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Chemotherapy-Induced Peripheral Neuropathy: A Current Review

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting side effect experienced by patients receiving treatment for cancer. Approximately 30–40% of patients treated with neurotoxic chemotherapy will develop CIPN and there is considerable variability in its severity between patients. It is often sensory-predominant with pain and can lead to long-term morbidity in survivors. The prevalence and burden of CIPN late effects will likely increase as cancer survival rates continue to improve. In this review, we discuss the approach to peripheral neuropathy in patients with cancer and address the clinical phenotypes and pathomechanisms of specific neurotoxic chemotherapeutic agents.

INTRODUCTION

Peripheral neuropathies in cancer patients are most often due to neurotoxic chemotherapeutic agents, the so-called chemotherapy-induced peripheral neuropathy (CIPN); less frequently they occur as paraneoplastic, immune-mediated, or neoplastic neuropathies. CIPN is often a painful, dose-limiting side-effect that likely will increase in prevalence due to the progress made in cancer survival. CIPN is a common clinical problem; approximately 30–40% of patients receiving neurotoxic chemotherapy will suffer from this condition and it significantly increases the annual costs of healthcare[1]. Several classical chemotherapeutics (platinum, vinca alkaloids, taxanes) are well-established causes of CIPN. Newer agents also induce this side-effect despite different modes of more targeted cellular action. In this review, we will discuss the approach to peripheral neuropathy in the patient with cancer and provide an updated assessment of the neurotoxic mechanisms and clinical phenotypes of the specific chemotherapeutic agents.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study concept & design, data acquisition & analysis, and to drafting manuscript & figures.

POTENTIAL CONFLICTS OF INTEREST

None

APPROACH TO PERIPHERAL NEUROPATHY IN PATIENT WITH CANCER

When evaluating a patient with cancer that develops a neuropathy, determining whether they have CIPN requires an analysis of the administered drugs, the cumulative dosage, as well as the clinical characteristics and time course of the neuropathic symptoms. First, *has the patient received a neurotoxic chemotherapeutic?* The taxanes, platinum drugs, vinca alkaloids, thalidomide and bortezomib, all have a high likelihood of inducing CIPN. For some other drugs (such as cyclophosphamide or methotrexate) the likelihood is low with only single cases reported in the literature. Second, *it is important to consider the route of drug administration*. Methotrexate is rarely associated with neurological toxicity except when administered intrathecally[2]. Bortezomib neurotoxicity decreases with subcutaneous administration[3]. Third, *has the patient received a drug dose commensurate with developing CIPN?* Symptoms of CIPN typically begin during the first two months of treatment, progress while chemotherapy continues, and then stabilize soon after treatment is completed. While most CIPN occurs in a dose dependent fashion, other drug-specific features may be present such as the acute neurotoxicity of paclitaxel and oxaliplatin, or the worsening of neuropathy after discontinuation of cisplatin (coasting). It would be unexpected for CIPN to appear weeks or months after the last dose of neurotoxic chemotherapy treatment. Table 1 shows a summary of most commonly used drugs, and also estimates a cumulative dose associated with neuropathy for each drug when available.

Prior to making the diagnosis of CIPN in patients with cancer, it is important to consider other causes of neuropathy. Metabolic and endocrine-related neuropathies are rarely causes of acquired neuropathy in patients with cancer. Patients with diabetes mellitus may be at greater risk of developing CIPN [ref 23]. Paraneoplastic neuropathies usually occur at the onset of the cancer, but may rarely occur during treatment as in the dysimmune neuropathies of lymphomatous disorders[4, 5]. Direct neoplastic infiltration may occur in neurolymphomatosis[6–9], leukemia , and rarely carcinoma[10], and may mimic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)[8, 11]. Paraproteinemias are associated with several different types of neuropathy[12, 13]. Furthermore drug treatment of Waldenström's disease and multiple myeloma may involve the use of CIPN-causing medications (proteasome inhibitors, thalidomide, and related analogues), which can further complicate the determination of the etiology of the neuropathy. Bone marrow transplantation resulting in graft versus host disease can be associated with neuropathies such as Guillain-Barre Syndrome (GBS) and CIDP[14]. In chronic settings other autoimmune neuropathies may be seen[15–17]. Finally, one must consider amyloid deposition in peripheral nerves occurring in paraproteinemic neuropathies, multiple myeloma (MM), and Waldenström's disease[18, 19].

DRUG-SPECIFIC CLINICAL PRESENTATIONS AND NEUROTOXICITY IN CIPN

CIPN is primarily caused by neurotoxic effects on neurons. Sensory symptoms tend to be greater than motor or autonomic. Neuropathy may be based on anatomic changes (e.g. distal axonal degeneration) or on physiological changes. Neuropathic pain is likely augmented by

a combination of peripheral nerve hyperexcitability (via altered bioenergetics and ion channel expression) and central sensitization. The contribution of non-neuronal cells, such as Schwann cells to CIPN is not fully elucidated.

In most patients CIPN develops in a dose-dependent fashion after several cycles of neurotoxic chemotherapy administration and is typically dependent on the administered dose. Exceptions are the newer biological agents that induce a more idiosyncratic response as discussed below. Development of CIPN is an indication for dose reduction or discontinuation of the relevant chemotherapy agent. Discontinuation may hamper cancer treatment. Oncologists frequently weigh the risks of quality of life impairments from CIPN and benefits of possible cancer remissions or cures. When considering these options, it is important to note that conventional electrophysiology often does not mirror the patient`s symptoms and is difficult to use to monitor therapy. Furthermore, the Common Terminology Criteria for Adverse Events[20], which is used in most cancer clinical trials, is not a sensitive instrument for measuring neuropathy. Methodologies to assess CIPN in clinical trials have therefore been developed to provide improved evaluation tools and patient reported outcomes. The EORTC QLQ-CIPN20 is a 20-item quality of life questionnaire that quantifies symptoms and impairments of sensory, motor, and autonomic neuropathy and has been used in large oncology clinical trials[21]. A more recent methodology, the CIPN-R-ODS, was developed with Rasch analysis to build overall disability scales that provide a linear measurement of CIPN-related disability and will likely be utilized in future CIPN clinical trials[22]. Ideally, future CIPN clinical trial outcomes will also incorporate quantitative neurological exams and neurophysiology, such as those present in the Total Neuropathy Score clinical version (TNSc)[23]. Notably, the TNSc was recently subjected to Rasch analysis in patients with CIPN[24]; however, future validation studies will be required.

The majority of signs and symptoms due to CIPN arise from damage to dorsal root ganglion neurons or their axons, leading to acral pain, sensory loss and sometimes sensory ataxia. Motor, autonomic, and cranial nerve symptoms also may occur, but are less common. Most CIPN represents axonal damage in the form of a dying back neuropathy. There are however important exceptions. The widely used platinum compounds (carboplatin, cisplatin and oxaliplatin) cause a sensory neuronopathy. This selective vulnerability likely relates to the permeability of the blood-nerve barrier at the level of the dorsal root ganglion. For the neurologist trying to establish a causal relationship between chemotherapy treatment and development of neuropathy, the variability of presenting signs and symptoms in CIPN must be taken into consideration. Neurophysiology may also be helpful in this regard, providing the neurologist with data to distinguish between sensory neuronopathy, length-dependent sensorimotor neuropathy, or small fiber neuropathies. The clinical characteristics for the different medication classes are separately reviewed below.

Platinum compounds

The parent compound, cisplatin, has been in widespread use for forty years. It commonly causes ototoxicity with hearing loss and tinnitus, sensory neuropathy, nephropathy and myelosuppression. The latter two adverse events are manageable by pre-hydration of patients with normal saline or bone marrow stimulating agents (erythropoietin and G-CSF).

The neuropathy and ototoxicity are only preventable with dose reduction or cessation of drug. Significant, dose-related moderate or severe hearing loss (20%) and tinnitus (40%) are reported in patients treated with cisplatin. It is often permanent[25]. Since both CIPN and hearing loss are dose-related, they occur concurrently in many patients but there is not a clear mechanistic or risk-based relationship between these effects. All of the platinum agents in routine use cause long-term peripheral sensory damage, much of which is due to neuronopathy[26]. This occurs in 30–40% of patients treated with oxaliplatin and cisplatin and in the same proportion of patients treated with the commonly used combination of paclitaxel and carboplatin[27]. Of the platinum compounds cisplatin seems to be most frequently involved in peripheral neurotoxicity[28]. Carboplatin is considered as less neurotoxic than cisplatin[29]. Treatment schedules[30] and formulations[31] can influence toxicity. In addition to the chronic neurotoxicities observed in all platinum-based compounds[32], oxaliplatin is frequently associated with transient acute effects. Oxaliplatin acute neuropathic pain typically involves cold-induced dysesthesia that are most severe in the hands, face, and oral cavity. Cold wind on the face or cold drinks may induce intense pain. The symptoms typically begin with the second or third cycle of treatment and last for 2–4 days after drug infusion.

An important characteristic of platinum-based CIPN is the so-called “coasting” phenomenon. This refers to the observation that CIPN from platinum-based (especially cisplatin and oxaliplatin) agents may worsen for several months following the discontinuation of therapy. Coasting is disturbing for both the patient and the physician, who are expecting stabilization or improvement of neuropathic symptoms after the chemotherapy is stopped.

Much of the basic research into platinum-based CIPN pathomechanisms has focused on neurotoxic damage to dorsal root ganglion sensory neurons (Figure 1). Platinum-based compounds (cisplatin, oxaliplatin, carboplatin and analogs) damage dorsal root ganglia neurons by forming adducts with nuclear and mitochondrial DNA. Animal studies have shown that this leads to neuronal apoptosis due to aberrant entry into the cell cycle[33, 34], which corresponds to the clinical pattern of a neuronopathy. There is also direct damage to mitochondria due to impairment of mitochondrial DNA transcription, which has been theorized to underlie “coasting”[35]. Platinum adducts with nuclear DNA are repaired by nucleotide excision repair. This DNA repair process is not present in mitochondria. The accumulated and unrepaired Pt-DNA adducts in mitochondria may then lead to gradual attrition of intrinsic mitochondrial proteins due to failure of transcription after cessation of drug therapy. The acute symptoms of cold-induced dysesthesia in the hands and mouth from oxaliplatin are likely due to its effect on voltage-gated sodium channel kinetics[36, 37]. This acute neurotoxicity is temporally independent of cumulative sensory toxicity but there is a correlation between the severity of dysesthesiae and the likelihood of developing the fixed sensory neuropathy[38].

Anti-microtubule Agents

Taxanes—Taxanes (paclitaxel, docetaxel, cabaliztaxel) are widely used in oncology, and typically cause a dose-dependent, painful, length-dependent, sensory neuropathy due to

dying back axonopathy. It may be partially reversible after treatment is discontinued. Of note, cabaliztaxel appears to have less cumulative toxicity[39], but can cause dysgeusia[40]. Additionally, an acute, transient pain syndrome occurs in over half of patients treated with paclitaxel. It is characterized primarily by aching musculoskeletal pain[41]. This syndrome is not clearly due to nerve damage; however, it shares many clinical features with CIPN and may correlate with the development of paclitaxel-induced CIPN[42].

Taxanes stabilize the dynamic assembly of polymer microtubule subunits. While they are thought to primarily exert their cancer-killing effects via disruption of microtubule-mediated cell division, it is less clear how they cause CIPN. Microtubules serve as the track for axonal transport, and taxanes interrupt this *in vitro*, which may lead to neuropathy[43] (Figure 1). Other data demonstrate damage to mitochondria that may underlie a metabolic axonal failure in CIPN[44, 45]. An intriguing novel study using the zebra fish model suggested that paclitaxel-induced neuropathy may depend on interactions between skin nerve endings and epidermal basal keratinocytes through the matrix metalloproteinase MMP-13[46].

Vinca alkaloids—Vinca alkaloids are used for the primary treatment of hematological malignancies, and typically cause a length-dependent sensory neuropathy, often with some degree of motor involvement[47–50]. They may cause long-term, residual neuropathic, late effects, in particular in the pediatric and young adult population. In addition vascular effects such as Raynaud syndrome can appear[51]. Cranial nerve and autonomic dysfunction occur but are rare[52].

In contrast to the taxanes, vinca alkaloids destabilize microtubule formation; however, the resulting impact on axonal transport and mitochondria function in neurons appears similar[53]. Recent preclinical data point to SARM1 as playing a key role in axonal degeneration due to vincristine toxicity, a finding that is likely is generalizable to other causes of CIPN. SARM1 is a protein that promotes Wallerian degeneration. Genetic deletion of SARM1 prevents development of neuropathy in vincristine treated mice[54].

New anti-microtubule agents—Over the past several years, new chemotherapy agents have come to market that also impact microtubule dynamics. Eribulin and ixabepilone are two drugs used to treat breast cancer and cause an axonal sensorimotor peripheral neuropathy[55]. These drugs bind to the same site and have the same effect on microtubule dynamics as the taxanes. A new pharmaceutical approach is the conjugation of a chemotherapy agent with tumor specific antibodies as used in brentuximab vedotin where an antibody to CD30 (present on lymphoma) is conjugated to a microtubule toxin (monomethyl auristatin E). Despite the targeting to lymphoma, brentuximab vedotin causes an off-target peripheral neuropathy in 30–50% of patients[56]. Ado-trastuzumab emtansine combines an antibody against HER2 (breast cancer) and emtansine, which inhibits assembly of microtubule polymers and is associated with a high frequency of peripheral neuropathy [57].

Proteasome Inhibitors

Bortezomib exerts its anti-neoplastic actions by inhibiting proteasomes, the primary intracellular protein degradation machinery. Bortezomib causes a painful length-dependent small fiber predominant axonal sensory neuropathy[58]. It is a reversible distal axonopathy[59].

Recently it was discovered that subcutaneous delivery decreases the likelihood and severity of the neuropathy[3]. A small proportion of patients receiving bortezomib develop a severe polyradiculoneuropathy, which appears to be immune-mediated[60–62]. Newer generation proteasome inhibitors, carfilzomib and ixazomib, are reported to have a lower incidence of CIPN[63, 64].

Interestingly, despite the potential widespread cellular impact of proteasome inhibition, bortezomib appears to be neurotoxic due to interference with microtubule and mitochondrial function Bortezomib increases microtubule polymerization and mitochondrial exhibit decreased axonal transport and function in sensory neurons[45, 65, 66]. but the precise mechanism of how this occurs is unclear. Other mechanisms may also be important in bortezomib induced peripheral neuropathy, including nuclear accumulations of ubiquinated proteins and altered protein transcription in sensory ganglion neurons [67, 68].

Thalidomide

A sensory-predominant neuropathy develops with long term thalidomide treatment[69], which is used in treatment of multiple myeloma[70]. The neurotoxicity was well-known when the drug was introduced as a sedative in the 1960s[71]. Deficit persisted in 75% of patients in long term follow up in the older studies. Lenalidomide and pomalidomide are newer formulations, which appear to have less neurotoxicity[72, 73].

Thalidomide and its analogues are thought to cause neuropathy via its anti-angiogenic effects[74], and it has been theorized that impaired angiogenesis may play a significant role in CIPN from other agents[74, 75].

Immune check point inhibitors

Although not directly neurotoxic, immune-mediated neuropathies occur in association with use of the newer classes of immune check point inhibitors, which are being used in the treatment of melanoma and increasingly other tumors. Ipilimumab and tremelimumab target the human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), leading to activation of cytotoxic T lymphocyte attack on cancer cells. Pembrolizumab and nivolumab are novel immune enhancing monoclonal antibody treatments for cancer (metastatic melanoma, non-small cell lung cancer, glioma) that target the PD-1 receptor, which regulates cell death in immune cells. A variety of neurological side effects have been reported with these immune check point inhibitors, including peripheral and central nervous system disorders, some of which are life threatening[76, 77]. The reported neuropathy cases often closely resemble acute or chronic inflammatory demyelinating neuropathies[78] or vasculitic neuropathies[79]. Although they are considered as rare, they may occur in up to 3% of patients[76]. Treatment of these side effects is discontinuation of the immune-enhancing chemotherapy and institution of immunotherapy (steroids and/or IVIG), which is reported to be beneficial in many patients.

LATE EFFECTS OF CHEMOTHERAPY ON THE NERVOUS SYSTEM

The major late effect of chemotherapy agents on the nervous system is the residua of CIPN, much of which persists as a chronic pain syndrome. Discussion of a new late effect is

emerging in the oncology and cancer survivor environment. Long term cognitive impairments after chemotherapy are being described in animal models[80] and in patients[81]. The mechanistic basis for this phenomenon, referred to as “chemobrain”, is that chemotherapeutic agents may affect neurogenesis in the adult brain. Cranial irradiation would be expected to potentiate this effect. Although this field is of great interest to investigators and patients, there is little research available yet. As cancer survivorship increase, it will likely become an important area for study.

TREATMENT AND PREVENTION OF CIPN

Unfortunately, there are no preventative treatments for CIPN[82, 83]. It is challenging to understand why drugs directed towards killing rapidly dividing cancer cells also target non-dividing, post-mitotic neurons. Developing CIPN-preventing agents is complicated by the concern that any agent may also decrease the efficacy of the chemotherapeutic. Preventative strategies must depend on either separating the mechanism of neurotoxicity from the mechanism of cancer cytoxicity or identifying cell properties unique to neuronal cells (e.g. receptor sensitivity to neuronal growth factors). Despite intense research efforts, this mechanism-based approach has not brought an effective treatment forward.

A second approach would be to identify patient-specific risk factors that could then be used in planning chemotherapeutic strategies for each patient. It is likely that many factors impact CIPN susceptibility including dose, route of delivery, concomitant medications, age, pre-existing neuropathy and the type of cancer. Diabetes was a significant risk factor for the development of CIPN in a large cohort study of lung cancer patients treated with platinum and taxane drugs[27]. Genetic factors may also be important. Patients with Charcot-Marie-Tooth (CMT) disease can have increased susceptibility and severity of CIPN, especially in the setting of CMT1A and vinca alkaloids[84–87]. In many families disease gene carriers are minimally or asymptomatic. Multiple recent studies have revealed genetic variants associated with neurotoxic susceptibility to paclitaxel [88–98], vincristine [99–101], platinum compounds [102–105], bortezomib [99], thalidomide [101], and combinations [27, 106]. These studies have used a variety of techniques, including candidate gene and pathway analysis focused on cellular mechanisms implicated in CIPN [27, 88, 90, 99, 101, 102, 104–107], CMT genes[92], or more broad genome-wide association studies[91, 94, 95, 97, 98, 100]. Associations with RNA[96, 99] and protein [108] expressions have not been studied as intensely. The increased susceptibilities in these studies were relatively small (range of hazard/odds ratios 1.08–5.75) and there have been challenges with reproducibility[107, 109, 110], which may reflect population differences. Currently there are no genetic tests available that help predict CIPN in an individual patient. The rapid development of inexpensive genetic and epigenetic sequencing technologies, combined with increasingly powerful bioinformatics approaches, predict that these risk-based approaches will be successful in the future.

Another novel approach is to identify individual patient-specific mechanisms. Induced pluripotent stem (iPS) cells derived from patient fibroblasts may be used to generate specific neuron subtypes susceptible to CIPN such as dorsal root ganglion neurons[111]. These lines may then be used to predict susceptibility or therapeutic response of the individual patient or to model and study disease mechanisms, so-called disease in a dish[112].

For the present treatment of CIPN relies on reducing or discontinuing the offending agent when CIPN develops and treating the symptoms of neuropathic pain. The National Cancer Institute has sponsored 15 CIPN-directed clinical trials that studied its prevention (alpha lipoic acid, intravenous calcium/magnesium, vitamin E, acetyl-L-carnitine, or glutathione) and symptomatic treatment (nortriptyline, gabapentin, lamotrigine, amifostine, topical amitriptyline/ketamine, topical baclofen,/amitriptyline/ketamine, or duloxetine)[83]. Of these studies, only duloxetine was shown to help neuropathic pain in established CIPN[113]. Many other medications (gabapentin, topical preparations, etc.) are used in an off-label fashion. Novel electrostimulation techniques have shown early promise[114] but benefits need to be confirmed in ongoing larger randomized and controlled trials.

CONCLUSIONS

With the advent of newer and more targeted chemotherapies, there was hope that CIPN would wane as a significant clinical problem. Unfortunately, many of the older agents that cause CIPN continue to be mainstays of cancer therapy. Furthermore, many novel agents also have CIPN as a dose-limiting side-effect, whether as a direct toxicity or secondary due to immune-mediated processes. With improved cancer treatments and longer survival, the late effects of CIPN continue to produce a significant burden of suffering for cancer survivors.

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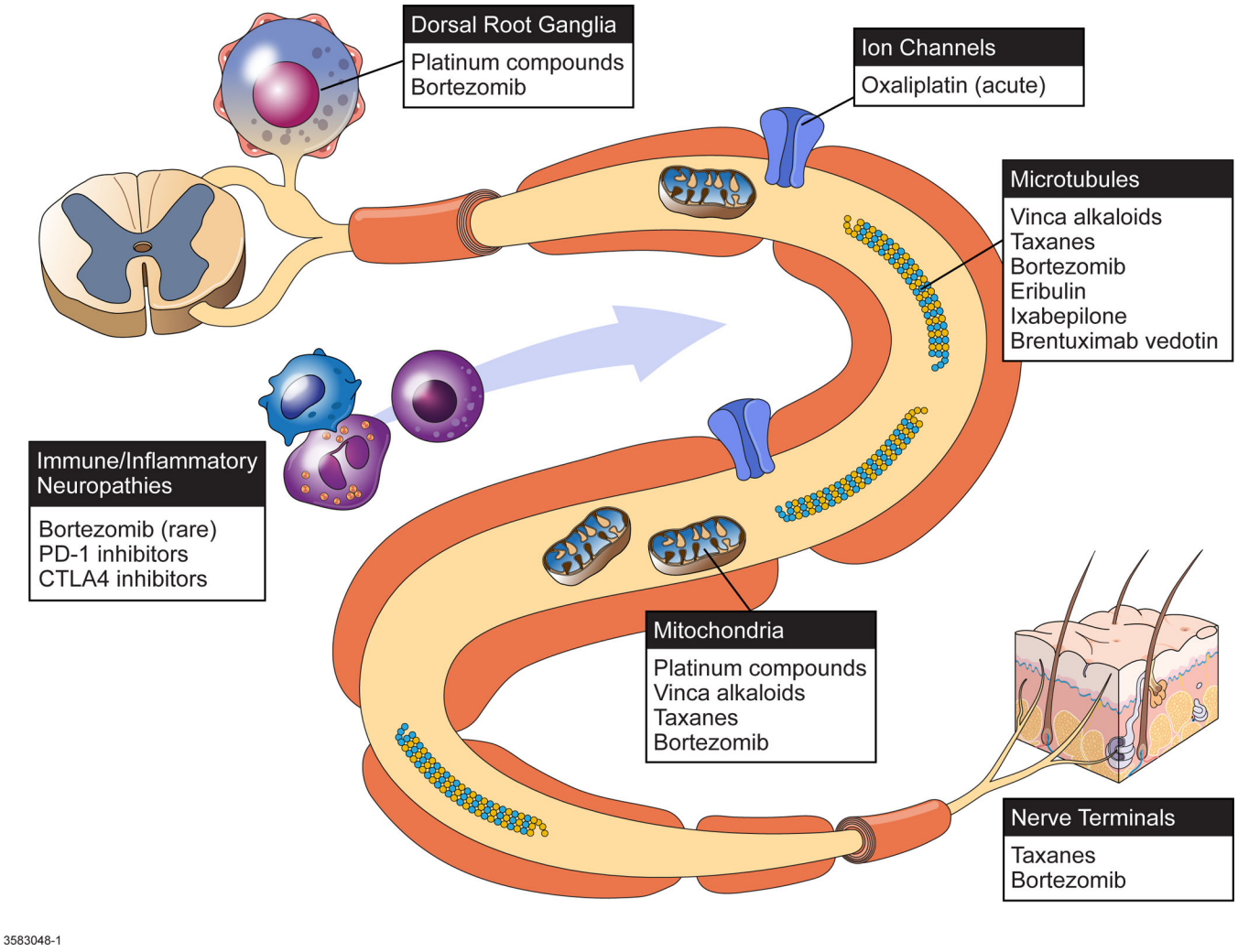

Figure 1.
Neurotoxic chemotherapeutic agents target multiple aspects of the sensory peripheral nerve.

Table 1

Chemotherapeutic agents that cause peripheral neuropathies and associated features

Mechanism of CIPN	Drug (and combinations)	Acute neuropathic symptoms	Type of chronic neuropathy	Additional features
Nuclear and mitochondrial DNA damage	Cisplatin		• Sensory neuropathy/ neuronopathy • Ataxia	• "Coasting" common • Cranial nerve involvement: hearing loss, tinnitus, ageusia • Lhermitte's phenomenon
	Carboplatin		Sensory neuropathy	
	Oxaliplatin	• Cold-induced dysesthesias (hand/face) • Muscle cramps	Sensory neuropathy	"Coasting" common
Destabilization of microtubule polymers	Vinca alkaloids: Vincristine Vinblastine Vinorelbine Vindesine	Taste impairment	Sensorimotor neuropathy	• Occasionally cranial nerves, mononeuropathies, autonomic features • Possible "coasting"
	Eribulin		• Demyelinating • Sensorimotor neuropathy	• Autonomic • Myokymia
	Brentuximab vedotin		Sensorimotor neuropathy	Conjugated antibody
	Ado-trastuzumab Emtansine		Sensorimotor neuropathy	Conjugated antibody
Stabilization of microtubule polymers	Docetaxel		Sensory neuropathy	Optic neuropathy (rare)
	Paclitaxel	Pain syndrome (myalgia)	Sensory neuropathy	
	Nab-paclitaxel		Sensorimotor neuropathy	
	Cabalitaxel		Sensory neuropathy	• Optic neuropathy • Reduced frequency of CIPN
	Ixabepilone		Sensory neuropathy	

Mechanism of CIPN	Drug (and combinations)	Acute neuropathic symptoms	Type of chronic neuropathy	Additional features
Proteasome inhibitor	Bortezomib Carfilzomib Ixazomib		• Small fiber neuropathy (common) • Severe polyradiculoneuropathy (rare)	less CIPN with subcutaneous delivery of bortezomib
Anti-angiogenesis	Thalidomide Lenalidomide Pomalidomide		Sensory neuropathy	Perioral neuropathic symptoms
Miscellaneous/ Unknown	Nelarabine			GBS like with myelopathy (rare)
	Suramin		Demyelinating neuropathy	
	Ifosfamide		Sensorimotor neuropathy	rare
	Pemetrexed		Rare motor predominant	