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# Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment

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## Abstract

Platinum-induced peripheral neurotoxicity (PIPN) is a common side effect of platinum-based chemotherapy that may cause dose reduction and discontinuation, with oxaliplatin being more neurotoxic. PIPN includes acute neurotoxicity restricted to oxaliplatin, and chronic non-length dependent sensory neuronopathy with positive and negative sensory symptoms and neuropathic pain in both upper and lower limbs. Chronic sensory axonal neuropathy manifesting as stocking-and-glove distribution is also frequent. Worsening of neuropathic symptoms after completing the last chemotherapy course may occur. Motor and autonomic involvement is uncommon. Ototoxicity is frequent in children and more commonly to cisplatin. Platinum-based compounds result in more prolonged neuropathic symptoms in comparison to other chemotherapy agents.

Patient reported outcomes questionnaires, clinical evaluation and instrumental tools offer complementary information in PIPN. Electrodiagnostic features include diffusely reduced/abolished sensory action potentials, in keeping with a sensory neuronopathy. PIPN is dependent on cumulative dose but there is a large variability in its occurrence. The search for additional risk factors for PIPN has thus far yielded no consistent findings. There are currently no neuroprotective strategies to reduce the risk of PIPN, and symptomatic treatment is limited to duloxetine that was found effective in a single phase III intervention study. This review critically examines the

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pathogenesis, incidence, risk factors (both clinical and pharmacogenetic), clinical phenotype and management of PIPN.

**Keywords**

chemotherapy; neurotoxicity; neuropathy; carboplatin; cisplatin; oxaliplatin; assessment; diagnosis; prevention; treatment

## Introduction

Platinum-based chemotherapy agents have been used for cancer treatment ever since the introduction of cisplatin in the 1970s, which followed the discovery of its anti-proliferative properties by Rosenberg and colleagues[1, 2]. Subsequently, the newer platinum derivatives, carboplatin and oxaliplatin, have been incorporated widely into the oncologist's armamentarium[3]. Unfortunately, despite their efficacy against a variety of solid tumors, the platinum compounds have several serious side effects that often limit their use. While some of the platinum-based chemotherapeutic side effects (myelosuppression, nephrotoxicity) may be mitigated, neurotoxicity continues to be a serious dose-limiting side effect that is without any proven preventative strategy. In this review, we aim to critically examine the clinical features of peripheral neurotoxicity due to platinum-based chemotherapy, discuss putative risk factors for its development, and describe clinical trials aimed at reducing its impact on patients with cancer.

## Search strategy and selection criteria

We performed a systematic search in PubMed and Scopus for relevant original research papers written in English reporting on humans from 1990 up to date with terms: 'chemotherapy-induced peripheral neurotoxicity', 'toxic neuropathy', 'peripheral neuropathy', 'neurotoxicity syndromes' combined with 'cisplatin', 'oxaliplatin', 'carboplatin'. We focused on controlled studies and large case series with adequate sample size, but selected single case reports or small case series were included for less established topics.

## Pathogenesis of Platinum-induced Peripheral Neurotoxicity

The sensory neurons of the dorsal root ganglia (DRG) are the primary target of peripheral neurotoxicity arising from platinum-based chemotherapy. It is widely accepted that binding of platinum to DNA is the primary inciting mechanism that leads to chronic damage to the DRG neuron, which can ultimately trigger apoptosis due to aberrant re-entry into the cell cycle pathway[4, 5]. Apoptosis of DRG neurons, as a result of mitochondrial dysfunction, oxidative stress and formation of DNA adducts and cross-links, leads to a non-length-dependent sensory neuronopathy (or ganglionopathy), which is a clinically-distinct syndrome from other causes of chemotherapy-induced peripheral neuropathy (CIPN) that tend to be a length-dependent or stocking-and-glove pattern. There is further evidence that there is not only damage to nuclear DNA, but also significant binding and damage to mitochondrial DNA[6], which may account for longer-term aspects of neuronal damage in

patients with platinum-induced peripheral neurotoxicity (PIPN), such as 'coasting' and length-dependent sensory neuropathic features.

Oxaliplatin is unique in that it also produces an acute neurotoxicity, characterized by cold-induced dysesthesias. The acute oxaliplatin neurotoxicity appears to be mediated by increased neuronal excitability and altered axonal refractoriness, possibly via oxaliplatin interaction with voltage-gated sodium channels and changes in kinetics of sodium channel inactivation[7]. Additionally, there appears to be an association between development of acute oxaliplatin neurotoxicity and susceptibility to the chronic neuropathy[8], which is intriguing given the disparate mechanisms of toxicity.

## Clinical Aspects of Platinum-induced Peripheral Neurotoxicity

### Clinical Presentations

PIPN includes acute and chronic peripheral neurotoxicity, the latter associated to all platinum-based compounds, while the former is restricted to oxaliplatin. Furthermore, it is generally regarded that cisplatin is more ototoxic, carboplatin is more myelosuppressive, and oxaliplatin is more neurotoxic [9]. A prospective, multicenter study focusing on oxaliplatin-induced peripheral neurotoxicity showed the acute and chronic neurotoxicity to occur in 85% and 73% of patients, respectively [10].

In keeping with the view that platinum-based compounds exert their toxicity at the sensory neuronal cell body, the chronic peripheral neurotoxicity primarily presents as a sensory neuronopathy (or ganglionopathy) with anterograde non-length dependent neuronal degeneration [11]. Positive sensory symptoms (numbness, tingling, paresthesia, neuropathic pain) and loss-of-function signs (reduction/loss of sensation to touch, vibration and joint position with reduced/absent deep tendon reflexes) usually appear in both upper and lower limbs. With prolonged treatment the neuronopathy can eventually evolve to other body segments in a non-length dependent pattern with sensory ataxia[12]. Additionally, chronic neuropathy manifesting as a pure sensory, stocking-and-glove distribution, axonal neuropathy has been observed in 50–70% of patients [13-16]. A long-term study showed sensory symptoms to be more prominent in the hands than the feet during chemotherapy; whereas by 18 months, symptoms were more severe in the feet than the hands [8]. Finally, Lhermitte's phenomenon has been reported in some patients, presumably secondary to DRG axonal degeneration within the spinal cord[17].

Motor and autonomic symptoms and signs are uncommon in patients treated with platinum-based compounds, but may be observed in severe cases [18]. Therefore, when motor and autonomic symptoms are predominant and/or there is an absence of sensory involvement, an alternative diagnosis should be considered. As an example, platinum-based compounds have been rarely associated with acute inflammatory demyelinating polyradiculoneuritis in patients with solid tumor [19-23], which appears to respond well to standard immunotherapy. Additionally, it is important to be aware that treatment with more than one neurotoxic agent may increase the likelihood of peripheral neuropathy[24], which may be associated with involvement of the autonomic system (especially parasympathetic heart innervation) [25].

Hearing loss and tinnitus are a progressive and irreversible adverse effect of platinum-based chemotherapy, frequently reported bilaterally in children and more commonly occurring to cisplatin than oxaliplatin [26]. Approximately 60% (range 26–90%) children receiving cisplatin develop irreversible bilateral hearing loss[27-31], which may have a deleterious effect in their speech, language, and social skills [27]. Cisplatin exposure has also been associated with cognitive dysfunction, the so-called “chemo-brain”, which is beyond the scope of this review [32].

## Time course

With all platinum-based compounds, chronic sensory neuropathy/neuronopathy development occurs with increasing cumulative dosage. As already stated, oxaliplatin is unique as it typically also causes acute neurotoxicity. The oxaliplatin acute neurotoxicity is characterized by transient paresthesia, dysesthesia and muscle cramps induced by cold exposure, a phenomenon often called cold allodynia or hyperalgesia that typically resolves before the next oxaliplatin cycle [33]. Symptoms reported by patients include paresthesia and/or dysesthesia in the perioral, pharyngeal and laryngeal regions, as well as in the distal limbs triggered and exacerbated by cold (especially when drinking beverages), abnormal breathing and swallowing, muscle spasms or cramps among other uncommon symptoms related to the acute oxaliplatin hyperexcitability syndrome[34, 35]. Acute peripheral neurotoxicity to oxaliplatin, documented either by clinical symptoms or quantitative sensory testing, has been demonstrated to be associated with the development of chronic peripheral neuropathy. This observation has the potential of making the acute neurotoxicity a predictor for selecting patients who may benefit from neuroprotective strategies [35, 36].

The large majority (89%) of a cohort of 346 patients under fluorouracil, leucovorin, and oxaliplatin (FOLFOX) reported at least one symptom of acute oxaliplatin neurotoxicity within the first cycle, namely sensitivity to cold (71%), throat discomfort (63%), or muscle cramps (42%), with a peak at day 3, later improvement, and incomplete remission between treatments [8]. According to a systematic review, acute oxaliplatin neuropathy (Common Terminology Criteria Adverse Events, CTCAE grades 1–4) occurred in 4–98% of patients, with moderate to severe toxicities commonly encountered in patients receiving a large dose of oxaliplatin (> 85 mg/m$^2$) and/ or combined drugs [37].

Another important feature of PIPN is ‘coasting’, i.e. worsening of neuropathy signs and symptoms for months after completing the last chemotherapy course[8]. This is an important factor in deciding when to discontinue therapy due to neuropathic symptoms, as impairments and disability may progress once the drug has been stopped. It has been hypothesized that coasting may be due to drug accumulation in the DRG and/or chronic neuronal damage from mitochondrial platinum-DNA adducts that impair mitochondrial function[6].

## Incidence and range of severity

The incidence of chronic PIPN is related to cumulative dose and dose per cycle [38], which in the case of cisplatin usually occurs with administration of 250–450 mg/m$^2$ [38, 39]. Almost all patients develop neuropathy after a cumulative cisplatin dose of 500–600 mg/ m$^2$, which is

severely disabling in approximately 10% of patients [12]. Studies investigating the association between chronic peripheral neurotoxicity and oxaliplatin doses reported threshold cumulative dose in symptomatic patients to range from 850 to 1800 mg/m$^2$ [40-43]. Carboplatin-induced peripheral neurotoxicity is less frequent and severe at conventional doses [44].

Incidence and severity of PIPN vary across studies[12]. Using a variety of neurological outcome measures, Phase III and prospective studies have reported cisplatin-induced peripheral neurotoxicity to occur as Grade 1 in 14–33%, Grade 2 in 0–33%, Grade 3 in 2–19% and Grade 4 in 0–4% of patients (Table 1). Likewise, oxaliplatin was reported to cause peripheral neurotoxicity of Grade 1 in 21–94%, Grade 2 in 5–42%, and Grade 3–4 in 3–19% [12] (Table 2). When neuropathy was assessed with specific neurological assessment tools (unlike the CTCAE), peripheral neuropathy was found in 17–100% of patients for cisplatin and 50–75% for oxaliplatin[12]. These findings suggest that, apart from the cumulative dose and dose per cycle that are known to influence the risk of PIPN, the ascertainment/diagnostic criteria strongly influence epidemiological data. Because of the heterogeneous tools utilized in the studies, a formal framework for the definition, classification and measurements of PIPN is of great importance [45].

## Recovery and late effects

When compared to other neurotoxic chemotherapeutics, platinum-based compounds result in more prolonged neuropathic symptoms, presumably due to the presence of irreversible damage to the DRG neuron. Earlier reports suggested chronic PIPN to be reversible after chemotherapy discontinuation [46], but more recent long-term clinical and nerve conduction studies (NCS) demonstrated its persistence up to 2–3 years with complete reversal occurring only in a minority of cases [47, 48]. Oxaliplatin also appears to cause more late chronic neurotoxicity when compared to cisplatin. Oxaliplatin-induced peripheral neurotoxicity may be present in 26–46% of patients at 12-month, in 24% of patients at 15–18-month [45], or even in 84% of patients at the 24-month follow-up [47]. On the other hand, cisplatin induced peripheral neurotoxicity may persist in 5–20% patients at one year [49, 50].

Interestingly, the chronic form of PIPN is reported to show less of a neuronopathy clinical picture, whereas there are increased length-dependent stocking-and-glove sensory polyneuropathy signs and symptoms [13-16]. Furthermore, the degree of intraepidermal nerve fiber loss in distal and proximal biopsies failed to demonstrate a neuronopathy pattern in studies of oxaliplatin-induced neuropathy[51, 52]. These findings suggest the presence of reversible neurotoxic effects and/or a length-dependent neuropathic component that arises with time. A cross-sectional observational study involving 121 childhood cancer survivor patients showed persistence of neuropathic symptoms in 53% patients after a median of 8.5 years[53]. In this study, late effects were primarily lower limb predominant sensory dysesthesia plus functional deficits of manual dexterity, distal sensation, and balance[53].

## Electrophysiology and Imaging

Traditional NCS often demonstrate a sensory neuronopathy pattern in PIPN due to involvement of DRG neurons[47, 54, 55]. Characteristically, there are diffusely low or absent

sensory nerve action potentials (SNAP) with normal sensory conduction velocities, which is not length-dependent. Unless the neurotoxicity is very severe, motor nerves are usually spared. Evidence of primary demyelination is lacking whereas secondary demyelination as a result of severe axonal loss may occur. SNAP abnormalities often precede sensory symptoms [56] and sural SNAP may provide important information in terms of neuropathy progression and has prognostic implications[57]. Specifically, the dorsal sural nerve (the distal lateral branch of the sural nerve) SNAP has been found to be more sensitive than the sural SNAP for detecting early CIPN [58]. In one study, decreased dorsal sural SNAP amplitude, assessed at mid-treatment, was able to predict the neurological outcome at chemotherapy completion [57].

Electrophysiological studies of acute oxaliplatin peripheral neurotoxicity have delineated a primary abnormality in neuronal excitability that may produce the cold-induced dysesthesias. Axonal excitability techniques[59] suggest abnormal functioning of axonal voltage-gated Na+ channels in motor and sensory axons with ‘neuromyotonic-type’ discharges in motor axons[7, 60, 61]. Paradoxically, motor axons show the most marked excitability changes (i.e. decreased superexcitability associated with slowing of inactivation of nodal voltage-gated sodium channel), despite that the sensory symptoms are the most important acute side-effect of oxaliplatin toxicity [33]. Animal models have further indicated a crucial role of Nav1.6 [62]. A clinical report using blockade of peripheral myelinated A-fibers in combination with quantitative sensory testing (QST) implicated this this neuronal population as driving symptoms[63].

Nerve imaging has also provided insights into PIPN. Nerve high-resolution ultrasound in oxaliplatin induced neuropathy showed normal cross sectional area in the non-entrapment sites and increased cross sectional area in the entrapment sites with no NCS evidence of entrapment [64, 65], which suggests these patients may be prone to develop entrapment neuropathies. Using magnetic resonance imaging diffusion tensor imaging, hypertrophy was observed in the DRGs, but not the proximal nerve segments, in a study of 20 patients with oxaliplatin-induced peripheral neuropathy [66].

While electrophysiology and imaging may provide valuable ancillary data regarding PIPN, it is worth noting that most patients with PIPN do not undergo this advanced testing. Most patients with PIPN are diagnosed clinically based on bedside signs and symptoms. Ancillary testing is not performed both due to the limited availability of the described modalities as well as the practicality and costs of performing many of these tests in a busy oncological practice. Depending on the practice, the described testing may be used in selected cases when the diagnosis is in doubt or if it is being performed for research purposes.

## Risk Factors and Pharmacogenetics

The identification of risk factors that predict a worse neurological outcome in cisplatin-treated patients has been limited by the frequent use of the drug in combination with other neurotoxic agents (typically taxanes). In fact, while it is well known since the earliest stages of its clinical use that the severity of cisplatin neurotoxicity is dependent on both single and total dose administered [67], more refined and recent searches for additional risk factors failed

to provide reliable evidence supporting the role of other predictors. Moreover, while subsequent studies confirmed that the incidence of cisplatin-induced peripheral neurotoxicity is related not only to dose per cycle and cumulative dose, but also to duration of infusion [68], these factors were not associated with long-term toxicity in a clinical follow-up study designed to evaluate adverse late effects in adult survivors of childhood cancer [69]. Since cisplatin is used both in pediatric as well as in adult cancer treatment, age has been specifically investigated as a possible risk factor, without any evidence in support of this hypothesis [70].

Data are easier to interpret when oxaliplatin neurotoxicity is considered. Nearly all the patients treated with oxaliplatin experience acute, cold-related symptoms within hours from drug administration, although the severity of these symptoms might be different [57, 71, 72]. However, the susceptibility of individual patients to chronic oxaliplatin-induced peripheral neurotoxicity is highly variable. This individual variability has been reproduced also in animal models, since different strains of mice chronically treated with oxaliplatin show a wide range of phenotypes in terms of severity as well as of type of neurological impairment [73].

This remarkable variability still needs to be fully explained because different studies have failed to unequivocally indicate which might be the risk factors or the predictors for the final neurological outcome in each patient. Apart from cumulative dose, which is clearly associated with more severe neurotoxicity [74-78], several other apparently obvious risk factors for peripheral nerve damage failed to demonstrate consistent results in different studies [78]. This is the case for diabetes [79-81], age [76, 81-83], previous chemotherapy [74], while other risk factors less commonly associated to increased incidence of peripheral neuropathies, such as body mass index [80, 82] and smoking [80, 84], were occasionally reported.

The most recent systematic review on oxaliplatin neurotoxicity-associated risk factors [78] analyzed 322 papers focused on oxaliplatin-induced peripheral neurotoxicity and identified 72 studies on risk/prognostic factors. Among them, 15 reported clinical or patient-related factors (i.e patient demographics, baseline laboratory findings, comorbid disease, cancer diagnosis and nature and severity of neuropathy symptoms) and were further analyzed according to the STROBE Statement checklist [85]. Among the selected studies, only 3 were prospective, and in most cases the distinction between acute and chronic symptoms induced by oxaliplatin was missing or unclear. Moreover, the methods used to assess the neurotoxic effect of oxaliplatin were highly variable across the 15 studies. Another major issue was related to the sample size of the studies, since only 4 of them investigated more than 200 patients, while 7 reported the results obtained in less than 60 patients. It is remarkable that the 2 largest studies (examining 1585 and 3359 patients, respectively) [86, 87], failed to observe any significant association with demographic or clinical risk factors.

The conclusions of the systematic review of the available data can be summarized in the following practical points: a) the identification of specific symptoms of acute neurotoxicity induced by oxaliplatin can be helpful to predict the onset of more severe chronic neurotoxicity [88, 89]; b) there is no clear evidence for a different neurotoxicity between the 2 most commonly used chemotherapy regimens including oxaliplatin (i.e. FOLFOX and

XELOX), despite different dose per cycle and interval between cycles [45]; c) abnormal laboratory findings (i.e. low hemoglobin levels, hypoalbuminemia, hypomagnesemia, high serum chlorine levels) [81, 87] resulted to be associated with high risk of more severe neurotoxicity, but further research (particularly well designed prospective trials in homogeneous populations evaluated with proper neurological assessment) is required in order to prove their validity to predict chronic oxaliplatin-induced peripheral neurotoxicity [45].

Since demographic and clinical risk factors are still missing, a more sophisticated approach based on different pharmacogenetic methods have been attempted by several authors to solve the problem of early prediction of more severe neurological outcome in oxaliplatin-treated patients. Unfortunately, also using this approach no reliable predictors have been identified despite extensive investigation. This topic has been thoroughly reviewed considering several anticancer treatments [90-93]. Platinum-based drugs (particularly oxaliplatin) are among the most frequently neurotoxic anticancer drugs investigated in pharmacogenetics studies, GSTP1 Ile105Val polymorphism being the most frequent candidate gene[94], with very conflicting results in different analyses. Several other genetic associations have been reported, but also in these cases not subsequently validated. Although it is possible that no genetic predictors could eventually be found (similar analysis performed in mice where oxaliplatin administration resulted in different neurotoxicity failed to identify relevant genetic associations) [73], several major flaws have been identified in most of the reported clinical studies. To summarize, these are the major potential bias sources to be corrected in future studies: a) from the statistical standpoint, use of adequate sample size, adjustment for multiple comparison and comparison with appropriate validation cohorts; b) regarding patients assessment, identification of an accurate endpoint and selection of a reliable outcome measure; c) concerning biological samples and their analysis, selection of the most suitable approach (genome wide association studies, single nucleotide polymorphisms panels, gene expression studies) and validation of peripheral nervous system protein expression.

## Prevention of Platinum-induced Peripheral Neurotoxicity: Clinical Trial Strategies

There are currently no evidence-based pharmacologic or supplement interventions for prevention of CIPN with platinum-based compounds (Table 3).[95] Many agents have been tested to prevent CIPN, but have either shown no effect or there was an effect in a small sample study not confirmed in larger studies (for extensive review, see Hershman et al.[95]). As a recent example, calcium and magnesium infusions were not found to be beneficial in prevention of oxaliplatin CIPN in a large phase III randomized study[96]. The largest non-pharmacologic intervention study was Exercise for Cancer Patients (EXCAP), which was a randomized moderate-intensity, home-based, six-week progressive walking and resistance exercise program in patients undergoing taxane, platinum, or vinca alkaloid-based chemotherapy, as compared to usual care.[97] Out of the 355 randomized patients, 39 (11%) patients received platinum-based chemotherapy. Patients in the exercise had significantly less temperature sensitivity and less sensory neuropathy symptoms. Since this was a

secondary analysis of a previously conducted study on fatigue, a large prospective study is planned to confirm these findings. However, it does appear the exercise may have beneficial protective effects on CIPN from several chemotherapeutic agents including platinum-based drugs, although the numbers with this particular chemotherapeutic class were limited.

Several ongoing prevention studies are evaluating the role of pharmacologic prevention strategies in PIPN. Oxidative stress from chemotherapy is the primary inducer of mitochondrial damage and neutralization of reactive oxygen species is a potential preventative strategy for platinum-induced peripheral neurotoxicity. Calmangafodipir, derived from a magnetic resonance imaging contrast agent known as mangafodipir, mimics the mitochondrial enzyme manganese superoxide dismutase, which reduces reactive oxygen species and subsequent nerve injury after platinum-based chemotherapy exposure. [98, 99] In a placebo-controlled, double-blinded randomized phase II study in patients with metastatic colorectal cancer, calmangafodipir reduced CIPN associated symptoms during and after treatment. [100] Two international trials, POLAR A and POLAR M, are currently evaluating the efficacy of calmangafodipir for the prevention of oxaliplatin-induced neuropathy in colorectal cancer patients. (Polar M: ). These phase III, multicenter, placebo-controlled trials are evaluating stage II and III patients in POLAR A, while POLAR M is being conducted in metastatic patients. Results are expected by the end of 2020.

While the published data on the analgesic effects of duloxetine for treatment of neuropathic pain is supported,[101] emerging preclinical data suggest that duloxetine may also be effective for prevention of CIPN as well. A new NCI-funded clinical trial is currently undergoing protocol development to evaluate the efficacy of duloxetine for prevention of oxaliplatin-induced neuropathy (NCI, Ellen Smith PI).

Other interesting platinum-based peripheral neurotoxicity pathways being explored are in early stages of development. One pathway focuses on cellular transport of platinum-based compounds and aims to perform genetic or pharmacological knockout of transporters localized to the DRG in mice, such as OATP1B2 (OATP1B1 in humans), organic cation transporter novel type (OCTN2) protects against CIPN associated with and platinum-based drugs. [102, 103] A second molecule of interest is apyrimidinic endonuclease/redox effector factor-1 (APE1), which can be pharmacologically induced to increase DNA base excision repair, while simultaneously showing anti-cancer effects[104]. Both of these pathways are nearing translation into human clinical trials for CIPN prevention.

## Treatment of Established Platinum-induced Peripheral Neurotoxicity: Clinical Trial Strategies

Prompt recognition of progressive CIPN symptoms remains the primary cornerstone of management of CIPN from these platinum-based agents, in order to reduce severity of symptom and risk of permanent injury. Early referral to physical therapy and rehab medicine is important for evaluation of functional deficits and falls risk. Depending on the severity of CIPN, dose reduction or dose holds are often necessary to manage the cumulative toxicity of all of these agents. The Stop and Go Approach which consists of stopping therapy before severe neurotoxicity develops, and later reintroducing oxlaliplatin did not yield significant

differences in grade 3 or 4 CIPN. This approach is not routinely used in clinical care[105]. Additional management strategies include use of supportive care medications such as the traditional anti-neuropathic pain medications of antiepileptics and antidepressants. Despite the widespread use of these medications, to date duloxetine, a serotonin-norepinephrine reuptake inhibitor has been the only drug found to be associated with a significant reduction in neuropathic pain in CIPN in a randomized phase III intervention study (Table 3). [101] The mechanism of duloxetine-induced analgesia is due to the blocking of serotonin and norepinephrine transporters, as well as blocking of sodium channel currents and affecting the descending inhibitory pain neural networks [106-109] Additional novel therapeutic strategies are currently in development.[110]

## Conclusions & Future Directions

Peripheral neurotoxicity from platinum-based compounds continues to be a serious dose-limiting side effect without any proven preventive therapies, despite intensive investigations over the past several decades. Given their efficacy to treat cancer, platinum-based chemotherapeutics are not going away anytime soon. Therefore, there will continue to be a critical need to better understand of PIPN, rigorously quantify its impairments, and develop effective preventative and treatment strategies. Furthermore, there continues to be active drug development for new platinum-based compounds, which is using several approaches[111]. First, platinum-compounds are being formed with novel attached side groups (for example, phenanthriplatin[112]), which cause diverse DNA adducts less susceptible to known mechanisms of drug resistance. Second, new platinum formulations have been developed that alter drug pharmacokinetics, such as liposomal cisplatin, which has been purported to be less neurotoxic[113]. Finally, platinum drugs are being conjugated with bioactive compounds in order to increase efficacy and better target cancer. The approach of combining platinum with a molecule that can be targeted to specific cancer has been used with microtubule-targeting drugs, such as brentuximab vedotin and ado-trastuzumab emtasnsine[114, 115]. Notably, in those cases, the attached compound was expected to reduce off-target effects; however, CIPN continues to be a serious side-effect, raising questions about specificity. As these newer formulations of platinum-based compounds enter the clinical practice, detailed characterization of their neurotoxicity will continue to be essential.

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**Table 1.**

Incidence of cisplatin-induced peripheral neuropathy in prospective clinical studies

| Study | Design | Pts (N) | Cancer type(s) | Clinical features of cisplatin-induced peripheral neuropathy | | |
|---|---|---|---|---|---|---|
| | | | | Assessment methods | Duration of follow-up | Incidence |
| Swenerton (1992)[116] | Phase III | 210 | Ovarian | ECOG | After 6 CMT cycles | Grades 1-2: 52%; grade 3: 1% |
| Kemp (1996)[117] | Neuroprotection | 120 | Ovarian | NCI-CTC | Up to CMT cycle 6 | Grades 1-2: 55%; grade 3: 13% |
| Wozniak (1998)[118] | Phase III | 200 | NSCLC | SWOG | 1 year after CMT completion | Grades 3-4: 1% |
| Sutton (2000)[119] | Phase III | 90 | Uterus carcinosarcoma | GOG | Up to CMT cycle 8 | Grades 2: 8%; grade 3-4: 13% |
| Gatzmeier (2000)[120] | Phase III | 206 | NSCLC | NCI-CTC, QLQ-C30 | Up to median 3 months after CMT | Grades 1-2: 12%; grades 3-4: 1% |
| Wachters (2003)[121] | Phase III | 119 | NSCLC | NCI-CTC, QLQ-C30 | 6 months after CMT completion | Grades 1-2: 22%; grades 3-4: 1% |
| Fleming (2004)[122] | Phase III | 129 | Endometrium | NCI-CTC, FACT/GOG-Ntx | 12 months after CMT completion | Grades 1-2: 3%; grades 3-4: 1% |
| Al-Batran (2008)[123] | Phase III | 112 | GE | NCI-CTC | Median follow-up 6 months | Grades 1-2: 20%; grades 3-4: 2% |
| Homesley (2009)[124] | Phase III | 261 | Endometrium | NCI-CTC, FACT/GOG-Ntx | 47 months median follow-up after CMT completion | Grades 1-2: 28%; grades 3-4: 2% |
| Chen (2013)[125] | Phase III/IVb | 158 | Nasopharingeal | WHO | Median follow-up 70 months | Grade 3-5: 2% |
| Friedrich (2013)[126] | Prospective | 49 | Medulloblastoma | NCI-CTCAE | Median follow-up 3.7 years | Grades 2-3: 51%, any grade: 74% |
| Conroy (2014)[127] | Phase II/III | 128 | Oesophagus | NCI-CTCAE | Median follow-up 25.3 months | Grades 1-2: 1%; grades 3-4: 0% |
| Yamada (2015)[128] | Phase III | 337 | Gastric | NCI-CTCAE | Median follow-up 25.9 months | Grades 3-4: 0%, any grade: 24% |
| Bando (2016)[129] | Phase III | 343 | Gastric | NCI-CTCAE | Median follow-up 13.5 months | Grades 3-4: 0% |
| Fung (2017)[130] | Prospective | 952 | Testis | Ad-hoc PRO questionnaire | Median 4.3 years after CMT | Any neuropathy: 21-29% |
| Ramaswamy (2017)[131] | Prospective | 163 | Gallbladder | NR | NR | Grades 2-3: 3%, |

CMT: chemotherapy; ECOG: Eastern Cooperative Oncology Group criteria; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group-Neurotoxicity scale; GE: gastroesophageal; GOG: GOG: Gynecologic Oncology Group criteria; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NR: not reported; NSCLC: non-small cell lung cancer; QLQ-C30: European Organization for the Treatment of Cancer quality of life questionnaire-30 items; PRO: Patient Reported Outcome; RCT: Randomized Controlled Trial; SWOG: South West Oncology Group criteria.

**Table 2.**

Incidence of oxaliplatin-induced peripheral neuropathy in prospective clinical studies

| Study | Design | Pts (N) | Cancer type(s) | Clinical features of oxaliplatin-induced peripheral neuropathy | | |
|---|---|---|---|---|---|---|
| | | | | Assessment methods | Duration of follow-up | Incidence |
| Giacchetti (2000)[132] | Phase III | 100 | CRC | Specific neuropathy scale | Median follow-up 19 months | Grades 1-2: 45%; grades 3-4: 10% |
| de Gramont (2000)[133] | Phase III | 209 | CRC | NCI-CTC | Median follow-up 8 months | Grades 1-2: 50%; grades 3-4: 18% |
| Rothenberg (2003)[134] | Phase III | 303 | CRC | NCI-CTC-derived scale | Maximum follow-up 14 months | Grades 1-2: 48-49%; grades 3-4: 2.−3% |
| André (2004)[135] | Phase III | 1108 | CRC | NCI-CTC | Median follow-up 38 months | Grades 1-2: 80%; grade 3: 12% |
| Tournigand (2006)[105] | Phase III | 612 | CRC | NCI-CTC | Median follow-up 31 months | Grades 1-2: 71-78%; grades 3-4: 13-18% |
| Land (2007)[136] | Phase III | 189 | CRC | NCI-CTC, FACT/GOG-Ntx, NCI-Sanofi | Up to 18 months after CMT completion | Grades 1-2: 61-68%; grades 3-4: 3% |
| Al-Batran (2008)[123] | Phase III | 112 | GE | NCI-CTC, oxaliplatin scale | Median follow-up 6 months | Grades 1-2: 49%; grades 3-4: 14% |
| Cassidy (2008)[137] | Phase III | 1304 | CRC | NCI-CTC | Median follow-up 30 months | Grades 1-2: 16%; grades 3-4: 4% |
| Cunningham (2008)[138] | Phase III | 452 | GE | NCI-CTC | Median follow-up 17 months | Grades 1-2: 75%; grades 3-4: 7% |
| Allegra (2009)[139] | Phase III | 2647 | CRC | NCI-CTC | Up to 1 year after CMT completion | Grade 2: 29-33%; grade 3: 14-16% |
| Poplin (2009)[140] | Phase III | 272 | Pancreas | NCI-CTC | NR | Grade 3: 10% |
| Qvortrup (2010)[141] | Phase III | 139 | CRC | NCI-CTC | Median follow-up 14 months | Grade 2: 27-42%; grade 3: 16-19% |
| Argyriou (2012)[142] | Prospective | 150 | CRC | NCI-CTC, NCS, TNS | Up to 1 month after CMT completion | Grades 1-2: 45-73%; grade 3: 10-18% |
| Conroy (2014)[127] | Phase II/III | 131 | Oesophagus | NCI-CTCAE | Median follow-up 25.3 months | Grades 1-2: 47%; grades 3-4: 0% |
| Yamada (2015)[128] | Phase III | 339 | Gastric | NCI-CTCAE | Median follow-up 25.9 months | Grades 3-4: 5%, any grade: 86% |
| Bando (2016)[129] | Phase III | 343 | Gastric | NCI-CTCAE | Median follow-up 13.5 months | Grades 3-4: 4.5-5.3% |
| Lonardi (2016)[143] | Phase III | 3759 | CRC | NCI-CTC | Maximum follow-up 3 years | Grade 2: 8-23%; grade 3: 1-8% |
| Ramaswamy (2017)[131] | Prospective | 163 | Gallbladder | NR | NR | Grades 2-3: 9%, |
| Iveson (2018)[144] | Phase III | 6022 | CRC | FACT/GOG-Ntx | Maximum follow-up 8 years | Grades 1-2: 77-87%; grades 3-4: 16-18% |

CMT: chemotherapy; CRC: colorectal cancer; FACT/GOG-Ntx: Functional Assessment of Cancer Therapy Scale/Gynecologic Oncology Group-Neurotoxicity scale; GE: gastroesophageal; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NCI-Sanofi: oxaliplatin Sanofi questionnaire; NCS: Nerve Conduction Study; NR: not reported; TNS: Total Neuropathy Score.

**Table 3;**

Prevention and Treatment of PIPN in prospective randomized placebo-controlled clinical trials

| Intervention | Proposed mechanism of action | Chemotherapy drug | Sample size | Outcome measure | Results | Reference |
|---|---|---|---|---|---|---|
| **Prevention** | | | | | | |
| Amifostine (AM) | Cytoprotective agent via detoxification and ROS scavenging | Platinum | 242<br>AM:122<br>PL: 120 | NCI-CTC after 6 cycles | NCI-CTC<br>grade 1 toxicity: AM: 29%, PL: 31%, grade 2: AM: 29%, PL: 35%, grade 3: AM: 9%, PL: 15%,<br>**P=0.029** | Kemp 1996[145] |
| Amifostine (AM) | Cytoprotective agent via detoxification and ROS scavenging | Carboplatin/paclitaxel | 187<br>AM: 93<br>PL: 94 | NCI-CTC Grade 3-4 neurotoxicity | AM: 3.7% (95% CI, 2.1 to 5.3)<br>PL: 7.2% (95% CI, 5.0 to 9.4)<br>**P=0.021** | Lorusso 2003[146] |
| Amitiptyline (AMI) | Affects descending noradrenergic pathways | Vinca alcaloids, platinum, or taxanes | 99<br>AMI:54<br>PL: 45 | Visual analogue scale (VAS) twice per week | No significant difference in neuropathy score at median of 19-21 wk follow up between AMI and PL groups<br>**P=n.s.** | Kautio 2009[147] |
| Calcium and magnesium (CaMg) infusions | Inhibits oxalate's action on Na+ channels | Oxaliplatin | 353<br>CaMg/CaMg:118, CaMg/PL:116<br>PL/PL: 119 | Sensory subscale of the EORTC QLQ-CIPN20 and CTCAE | CTCAE grade ≥ 2 neurotoxicity<br>CaMg/CaMg: 43%, CaMg/PL: 46%, PL/PL: 45%<br>**P=n.s.** | Loprinzi 2013[148] |
| Diethyldithio-carbamate (DDTC) | Chelation tissue-bound platinum | Platinum | 214<br>DDTC: 106<br>PL: 108 | NCI-CTC | DDTC: 13%,<br>PL: 12%;<br>**P=n.s.** | Gandara 1995[149] |
| Glutathione (GSH) | Antioxidant; decreases DRG platinum | Paclitaxel/carboplatin | 185<br>GSH: 94<br>PL: 91 | EORTC-QLQ-CIPN20 and CTCAE | Peripheral Neuropathy:<br>**P=0.21**<br>CTCAE grade ≥ 2neurotoxicity: GSH: 38%, PL: 33%<br>**P=0.449** | Leal 2013[150] |
| Glutathione (GSH) | Antioxidant; decreases DRG platinum | Cisplatin | 151<br>GSH: 74<br>PL: 77 | NCI-CTC | GSH: 39%, PL: 49%; P = .22 | Smyth 1997[151] |
| Vitamin E (Vit. E) | Antioxidant | Taxane, cisplatin, carboplatin, oxaliplatin, or combination | 189<br>Vit. E: 96<br>PL: 93 | CTCAE v 3.0 | Grade 2+: Vit E: 34%; PL: 29%;<br>**P=0.43** | Kottschade 2011[152] |
| Recombinant human leukemia inhibitory factor (rhuLIF) | Neuroprotective growth factor effect | Carboplatin and paclitaxel | 117<br>rhuLIF 2 μg/kg: 36;<br>rhuLIF 4 μg/kg: 39;<br>PL: 42 | CPNE score at cycle 4 | No significant differences seen in CPNE between time points for any treatment groups<br>**P=n.s.** | Davis 2005[153] |
| Calmangafodipir | Mimics the mitochondrial enzyme manganese superoxide dismutase by | FOLFOX-6 Folinic acid, 5-fluorouracil oxaliplatin | 173<br>PL= 60<br>Cal 2 μmol/kg=57; | CTCAE; Leonard Scale Questionnaire; NCI- | Trend toward decreased physician graded neurotoxicity<br>**P=0.16** | Glimelius 2017[154] |

| Intervention | Proposed mechanism of action | Chemotherapy drug | Sample size | Outcome measure | Results | Reference |
|---|---|---|---|---|---|---|
| **Prevention** | | | | | | |
| | protecting cells from oxidative stress | | 5 μmol/kg=45, 10 μmol/kg=11 | Sanofi ; cold allodynia test | Decreased PRO symptoms **P<0.01** | |
| Stop-and-Go Approach (earlier interruption of oxaliplatin and maintenance chemotherapy without it) | Less neurotoxic chemotherapy is administered before severe neurotoxicity develops | FOLFOX4 (Arm A) vs FOLFOX7 (Arm B) | 620 | NCI-Common Terminology Criteria for Adverse Events (CTCAE) | Grade 3 sensory neuropathy in 17.9% of the patients in arm A v 13.3% of patients in arm B **P=0.12** | Tournigand 2006[155] |
| Non Pharmacological Intervention Exercise (E) during chemotherapy vs Control group (C) | Reduction of inflammation; affects sensory processing in the brain | Taxane-, platinum-, or Vinca alkaloid-based | 355 E: 155 C: 185 | Patients reported grading of CIPN symptoms | Decreased temperature sensitivity **P=0.045** Decreased sensory symptoms **P=0.061** | Kleckner, 2018[97] |
| **Treatment** | | | | | | |
| Gabapentin | Inhibition of voltage-dependent calcium channels in DRG | Vinca alkaloids, platinum, or taxanes | 115 G/P: 57 P/G: 58 | NRS and ENS for ‘average’ daily pain at baseline and at the end of study | NSR scores for ‘average’ pain at study entry G/P; 4.3, P/G; 3.6 **P=0.06** at 1st phase G/P; 3.3, P/G; 3.1 **P=0.8** at 2nd phase G/P; 3.1 P/G 2.5 **P=0.2** | Rao, 2007[156] |
| Duloxetine (Dulox) | serotonin and norepinephrine reuptake inhibitor; sodium channel inhibition | Taxane or platinum | 231 Grp A: 115, dulox then cross over PL Grp B: 116, PL then cross over to dulox | BPI-SF “average pain” item | Grp A average pain decreased more than Grp B **P=0.003** | Smith 2013[157] |
| Topical amitriptyline, ketamine, with or without Baclofen (BAK) | Amitriptyline: alters sodium channel and adenosine A receptor Ketamine: blocks NMDA receptors Baclofen: GABA agonist | Vina alcaloids, platinum, taxanes, or thalidomide | 203 BAK: 101 PL: 102 | Change in sensory subscale EORTC-QLQ-CIPN20 score at 4 wks | Mean change from baseline of sensory subscale for BAK (8.1) versus PL (3.8) **P=0.053** | Barton 2011[158] |
| Lamotrigine (Lam) | Inhibits sodium channels, blocking release of glutamate and aspartate | Vinca alcaloids, platinum, or taxanes | 131 Lam: 63; PL: 62 | NRS and ENS at 10 wks | Mean NRS change from baseline for Lam (0.3) versus PL (0.5) **P=0.56** Mean ENS change from baseline for Lam (0.4) versus PL (0.3) **P=0.3** | Rao 2008[159] |

BPI-SF: Brief Pain Inventory-Short Form; CPNE: Standardized Composite Peripheral Nerve Electrophysiology Score; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; DRG: Dorsal Root Ganglia; ENS: Eastern Cooperative Oncology Group Neuropathy Scale; EORTC QLQ-CIPN20: European Organization for the Treatment of Cancer quality of life questionnaire-CIPN twenty item scale; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCI-Sanofi: oxaliplatin Sanofi questionnaire; NRS: Numerical Rating Scale; n.s: Not Statistically Significant; PL: Placebo; PRO: Patient Reported Outcome; ROS: Reactive Oxygen Species; VAS: Visual Analogue Scale;