tel: +41 21 314 12 91; fax: +41 21 314 12 56; e-mail: thierry.kuntzer@chuv.ch

Curr Opin Neurol 2013, 26:481–488

DOI:10.1097/WCO.0b013e328364eb07

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 [33▪▪,49,50▪▪,51,52▪]. 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 [50▪▪,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 [52▪]. 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 antihyperalgesic 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]	Etanercept [10]
		Tacrolimus [11]	
Mitotoxicity and oxidative stress (2)		Paclitaxel [12–14]	Glutamine [15], vitamin E [16,17], AV411 (ibudilast) [18], EPO, [19], olesoxime and acetyl-N-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▪]	
Microtubular function disruption (3)		Vincaalcaloids	NSAIDs [28], propentofylline [29]
		Paclitaxel [12]	
		Epothilones [30]	
Voltage-gated ion channel dysfunction (4)	Sodium channels	Oxaliplatin [31]	Lidocaine [32], pregabalin and gabapentin [8], glutathione, glutamine and oxcarabazepine [33▪▪], calcium or magnesium salts [34]
	Potassium channels	Cisplatin [35]	Retigabine [36]
		Oxaliplatin [37,38]	
	Calcium channels	Cisplatin [35]	Nimodipine and calmodulin inhibitors [39], calcium or magnesium salts [8]
		Paclitaxel [40]	
Dysfunction of TRP family of ion channels (5)	Ankyrin 1 (TRPA1)	Paclitaxel [6]	HC0300031 [41][a]
		Oxaliplatin [42]	
	Vanilloid 1 (TRPV1)	Cisplatin [43]	Capsazepine and SB366791 [41][a]
	Vanilloid 4 (TRPV4)	Paclitaxel [6]	RN1734 [41][a]
DRG neuronal apoptosis (6)		Cisplatin [44]	
		Bortezomib [4]	
Demyelination (7)	Decreased myelin sheath methylation	Nitrous oxide [45]	Vitamin B12 [45]
	Immune-based demyelination	Etanercept, infliximab, adalimumab [46]	IVIG [47]
		Oxaliplatin [47]	IVIG [47]
Reduction of VEGF neuroprotective effect (8)	?	Bevacizumab [27▪]	
		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.
[a]HC0300031, RN1734, capsazepine, and SB366791 are antagonists of TRPA1, TRPV1, and TRPV4, respectively.

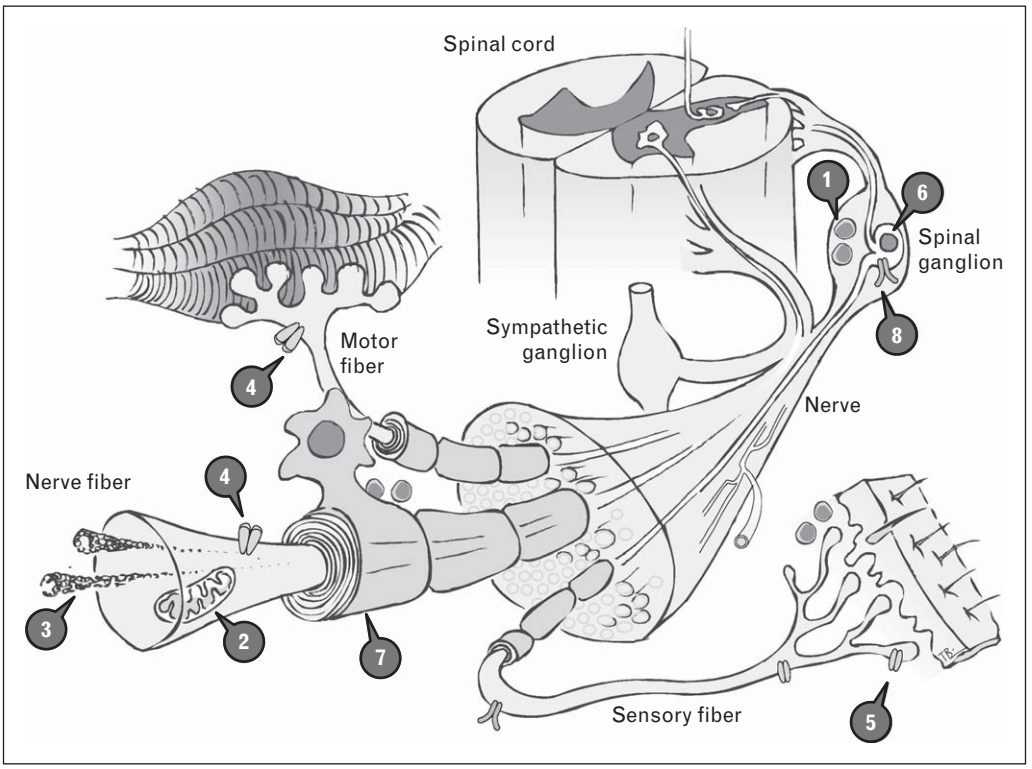

FIGURE 1. Neuronal targets of drug-induced peripheral neuropathy (numbers refer to Table 1).

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 dysruption, 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 (TNFα), interleukin 1 beta (IL-1β), 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. TNFα 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 TNFα-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 $Na_v1.6$ [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, DYNC1I1*) [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 preclinical models, showing some positive effects.

The outcome of DIPN as a neurological complication associated with immune modulators (TNFα 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.

Acknowledgements

None.

Conflicts of interest

T.K. has an unrestricted educational grant from CSL-Behring AG Switzerland for clinician-initiated research and has performed consultancy work for Actelion Pharmaceuticals Ltd.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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

1. Balayssac D, Ferrier J, Descoeur J, *et al.* Chemotherapy-induced peripheral neuropathies: from clinical relevance to preclinical evidence. Expert Opin Drug Saf 2011; 10:407–417.
2. Johnson DC, Corthals SL, Walker BA, *et al.* Genetic factors underlying the risk of thalidomide-related neuropathy in patients with multiple myeloma. J Clin Oncol 2011; 29:797–804.
3. Saifee TA, Elliott KJ, Rabin N, *et al.* Bortezomib-induced inflammatory neuropathy. J Peripher Nerv Syst 2010; 15:366–368.
4. Broyl A, Corthals SL, Jongen JL, *et al.* Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial. Lancet Oncol 2010; 11:1057–1065.
5. Kim HJ, Oh GS, Lee JH, *et al.* Cisplatin ototoxicity involves cytokines and STAT6 signaling network. Cell Res 2011; 21:944–956.
6. Materazzi S, Fusi C, Benemei S, *et al.* TRPA1 and TRPV4 mediate paclitaxel-induced peripheral neuropathy in mice via a glutathione-sensitive mechanism. Pflugers Arch 2012; 463:561–569.
7. Negi G, Kumar A, Sharma SS. Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF-kappaB and Nrf2 cascades. J Pineal Res 2011; 50:124–131.
8. Amptoulach S, Tsavaris N. Neurotoxicity caused by the treatment with platinum analogues. Chemother Res Pract 2011; 2011:843019.
9. Zheng X, Ouyang H, Liu S, *et al.* TNFalpha is involved in neuropathic pain induced by nucleoside reverse transcriptase inhibitor in rats. Brain Behav Immun 2011; 25:1668–1676.
10. Spicarova D, Nerandzic V, Palecek J. Modulation of spinal cord synaptic activity by tumor necrosis factor alpha in a model of peripheral neuropathy. J Neuroinflamm 2011; 8:177.
11. Renard D, Gauthier T, Venetz J-P, *et al.* Late onset tacrolimus-induced life-threatening polyneuropathy in a kidney transplant recipient patient. Clin Kidney J 2012; 5:323–326.
12. Shemesh OA, Spira ME. Paclitaxel induces axonal microtubules polar reconfiguration and impaired organelle transport: implications for the pathogenesis of paclitaxel-induced polyneuropathy. Acta Neuropathol 2010; 119:235–248.
13. Xiao WH, Zheng H, Zheng FY, *et al.* Mitochondrial abnormality in sensory, but not motor, axons in paclitaxel-evoked painful peripheral neuropathy in the rat. Neuroscience 2011; 199:461–469.
14. Xiao WH, Bennett GJ. Effects of mitochondrial poisons on the neuropathic pain produced by the chemotherapeutic agents, paclitaxel and oxaliplatin. Pain 2012; 153:704–709.
15. Stubblefield MD, Vahdat LT, Balmaceda CM, *et al.* Glutamine as a neuroprotective agent in high-dose paclitaxel-induced peripheral neuropathy: a clinical and electrophysiologic study. Clin Oncol 2005; 17:271–276.
16. Argyriou AA, Kalofonos HP. Vitamin E for preventing chemotherapy-induced peripheral neuropathy. Support Care Cancer 2011; 19:725–726. [author reply 727–728]
17. Kottschade LA, Sloan JA, Mazurczak MA, *et al.* The use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: results of a randomized phase III clinical trial. Support Care Cancer 2011; 19:1769–1777.
18. Ledeboer A, Hutchinson MR, Watkins LR, *et al.* Ibudilast (AV-411). A new class therapeutic candidate for neuropathic pain and opioid withdrawal syndromes. Expert Opin Investig Drugs 2007; 16:935–950.
19. Cervellini I, Bello E, Frapolli R, *et al.* The neuroprotective effect of erythropoietin in docetaxel-induced peripheral neuropathy causes no reduction of antitumor activity in 13762 adenocarcinoma-bearing rats. Neurotox Res 2010; 18:151–160.
20. Xiao WH, Zheng FY, Bennett GJ, *et al.* Olesoxime (cholest-4-en-3-one, oxime): analgesic and neuroprotective effects in a rat model of painful peripheral neuropathy produced by the chemotherapeutic agent, paclitaxel. Pain 2009; 147:202–209.
21. ■ Wang X-M, Lehky TJ, Brell JM, *et al.* Discovering cytokines as targets for chemotherapy-induced painful peripheral neuropathy. Cytokine 2012; 59:3–9.

Inflammation and cytokine dysregulation are among the mechanisms often mentioned leading to DIPN. This study nicely reviews this fact and discusses potential therapeutic targets

22. Zheng H, Xiao WH, Bennett GJ. Mitotoxicity and bortezomib-induced chronic painful peripheral neuropathy. Exp Neurol 2012; 238:225–234.
23. ■ Di Cesare Mannelli L, Zanardelli M, Failli P, *et al.* Oxaliplatin-induced neuropathy: oxidative stress as pathological mechanism. Protective effect of silibinin. J Pain 2012; 13:276–284.

Another potential mechanism, another therapeutic option: oxidative stress and mitotoxicity and their prevention or treatment with an antioxidant.

24. Xiao WH, Zheng H, Bennett GJ. Characterization of oxaliplatin-induced chronic painful peripheral neuropathy in the rat and comparison with the neuropathy induced by paclitaxel. Neuroscience 2012; 203:194–206.
25. Opii WO, Sultana R, Abdul HM, *et al.* Oxidative stress and toxicity induced by the nucleoside reverse transcriptase inhibitor (NRTI)–2',3'-dideoxycytidine (ddC): relevance to HIV-dementia. Exp Neurol 2007; 204:29–38.
26. Garrido JJ. Vascular endothelial growth factor and HDAC 6: a neuroprotective signalling pathway against cancer therapy-induced neuropathy. Brain 2012; 135 (Pt 9):2579–2580.
27. ■ Verheyen A, Peeraer E, Nuydens R, *et al.* Systemic antivascular endothelial growth factor therapies induce a painful sensory neuropathy. Brain 2012; 135 (Pt 9):2629–2641.

Very interesting study on the mechanisms of anti-VEGF compound neurotoxicity.

28. Bujalska M, Makulska-Nowak H. Bradykinin receptors antagonists and nitric oxide synthase inhibitors in vincristine and streptozotocin induced hyperalgesia in chemotherapy and diabetic neuropathy rat model. Neuro Endocrinol Lett 2009; 30:144–152.
29. Sweitzer SM, Pahl JL, DeLeo JA. Propentofylline attenuates vincristine-induced peripheral neuropathy in the rat. Neurosci Lett 2006; 400:258–261.
30. Argyriou AA, Marmiroli P, Cavaletti G, *et al.* Epothilone-induced peripheral neuropathy: a review of current knowledge. J Pain Symptom Manage 2011; 42:931–940.
31. Sittl R, Lampert A, Huth T, *et al.* Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy via sodium channel subtype Na(V)1.6-resurgent and persistent current. Proc Natl Acad Sci U S A 2012; 109:6704–6709.
32. Berger JV, Knaepen L, Janssen SP, *et al.* Cellular and molecular insights into neuropathy-induced pain hypersensitivity for mechanism-based treatment approaches. Brain Res Rev 2011; 67:282–310.
33. ■■ Argyriou AA, Bruna J, Marmiroli P, *et al.* Chemotherapy-induced peripheral neurotoxicity (CIPN): an update. Crit Rev Oncol Hematol 2012; 82:51–77.

Very well written and thorough review of CIPN addressing the most important aspects of commonly encountered chemotherapeutic agents responsible for peripheral neuropathies.

34. Ishibashi K, Okada N, Miyazaki T, *et al.* Effect of calcium and magnesium on neurotoxicity and blood platinum concentrations in patients receiving mFOLFOX6 therapy: a prospective randomized study. Int J Clin Oncol 2010; 15:82–87.
35. Scott RH, Woods AJ, Lacey MJ, *et al.* An electrophysiological investigation of the effects of cisplatin and the protective actions of dexamethasone on cultured dorsal root ganglion neurones from neonatal rats. Naunyn Schmiedebergs Arch Pharmacol 1995; 352:247–255.
36. Nodera H, Spieker A, Sung M, *et al.* Neuroprotective effects of Kv7 channel agonist, retigabine, for cisplatin-induced peripheral neuropathy. Neurosci Lett 2011; 505:223–227.
37. Kagiava A, Tsingotjidou A, Emmanouilides C, *et al.* The effects of oxaliplatin, an anticancer drug, on potassium channels of the peripheral myelinated nerve fibres of the adult rat. Neurotoxicology 2008; 29:1100–1106.
38. Dimitrov AG, Dimitrova NA. A possible link of oxaliplatin-induced neuropathy with potassium channel deficit. Muscle Nerve 2012; 45:403–411.
39. Jaggi AS, Singh N. Mechanisms in cancer-chemotherapeutic drugs-induced peripheral neuropathy. Toxicology 2012; 291:1–9.
40. Kawakami K, Chiba T, Katagiri N, *et al.* Paclitaxel increases high voltage-dependent calcium channel current in dorsal root ganglion neurons of the rat. J Pharmacol Sci 2012; 120:187–195.
41. Chen Y, Yang C, Wang ZJ. Proteinase-activated receptor 2 sensitizes transient receptor potential vanilloid 1, transient receptor potential vanilloid 4, and transient receptor potential ankyrin 1 in paclitaxel-induced neuropathic pain. Neuroscience 2011; 193:440–451.
42. Nassini R, Gees M, Harrison S, *et al.* Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. Pain 2011; 152:1621–1631.
43. Ta LE, Bieber AJ, Carlton SM, *et al.* Transient receptor potential vanilloid 1 is essential for cisplatin-induced heat hyperalgesia in mice. Mol Pain 2010; 6:15.
44. McDonald ES, Windebank AJ. Cisplatin-induced apoptosis of DRG neurons involves bax redistribution and cytochrome c release but not Fas receptor signaling. Neurobiol Dis 2002; 9:220–233.
45. Hsu CK, Chen YQ, Lung VZ, *et al.* Myelopathy and polyneuropathy caused by nitrous oxide toxicity: a case report. Am J Emerg Med 2012; 30:1016; e3–6.

46. Stubgen JP. Drug-induced dysimmune demyelinating neuropathies. J Neurol Sci 2011; 307:1–8.

47. Yoon JY, Nam TS, Kim MK, *et al.* Acute inflammatory demyelinating polyradiculoneuropathy in a patient receiving oxaliplatin-based chemotherapy. Asia Pac J Clin Oncol 2012; 8:201–204.

48. Camdessanche JP, Jousserand G, Franques J, *et al.* A clinical pattern-based etiological diagnostic strategy for sensory neuronopathies: a French collaborative study. J Peripher Nerv Syst 2012; 17:331–340.

49. Chopra K, Tiwari V. Alcoholic neuropathy: possible mechanisms and future treatment possibilities. Br J Clin Pharmacol 2012; 73:348–362.

50. ■■ Grisold W, Cavaletti G, Windebank AJ. Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention. Neuro-oncology 2012; 14 (Suppl 4):iv45–54.

This is an excellent CIPN review, addressing, for each chemotherapeutic agent, the clinical features, laboratory studies, prognosis and potential treatment of secondary neurotoxicity.

51. Argyriou AA, Cavaletti G, Briani C, *et al.* Clinical pattern and associations of oxaliplatin acute neurotoxicity: a prospective study in 170 patients with colorectal cancer. Cancer 2013; 119:438–444.

52. ■ Cavaletti G, Cornblath DR, Merkies IS, *et al.* The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. Ann Oncol 2013; 24:454–462.

Important study addressing clinical outcome measures in CIPN and comparing various published evaluation scales.

53. Kautio AL, Haanpaa M, Kautiainen H, *et al.* Burden of chemotherapy-induced neuropathy: a cross-sectional study. Support Care Cancer 2011; 19:1991–1996.

54. Kautio A-L, Haanpaa M, Kautiainen H, *et al.* Oxaliplatin scale and National Cancer Institute: common toxicity criteria in the assessment of chemotherapy-induced peripheral neuropathy. Anticancer Res 2011; 31:3493–3496.

55. Bentzen AG, Balteskard L, Wanderas EH, *et al.* Impaired health-related quality of life after chemoradiotherapy for anal cancer: late effects in a national cohort of 128 survivors. Acta Oncol 2013; 52:736–744.

56. Stubblefield MD, McNeely ML, Alfano CM, *et al.* A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. Cancer 2012; 118 (8 Suppl):2250–2260.

57. Baxter CG, Marshall A, Roberts M, *et al.* Peripheral neuropathy in patients on long-term triazole antifungal therapy. J Antimicrob Chemother 2011; 66: 2136–2139.

58. Tolaney SM, Najita J, Sperinde J, *et al.* A phase II study of ixabepilone and trastuzumab for metastatic HER2-positive breast cancer. Ann Oncol 2013; 24:1841–1847.

59. Rummel MJ, Niederle N, Maschmeyer G, *et al.* Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013; 381:1203–1210.

60. Palmer M, Chersich M, Moultrie H, *et al.* Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa. AIDS 2013; 27:781–785.

61. Shimizu T, Yokoi T, Tamaki T, *et al.* Comparative analysis of carboplatin and paclitaxel combination chemotherapy schedules in previously untreated patients with advanced nonsmall cell lung cancer. Oncol Lett 2013; 5:761–767.

62. Anter AH, Abdel-Latif RM. The safety and efficacy of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) combination in the front-line treatment for patients with advanced gastric or gastroesophageal adenocarcinoma: phase II trial. Med Oncol 2013; 30:451.

63. Lozeron P, Denier C, Lacroix C, *et al.* Long-term course of demyelinating neuropathies occurring during tumor necrosis factor-alpha-blocker therapy. Arch Neurol 2009; 66:490–497.

64. Lauria G, Merkies IS, Faber CG. Small fibre neuropathy. Curr Opin Neurol 2012; 25:542–549.

65. Tan IL, Polydefkis MJ, Ebenezer GJ, *et al.* Peripheral nerve toxic effects of nitrofurantoin. Arch Neurol 2012; 69:265–268.

66. Merkies IS, Lauria G, Faber CG. Outcome measures in peripheral neuropathies: requirements through statements. Curr Opin Neurol 2012; 25:556–563.

67. Frigeni B, Piatti M, Lanzani F, *et al.* Chemotherapy-induced peripheral neurotoxicity can be misdiagnosed by the National Cancer Institute Common Toxicity scale. J Peripher Nerv Syst 2011; 16:228–236.

68. Driessen CML, de Kleine-Bolt KME, Vingerhoets AJJM, *et al.* Assessing the impact of chemotherapy-induced peripheral neurotoxicity on the quality of life of cancer patients: the introduction of a new measure. Support Care Cancer 2012; 20:877–881.

69. Park SB, Lin CS, Kiernan MC. Nerve excitability assessment in chemotherapy-induced neurotoxicity. J Vis Exp 2012. [Epub ahead of print]

70. Namer B, Pfeffer S, Handwerker HO, *et al.* Axon reflex flare and quantitative sudomotor axon reflex contribute in the diagnosis of small fiber neuropathy. Muscle Nerve 2013; 47:357–363.

71. Authier N, Balayssac D, Marchand F, *et al.* Animal models of chemotherapy-evoked painful peripheral neuropathies. Neurotherapeutics 2009; 6:620–629.

72. Bruna J, Ale A, Velasco R, *et al.* Evaluation of preexisting neuropathy and bortezomib retreatment as risk factors to develop severe neuropathy in a mouse model. J Peripher Nerv Syst 2011; 16:199–212.

73. Khasabova IA, Khasabov S, Paz J, *et al.* Cannabinoid type-1 receptor reduces pain and neurotoxicity produced by chemotherapy. J Neurosci 2012; 32: 7091–7101.

74. Bhattacharya MR, Gerdts J, Naylor SA, *et al.* A model of toxic neuropathy in Drosophila reveals a role for MORN4 in promoting axonal degeneration. J Neurosci 2012; 32:5054–5061.

75. Schellingerhout D, LeRoux LG, Hobbs BP, *et al.* Impairment of retrograde neuronal transport in oxaliplatin-induced neuropathy demonstrated by molecular imaging. PLoS One 2012; 7:e45776.

76. Shiga K, Tanaka E, Isayama R, *et al.* Chronic inflammatory demyelinating polyneuropathy due to the administration of pegylated interferon alpha-2b: a neuropathology case report. Intern Med 2012; 51:217–221.

77. Mir O, Alexandre J, Tran A, *et al.* Relationship between GSTP1 Ile(105)Val polymorphism and docetaxel-induced peripheral neuropathy: clinical evidence of a role of oxidative stress in taxane toxicity. Ann Oncol 2009; 20:736–740.

78. Nodera H, Rutkove SB. Long-term nerve excitability changes by persistent Na+ current blocker ranolazine. Neurosci Lett 2012; 524:101–106.

79. ■ Suter MR, Kirschmann G, Laedermann CJ, *et al.* Rufinamide attenuates mechanical allodynia in a model of neuropathic pain in the mouse and stabilizes voltage-gated sodium channel inactivated state. Anesthesiology 2013; 118:160–172.

Very interesting study on ion-channel dysfunction as a mechanism of DIPN, and the potential therapeutic implications.

80. Kagiava A, Kosmidis EK, Theophilidis G. Oxaliplatin-induced hyperexcitation of rat sciatic nerve fibers: an intra-axonal study. Anticancer Agents Med Chem 2013; 13:373–379.

81. Schulze C, McGowan M, Jordt SE, *et al.* Prolonged oxaliplatin exposure alters intracellular calcium signaling: a new mechanism to explain oxaliplatin-associated peripheral neuropathy. Clin Colorectal Cancer 2011; 10:126–133.

82. ■ Nilius B, Appendino G, Owsianik G. The transient receptor potential channel TRPA1: from gene to pathophysiology. Pflugers Arch 2012; 464:425–458.

This study reviews one of the recently described potential causes of DIPN – dysregulation of transient receptor potential family of ion channels.

83. Nilius B, Honore E. Sensing pressure with ion channels. Trends Neurosci 2012; 35:477–486.

84. Chester AC, Sandroni P. Case report: peripheral polyneuropathy and mefloquine prophylaxis. Am J Trop Med Hyg 2011; 85:1008–1009.

85. Milatovic D, Jenkins JW, Hood JE, *et al.* Mefloquine neurotoxicity is mediated by nonreceptor tyrosine kinase. Neurotoxicology 2011; 32:578–585.

86. Sissung TM, Mross K, Steinberg SM, *et al.* Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. Eur J Cancer 2006; 42:2893–2896.

87. Sissung TM, Baum CE, Deeken J, *et al.* ABCB1 genetic variation influences the toxicity and clinical outcome of patients with androgen-independent prostate cancer treated with docetaxel. Clin Cancer Res 2008; 14:4543–4549.

88. Egbelakin A, Ferguson MJ, MacGill EA, *et al.* Increased risk of vincristine neurotoxicity associated with low CYP3A5 expression genotype in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2011; 56:361–367.

89. Dzagnidze A, Katsarava Z, Makhalova J, *et al.* Repair capacity for platinum-DNA adducts determines the severity of cisplatin-induced peripheral neuropathy. J Neurosci 2007; 27:9451–9457.

90. Favis R, Sun Y, van de Velde H, *et al.* Genetic variation associated with bortezomib-induced peripheral neuropathy. Pharmacogenet Genom 2011; 21:121–129.

91. McWhinney SR, Goldberg RM, McLeod HL. Platinum neurotoxicity pharmacogenetics. Mol Cancer Ther 2009; 8:10–16.

92. Arrieta O, Hernandez-Pedro N, Fernandez-Gonzalez-Aragon MC, *et al.* Retinoic acid reduces chemotherapy-induced neuropathy in an animal model and patients with lung cancer. Neurology 2011; 77:987–995.

93. Albers JW, Chaudhry V, Cavaletti G, *et al.* Interventions for preventing neuropathy caused by cisplatin and related compounds. Cochrane Database Syst Rev 2011; CD005228.

94. ■ Weber B, Largillier R, Ray-Coquard I, *et al.* A potentially neuroprotective role for erythropoietin with paclitaxel treatment in ovarian cancer patients: a prospective phase II GINECO trial. Support Care Cancer 2013; 21: 1947–1954.

Erythropoietin as a growth factor has promising neuroprotective effects demonstrated in this trial.

95. Costa R, Motta EM, Dutra RC, *et al.* Antinociceptive effect of kinin B(1) and B(2) receptor antagonists on peripheral neuropathy induced by paclitaxel in mice. Br J Pharmacol 2011; 164:681–693.