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**REVIEW**

# Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives

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## ABSTRACT

**Background.** Chemotherapy with taxanes and platinum compounds has resulted in substantial survival benefits both in adjuvant and metastatic settings. However, as a side effect, such chemotherapy may cause peripheral neuropathy (CIPN) which may result in discontinuation of treatment, and if it persists after treatment completion, has a negative impact on quality of life (QoL).

**Results.** Symptoms of CIPN are sensory, like pain, numbness, and tingling, typically located in the hands and feet. For oxaliplatin, there is an acute form of CIPN, resulting in paraesthesias in the mouth and throat during or shortly after the infusion triggered by exposure to cold. Risks factors for CIPN include preexisting neuropathy, either from treatment with other neurotoxic agents, or from comorbid conditions. The incidence of CIPN is related to dose per cycle, cumulative dose, and duration of infusion. While cisplatin-induced neuropathy is irreversible, CIPN induced by taxanes may persist for several years in about 30% of patients. Evidence from the literature is suggestive that CIPN is likely to be negatively associated with QoL. No agents have been identified to be recommended for the prevention of CIPN. For treatment of CIPN, the best available data supports a moderate recommendation for treatment with duloxetine and evidence is inconclusive regarding the use of tricyclic antidepressants (such as nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine.

**Conclusion.** Research is still needed to predict which patients are at high risk of developing CIPN during treatment and in whom CIPN will persist after completion of chemotherapy.

During the past two decades survival after cancer treatment has improved considerably. In 2012, close to 14 million persons in the US had survived a cancer diagnosed since 1975 [1] and in the Nordic countries the equivalent number is close to 1.1 million [2]. Part of this improvement has been achieved by using modern chemotherapy with cytotoxic agents like taxanes and platinum compounds. Docetaxel and paclitaxel are used in the treatment of a number of cancers (breast, ovary, non-small cell lung, gastric, head and neck, prostate) while cisplatin, carboplatin, and oxaliplatin are essential in the treatment of cancers of the testes, ovary, cervix uteri, head and neck, colon, and rectum. Common for these agents are that they may cause peripheral neuropathy (CIPN) during treatment and thereby limiting the dose delivered [3], thus reducing the likelihood of an effective treatment. However, CIPN may also persist after treatment completion and potentially reduce quality of life (QoL), thus becoming a major survivorship issue.

A number of systematic reviews have been published covering the literature on CIPN up to 2013 [4–6] to which the readers are referred for such comprehensive information. This paper gives a brief summary of the most pertinent details.

## Results

### *Symptoms and clinical findings*

In general the symptoms of CIPN are sensory and include pain (dysesthesias, allodynia, hyperpathia), tingling (paresthesias), and/or numbness that is

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typically located in the hands and feet. Motor symptoms are more common than autonomic symptoms and occur with taxanes but are rare with platinum drugs as they must cross the blood-brain barrier to affect the anterior horn cells. Motor symptoms often present as distal or general weakness, muscle cramps, or gait dysfunction. Autonomic symptoms can include constipation or diarrhea, abnormalities of sweating, and lightheadedness and/or dizziness with positional changes [6]. Other signs include mononeuropathies, sometimes involving the cranial nerves and L'hermitte's sign [6]. Clinical findings include low or absent Achilles tendon reflexes and CIPN may also be associated with loss of temperature and vibration sensation, or orthostatic hypotension [5,6]. For platinum drugs sensory ataxia is not uncommon as a clinical finding, when gait dysfunction is developed [7]. The diagnosis of CIPN is generally made on clinical grounds but electrophysiologic testing can help confirm the diagnosis of CIPN and exclude other etiologies of neuropathic signs and symptoms [5,6]. Skin biopsies can be useful to verify small fiber neuropathy [8].

### *Taxanes*

Taxanes include docetaxel, paclitaxel, and cabazitaxel. They act by inhibiting disassembly of microtubules by binding to the beta-tubulin in the microtubules, thereby resulting in apoptosis of the cell. Other mechanisms of taxanes may include oxidative stress in cancer cells, altered signaling pathway causing inactivation of Bcl-2, a key role player of apoptosis and inhibition of angiogenesis [9].

*Risk factors, incidence, and duration of CIPN.* Risks factors for taxane-induced CIPN include preexisting neuropathy, either from treatment with other neurotoxic agents, or from comorbid conditions like diabetes [3,5,10]. The incidence of CIPN varies with dose per cycle, duration of infusion, cumulative dose, and treatment schedule [5,6]. For paclitaxel severe (grades 3/4) sensory neuropathy occurs in 20–35% of patients receiving 250 mg/m$^2$ every third week compared to 5–12% in patients receiving less than 200 mg/m$^2$ every third week [6]. Data are not as clear for weekly schedules, some reporting more frequent and others less frequent occurrence of neuropathy [4–6]. The duration of infusion may also be important with a reported incidence of CIPN grades 3/4 in 13% of patients receiving a high-dose (250 mg/m$^2$) paclitaxel infused over three hours compared with 7% when the same dose was infused over 24 hours [6]. Paclitaxel-induced CIPN grades 2–4 seem to occur at a mean cumulative dose of above 715–1500 mg/m$^2$ and docetaxel-induced CIPN at a mean dose of 371–600 mg/m$^2$ [6]. The incidence of paclitaxel-induced PN seems to be higher than docetaxel-induced PN [5]. For docetaxel 100 mg/m$^2$ every third week, 0–17% of the patients experienced CIPN grades 3/4 and for docetaxel 75 mg/m$^2$ CIPN grades 3/4 were reported by 2–4% of the patients [6]. The incidence of CIPN after treatment with cabazitaxel appears to be much lower, for all grades between 5–8% and for grades 3/4 from 0–0.5% [11].

Management of CIPN in clinical trials has included dose reduction, delays, or treatment discontinuation. Data are scarce on duration of CIPN after discontinuation or completion therapy. In 50% of patients treated with paclitaxel, symptoms regressed within nine months but persisted in about 40% of patients at three years [5]. Other data suggest that up to 80% of breast cancer patients complained about numbness one year after adjuvant treatment with paclitaxel [12]. For docetaxel, 36% of patients still complained about CIPN 1–13 years after treatment completion [13] while others have reported CIPN in 23–32% of patients at a median of 34 months after docetaxel [14].

*Pathogenesis of CIPN.* The exact mechanism of taxane-induced CIPN remains unclear. One theory states that taxanes cause disruption of the microtubulin structure leading to impairment of transportation of proteins and other components within the nerve resulting in a dying back neuropathy. The longest axons in the human body are the neurons to the hands and feet and these depend highly on transportation of nutrients, explaining why hands and feet are most often affected in CIPN. Another theory includes a toxic effect on mitochondria in primary afferent neurons leading to a deficit in axonal energy supply and thereby a sensory neuropathy [5].

### *Platinum compounds*

Platinum compounds include cisplatin, carboplatin and oxaliplatin and are activated by non-enzymatic hydrolysis to form platinum derivates causing DNA cross linking and thereby inhibiting DNA synthesis.

*Risk factors, incidence, and duration of CIPN.* The main risk factor for cisplatin-induced CIPN is the cumulative dose with most patients completing a full course of cisplatin (cumulative dose of 300–450 mg m$^2$) developing CIPN [15]. Cumulative doses of 600 mg/m$^2$ are associated with debilitating sensory ataxia. Data on dose of cisplatin per cycle are conflicting, some reporting an increased risk with high doses [4], others no effect of single dose [6]. It is important to consider that symptoms

of cisplatin-induced neuropathy may worsen or appear weeks to several months after completion of therapy – so called coasting [6].

The risk of carboplatin-induced neuropathy seems to increase in patients older than 65 years and if the patients have been treated previously with other neurotoxic agents. The symptoms are often less severe and less frequent (4–6%) [4–6].

The oxaliplatin-induced neuropathy differs from the others as it manifests in two clinical different forms – acute and chronic neuropathy. The acute form is not known in other platinum-compounds and is characterized by peripheral nerve hyper-excitability symptoms. Patients may experience paraesthesias in the mouth and throat [laryngo pharyngo dysesthesias (LPD)] during or shortly after the infusion. Occasionally muscular contractions occur resulting in jaw tightness and muscle cramps. Besides the LPD's and cramps, symptoms of cold-induced paresthesias in the distal extremities also appear shortly after infusion. Acute neuropathy is seen in the majority of patients treated with oxaliplatin (86%) and is triggered by exposure to cold. It is usually transient and resolves within hours or days [5]. Since the risk of acute oxaliplatin-induced neuropathy may depend on the infusion rate, it is often recommended to administer oxaliplatin as a 2–6 hour infusion to prevent recurrent LPD [4]. However, other studies indicate that short time infusion of oxaliplatin is feasible and apparently does not increase the severity of sensory neuropathy [16].

The second form is a chronic sensory neuropathy, which manifests primarily as sensory paresthesias, dysesthesias and sensory ataxia most often located in the extremities and persists between cycles. The risk of severe neuropathy is dose dependent, typically occurring in 10–20% of patients at cumulative doses of 750–850 mg/m$^2$ of oxaliplatin [4], and 50% of patients receiving cumulative doses of 1170 mg/m$^2$ will develop grade 3 neuropathy. An association has been made between cold-induced allodynia in relation to treatment, and the development of chronic neuropathy [7]. The probability of CIPN by cumulative dose of oxaliplatin was similar in patients with and without diabetes [17].

Initial clinical assessment studies have indicated that the chronic oxaliplatin-induced neuropathy was largely reversible with about 15% of patients having symptoms of neuropathy two years after treatment discontinuation. However, adding patient-reported outcomes increased the prevalence to about 60% of patients reporting lasting neuropathic symptoms interfering with function [4]. Thus, there is considerable variation in these estimates depending on whether they were made by clinicians or reported by the patients.

*Pathogenesis of CIPN.* The dorsal root ganglion appears to be the primary site of neural damage leading to an anterograde axonal degeneration in cisplatin and carboplatin-induced neuropathy [6]. Post-mortem studies have shown that cisplatin accumulates in dorsal root ganglion and that platinum levels in neural tissue were not observed to decrease with time [18]. The pathogenesis of the oxaliplatin-induced neuropathy differs somehow and has not been clearly resolved; however studies have suggested that the acute form of neuropathy is not a result of structural damage [19] but rather due to peripheral nerve hyperexcitability [20]. The hypothesis is that oxalate released from oxaliplatin causes rapid chelation of Ca2 + thereby interacting with ion-channels (primarily Na+ channels) leading to sensory and motor nerves hyperexcitability [21]. The persisting form of oxaliplatin-induced CIPN may mimic that of cisplatin and may arise from accumulation of platinum in the dorsal root ganglion cells leading to an anterograde axonal degeneration [22].

### *Prevention of CIPN*

A number of agents including anticonvulsants, antidepressants, vitamins, minerals, and other chemoprotectants have been tested in the prevention of CIPN but with disappointing results. The recently published American Society of Clinical Oncology Clinical Practice Guidelines, including a review of the literature [23], concluded that there are no agents recommended for the prevention of CIPN. Table I shows a list of agents which should *not* be offered to the patients for prevention. The review also concluded that no recommendation can be made for the use of N-acetylcysteine, carbamazepine, glutamate, glutathionen for patients receiving cisplatin or oxaliplatin-based chemotherapy, goshajinkigan, omega-3 fatty acids, or oxycarbazepine for the prevention of CIPN [23]. In a recent explorative analysis, we found that the risk of docetaxel-induced CIPN was reduced

Table I. Clinicians should *not* offer following agents for the prevention of CIPN.

| |
|---|
| Acetyl-L-carnitine (ALC) |
| Amifostine |
| Amitriptyline |
| CaMg for patients treated with oxaliplatin-based chemotherapy |
| Diethyldithio-carbamate (DDTC) |
| Glutathione (GSH) for patients treated with paclitaxel/ carboplatin chemotherapy |
| Nimodipine |
| Org 2766 |
| All-trans-retinoic acid |
| rhuLIF |
| Vitamin E |

by the use of frozen gloves and socks [3], but these results need verification from randomized trials.

### *Treatment of CIPN*

Several drugs have been tested for treatment of CIPN including antidepressants, anticonvulsants and a tropical gel, reviewed in the American Society of Clinical Oncology Clinical Practice Guidelines [23]. The best available data supported a moderate recommendation for treatment with duloxetine based on a randomized study of 231 patients. Duloxetine resulted in a greater reduction in pain than placebo [24] and a subgroup analysis suggested that duloxetine may be more efficacious for oxaliplatin-induced than paclitaxel-induced neuropathy. All CIPN trials were considered to be inconclusive regarding the use of tricyclic antidepressants (such as nortriptyline), gabapentin or pregabalin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine. However, these may be used due to their utility for other neuropathic conditions.

### *Influence of CIPN on quality of life (QoL)*

A recent review of the literature [25] identified 25 studies examining the influence of CIPN on QoL. The studies varied with respect to study design, patient population (cancer sites), number of included patients (range 14–1643), chemotherapy used, and methods to assess CIPN and QoL which made it difficult to draw any firm conclusions. Among 11 studies directly assessing the association between CIPN and QoL, eight found a negative association while three found no association. Fourteen other studies did not assess directly the association between CIPN and QoL, but described CIPN and QoL. The findings suggested that CIPN was likely to be negatively associated with QoL, i.e. that patients with CIPN had a poorer QoL.

## Discussion

Chemotherapy with taxanes and platinum compounds has resulted in substantial survival benefits both in adjuvant and metastatic settings. However, CIPN is a serious side effect which may limit the efficacy of the chemotherapy, and if it persists after treatment completion, have a negative impact on QoL.

There seems to be a general agreement that occurrence of CIPN sets a limit to the doses of chemotherapy with taxanes and platinum compounds which can be given safely. It is also well known that combinations of these agents will result in greater neurotoxicity than single agent administration [3,4]. However, the estimates of occurrence of CIPN during treatment and the consequences on dose intensity vary between studies. Among 1725 Danish breast cancer patients receiving at least one dose of docetaxel in the adjuvant setting, overall 34% reported CIPN grade 2–4 during treatment, 11% after the first cycle and 24% at later cycles. Only 54–56% of patients with neuropathy after the first cycle completed the planned dose intensity (no dose modifications, 100% dose on time) compared with 79–83% of patients without neuropathy [3]. This is in contrast to data from the E1199 trial of 4554 breast cancer patients who received either weekly or every third week treatment with paclitaxel or docetaxel where the investigators reported neuropathy grade 2–4 in 13–22% of the patients [10]. The proportion of patients requiring dose reductions did not differ significantly between patients who developed neuropathy compared with patients who did not, and the median dose intensity was similar. In a multivariable analysis, there was no significant association between taxane-induced neuropathy and all measures of survival. The main difference between these two trials is that the Danish data were based on patient-reported outcomes (CIPN) while the US trial used clinician-reported outcomes. This is the most likely explanation for the discrepancy in occurrence of taxane-induced neuropathy. Since the Danish trial data are not yet mature for analysis of survival, we shall have to wait to see the effect of dose reductions if any.

Discrepancies between clinician- and patient-reported outcomes not only affect estimates of occurrence but also persistence of CIPN, clinicians typically reporting fewer events, of milder degree, and with a later onset than the patients [4]. In addition, many clinical trials stop assessment for toxicity at one month after treatment completion, leaving the remaining toxicities unresolved, but giving no estimates of duration of such toxicity. A number of different grading scales have been developed which are recommended for a more standardized assessment of CIPN [4] while the gold standard for diagnostic purposes is comprehensive clinical history, physical examination, and electrophysiological testing, however as previously described skin biopsies can be useful to verify small fiber neuropathy [8]. Lack of standardization has also affected the evaluation of effect of CIPN on QoL though most studies indicated that CIPN has a negative influence on QoL, but the evidence is not entirely conclusive [25].

Unfortunately, no effective treatment has been identified to prevent the occurrence of CIPN and the treatment options are not specific for CIPN but rather general as for other neuropathic conditions [23]. One reason for the lack of therapeutic options may be that the exact mechanisms causing CIPN remain to be clarified. Another area of research

is pharmacogenetic techniques to identify genetic polymorphisms which may determine differences in susceptibility to CIPN in individuals [4]. So far, such research has not resulted in tests which can be applied clinically.

## Conclusion

CIPN is a serious side effect of chemotherapy with taxanes and platinum compounds which may be dose limiting and persist or worsen after completion of treatment. CIPN is likely to have a negative influence on QoL. There is no effective prevention or treatment. A number of research areas are suggested.

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