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# Prevention and Management of Chemotherapy-Induced Polyneuropathy

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**Keywords**

Chemotherapy-induced peripheral neurotoxicity · Neuropathic pain · Side effects · Duloxetine · Neurotoxicity

**Abstract**

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a severe and common side effect caused by a variety of antineoplastic agents. Approximately 30–40% of patients treated with agents such as taxanes, vinca alkaloids, or platinum derivatives will develop CIPN. CIPN presents predominantly as a sensory axonal neuro(no)pathy with occasional motor and autonomic dysfunction exhibiting considerable variability of clinical symptoms ranging from mild tingling sensation to severe neuropathic pain. Typical symptoms include numbness ("minus symptom"), weakness, and abnormal gait as well as paresthesia and pain ("positive symptoms"). As CIPN symptoms potentially lead to long-term morbidity and can even aggravate after cessation of therapy, patients' quality of life can be tremendously affected. In view of improved breast cancer survival outcomes, the late effects of CIPN are an unmet need in these patients. Therefore, early detection and assessment of first symptoms is important to effectively prevent severe CIPN. Therapeutic options for patients with CIPN are still limited, and pharmacological treatment focuses primarily on reduction or relief of neuropathic pain. CIPN is usually acutely managed by dose reduction or discontinuation of causative chemotherapy, potentially compromising treatment outcome. Currently, there is no causative proven therapy for the prevention of CIPN.



## Introduction

Peripheral neurotoxicity due to antineoplastic therapy is a common and often dose-limiting side effect. The risk of potential short- and long-term impairment of quality of life must be balanced against the benefits of cancer treatment. Over the years the term "CIPN" has been well established to describe primarily chemotherapy-induced peripheral neuropathy but should also be used to describe neurotoxicity deriving from newer targeted agents. Putative targets of neurotoxicity therefore include dorsal root ganglia (leading to so-called neuronopathy), axon and axonal components (myelin, microtubules, mitochondria, vascular network) as well as distal nerve terminals [1]. CIPN in breast cancer is often caused by taxanes, whereas nanoparticle albumin bound (nab)-paclitaxel, carboplatin, eribulin, and vinorelbine may also lead to significant CIPN. Faced with improved survival outcomes of early and metastatic breast cancer, research into improving the quality of survivorship – notably CIPN – is still an unmet need in these patients. This review gives an overview of CIPN and summarizes the latest recommendations on diagnosis, prevention, and treatment of peripheral neuropathy.

## Incidence and Risk Factors

Incidence and severity of CIPN vary according to antineoplastic agents, cumulative dose, duration of exposure, scheduling, and combination of different agents.

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**Table 1.** Incidence and therapy-associated risk factors for selected antineoplastic agents [1, 6]

| Agent | Therapy-associated risk factors | | | |
|---|---|---|---|---|
| Cisplatin | Increased risk of neurotoxicity >300 mg/m$^2$ | | | |
| Incidence | Single dose[1] | Cumulative dose[2] | Infusion time | Duration of treatment |
| Grade 1–2 (14–63%) | Relevant | Relevant | Not relevant | Not relevant |
| Grade 3–4 (7–21%) | | | | |
| Clinical symptoms | Predominantly sensory neuropathy | | | |
| Taxanes +/– carboplatin | Increased risk of neurotoxicity (docetaxel: >100 mg/m$^2$; paclitaxel: 250 mg/m$^2$) | | | |
| Incidence | Single dose[1] | Cumulative dose[2] | Infusion time[3] | Duration of treatment |
| Grade 1–2 (20–50%) | Relevant | Relevant | Relevant | Not relevant |
| Grade 3–4 (6–20%) | | | | |
| Clinical symptoms | Predominantly sensory neuropathy; in higher doses myalgia and myopathies possible | | | |
| Eribulin | | | | |
| Incidence | Single dose | Cumulative dose | Infusion time | Duration of treatment |
| Grade 1–4 (–35%) | No data | No data | No data | No data |
| Grade 3–4 (–8%) | | | | |
| Clinical symptoms | Sensory neuropathy, myalgia | | | |

[1] Single dose: higher single doses carry the risk of increased neurotoxicity. [2] Cumulative doses: higher cumulative doses increase the risk of neurotoxicity. [3] Prolonged infusion time seems to reduce the risk of neurotoxicity.

Remarkably, paclitaxel and carboplatin combination treatment is generally associated with similar neurotoxicity to paclitaxel alone [2]. Examples are shown in Table 1. Clinical symptoms of CIPN reflect a predominantly sensory axonal neuro(no)pathy with occasional motor and autonomic involvement in a predominant "glove and stocking" distribution. Typically, primarily sensory fibres are affected but some cytostatic agents also cause a sensorimotor pattern. Typical symptoms include numbness, paresthesia, lancinating pain, abnormal gait, and motor weakness. It is important to consider that CIPN may persist for many years beyond antineoplastic therapy and is associated with an increased risk of falls [3]. After completion of paclitaxel chemotherapy, approximately one-half of patients improve over a period of 4–6 months [4]. In this study, up to 80% of patients still had neuropathic symptoms up to 2 years following completion of treatment. Of these patients, 25% still had severe symptoms such as numbness in hands and feet.

Strong independent individual risk factors for developing CIPN are diabetes mellitus, age [5], and concurrent exposure to other neurotoxic agents as well as pre-existing neuropathy. Furthermore, alcohol abuse, metabolic diseases such as renal insufficiency, hypothyroidism, vitamin deficiency (e.g., $B_1$, $B_6$, $B_{12}$), and pre-existing hereditary neuropathies like CMT1A are considered to be risk factors [6]. The search for genetic markers carrying a high risk for developing CIPN has been unsuccessful for use in clinical practice so far [7].

## Assessment and Diagnosis of CIPN

Symptoms of CIPN typically occur during the first 2 months of treatment, progress during active antineoplastic treatment, and then usually stabilize soon after treatment is completed. However, worsening of neuropathic symptoms after cessation of therapy called "coasting phenomenon" must be considered (e.g., paclitaxel). Coasting phenomenon is explained by drugs persisting in nerve axons after finishing therapy that lead to ongoing toxicity [8]. It should be acknowledged that there is considerable variability of symptoms depending on the agent used and the individual risk factors of the patient.

Typical clinical symptoms are predominantly sensory and usually include acral pain and paresthesia (tingling like pins and needles), accompanied by allodynia and hyperalgesia ("plus symptoms"). Sensory loss appears in a "glove and stocking type" distribution and leads to "minus" symptoms like numbness in hands and feet including impaired perception of light touch, vibration sense, and proprioception (tuning fork test) in clinical examination.

Vinca alkaloids and taxanes cause small fibre neuropathy, affecting the nerve terminals. As a result, patients experience the typical burning feet and hands and even lancinating pain. Decreased pain perception, hyperalgesia, and reduced temperature sensation are typical symptoms in clinical examination. Small fibre damage typically also shows autonomic involvement which may include abdominal pain, constipation, postural hypotension, disturbances of bladder, delayed gastric emptying, and reduced variability of heart rate.

## Neurophysiological Examination

Nerve conduction studies and electromyography may be helpful in characterizing neuropathies (e.g., axonal vs. demyelinating) and provide additional information. However, diagnosis of CIPN is preferentially based on patients' complaints (patient-reported outcomes and grading scales) and neurological examination (functional measures). A progressive reduction in sensory nerve action potential amplitude (compound muscle action potential if motor fibres are affected) indicates axonal degeneration and is followed by impairment of nerve conduction velocity. Again, patients' symptoms and severity of CIPN during therapy cannot be adequately reflected using conventional nerve conduction parameters. Of note, in small fibre neuropathies all findings based on standard neurophysiological techniques are normal and only skin biopsy (gold standard) may demonstrate degeneration of small C (heat) and Aδ (cold) fibres.

## Assessment Tools Including Patient-Reported Outcome Measurements

Various tools are available, some for clinical trials and some for daily clinical practice. Domains included in the assessment tools are often narrow but deliver important information [9]. Many trials confirmed that patient-reported outcome measurements identified a higher incidence and severity of treatment-related toxicities than did clinician-reported outcome measurements [10].

The typical example for a clinician-reported outcome measurement is represented by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). This assessment still remains the most commonly utilized tool. Cavaletti's Total Neuropathy Score clinical version (TNSc) can be used with good interrater reliability. As such, the TNS can detect very early changes occurring in the peripheral nervous system even at subclinical level.

Patient-reported outcome measurement assessment includes for example, the EORTC CIPN20 and the Fact-GOG-NTX12.

*EORTC CIPN20.* The CIPN20 is a 20-item quality of life questionnaire, which has been developed to elicit patients' experience of symptoms and functional limitations related to CIPN. The CIPN20 has three subscales: a sensory, motor, and autonomic subscale.

*Fact-GOG-NT.* This 12-question tool requests the user to circle or mark one number per line to indicate the response as it applies to the past 7 days. The forms can be filled out by either patient or caregiver while at the clinic. This type of tool also gives caregivers a chance to report their observations if the patient is not able to converse easily or does not want to report something that may affect the therapy [1].

In order to address symptomatic differences between chemotherapeutic agents (e.g., cisplatin and taxanes), various chemotherapy-specific scales have also been developed [11]. FACT-Taxane consists of both FACT-General and an added taxane subscale. The subscale has 16 items, including an 11-item neurotoxicity subscale and 5 additional taxane-specific questions related to the effects of arthralgia, myalgia, and skin changes.

## Prevention of CIPN

*Pharmacological Intervention*

To date, no suitable drug has been found to effectively prevent CIPN pharmacologically. Use of acetyl-L-carnitine, acetylcystein, α-lipoic acid, amifostine, amitriptyline, calcium/magnesium, carbamazepine, diethyldithiocarbamate, glutathione, gosha-jinki-gan, minocycline, nimodipine, omega-3 fatty acids, vitamin B, and also vitamin E has been investigated in the prevention of peripheral neuropathy in clinical trials. However, none of these has yet led to positive results [12–24]. Results, however, must be interpreted with caution: trials in this area are often underpowered and heterogeneous.

*Nurse-Led Intervention*

The efficacy of a nurse-led care program in improving quality of life outcomes in patients receiving adjuvant chemotherapy for breast cancer was investigated in a randomized trial (routine hospital care vs. both hospital and nurse-led care). The intervention included regular phone consultations every 1–2 weeks. The primary endpoint of difference in FACT-General score was surprisingly not reached. However various important secondary endpoints were reached. In summary, this study showed the complexity of factors that contribute to CIPN, and underline the potential role of non-pharmacological interventions such as modulation of pain perception of CIPN [25].

*Cryotherapy/Compression Therapy*

For non-pharmacological prevention of CIPN, cryotherapy with frozen socks or gloves seems to be effective, although evidence is still scarce. In a pilot trial with 20 breast cancer patients receiving weekly paclitaxel one limb was cooled, and the contralateral limb acted as a control. The hypothermia process reduces skin temperature by 1.5 ± 0.7 °C. The amount of skin cooling was significantly associated with preservation of motor nerve amplitude after 6 months ($p < 0.0005$) [26]. Another study with 40 patients confirms these observa-



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tions: when wearing frozen gloves and socks on the dominant side for 90 min during paclitaxel infusion, patients had diminished objective and subjective symptoms of CIPN as compared to the non-dominant, untreated side [27]. Larger studies still need to confirm these findings, and in particular practicability of the treatment as frozen socks and gloves can also cause significant discomfort.

Another protective effect may be noted for compression therapy using surgical gloves. In a small study with 42 patients receiving nab-paclitaxel, patients acted as their own control wearing surgical gloves on one hand and leaving the other hand ungloved. The gloved hand was compressed using gloves a size smaller. Less neuropathy was seen in the gloved versus the ungloved hand [28]. Compression therapy pursues the same approach as hypothermia by reducing blood flow in cold tissue as the fingertips of the glove-protected hand had a significant lower temperature than the ungloved hand.

*Exercise*

Early studies suggest a protective effect of exercise and functional training on CIPN, therefore it is advisable to encourage patients – if there are no contraindications – to strengthen their muscles and improve sensorimotor function [6].

*Acupuncture (Prevention and Therapy)*

Studies investigating the effectiveness of acupuncture to prevent or treat CIPN are often underpowered and without a control group and therefore not sufficient to support or refute its use. In a phase IIa single-arm clinical trial, acupuncture was useful for 27 breast cancer patients, who developed grade 2 CIPN due to weekly paclitaxel to prevent escalation of CIPN to higher grades (NCI-CTCAE, Version 4.0) [29]. Another single-arm observational study with only 10 patients with breast cancer showed effectiveness in reducing taxane-induced peripheral neuropathic pain [30]. In both studies, acupuncture was well tolerated, and patients reported no adverse events. However, study results are inconclusive (also in other patient populations) and do not allow a positive recommendation.

## Treatment of CIPN

Efficacious therapeutic options for patients with established CIPN are still limited. Special attention should therefore be paid to the onset and severity of the symptoms during the antineoplastic treatment in order to reduce the dose if necessary or to change antineoplastic therapy. If symptoms and functional limitations have occurred, detailed patient advice is necessary and effective.

*Behaviourally Based Techniques*

To reduce pain deriving from CIPN, the self-guided online cognitive and behaviourally based pain management intervention PROSPECT (Proactive Self-Management Program for Effects of Cancer Treatment) was successful in a pilot trial with 60 patients (mean age >60 years) [31]. In a randomized setting, patients received PROSPECT or standard care over 8 weeks. Patients in the intervention (PROSPECT) group had greater improvements in "worst" pain than patients with standard care alone.

*Exercise*

Physical exercise is often applied in multimodal settings; therefore, many patients receive this as part of their standard treatment. Owing to this fact, there is a lack of strong scientific evidence about its specific usefulness in the treatment of CIPN. Nevertheless, the number of studies showing the effectiveness of physical exercise and functional training (e.g., vibration training) is increasing [32, 33]. To improve coordination, sensorimotor function, and fine motor function the training should begin with the onset of manifest CIPN at the latest. It would be advisable to initiate exercise at the time potentially neurotoxic cancer treatment is initiated [6]. Improvement of physical function is particularly important in the prevention of malnutrition and improvement of physical function in order to prevent disability and falls, especially in elderly patients [3].

*Pharmacological Treatment*

As there are no pharmacological interventions to reduce numbness, paresthesia, or motor weakness, treatment for patients with chronic CIPN focuses on reduction or relief of neuropathic pain (so-called plus symptoms).

In a cross-over study by Smith et al. [34], duloxetine, a selective serotonin reuptake inhibitor, showed moderate clinical benefits in patients with painful CIPN. A total of 231 patients treated with platinum derivatives or taxanes with grade ≥1 neuropathy (according to NCI-CTCAE scale) and at least 4 points on a neuropathic pain scale of 0–10 points received duloxetine or placebo. More patients with duloxetine reported a significant decrease in neuropathic pain (59 vs. 38%), noting that the effect of duloxetine on platinum-induced neuropathic pain was greater than the effect of taxane-induced neuropathic pain.

If duloxetine treatment has failed or is not indicated, anticonvulsants or tricyclic antidepressants may have the potential for symptom control in patients with CIPN. However, evidence specifically in CIPN is still limited. As such, the treatment approach is analogous to usage of these drugs in other forms of neuropathic pain.

Mishra et al. [35] investigated the efficacy of amitriptyline, gabapentin, pregabalin or placebo in 120 cancer patients with neuropathic pain. In all 4 groups a signifi-

cant reduction of the pain level (VAS 100 mm) was achieved after the intervention. The most pronounced improvement of neuropathic pain was obtained in the pregabalin arm (compared to amitriptyline $p = 0.003$, gabapentin $p = 0.042$, and placebo $p = 0.042$).

In a study with 131 patients receiving lamotrigine or placebo after or during treatment with taxanes, vinca alkaloids, or platinum derivatives, no improvement in neuropathic pain could be shown. However, the lamotrigine arm detected a noticeably high dropout rate [36]. Opioids may be also useful to relieve neuropathic pain, but this has only been proven for neuropathic pain from causes other than antineoplastic therapies [37, 38].

Topical local interventions may be helpful, particularly in small fibre affection of peripheral nerves. Substantial pain relief in 31 out of 38 evaluable patients was shown in a phase II trial using 1% menthol cream to the affected area [39]. Since menthol cream has no noted side effects and is inexpensive, it could be worth investigating its use further, although randomized data are lacking. Non-CIPN studies showed benefit using 8% capsaicin-containing patches in patients with painful neuropathies [40] and attempts were made to try this also in patients with CIPN [38]. A topical 4% amitriptyline/2% ketamine preparation was studied in 462 patients in an RCT showing that neuropathic pain, numbness, or tingling could not be alleviated [41].

It must be acknowledged, however, that perception of neuropathic pain may be aggravated by sleep disturbance, anxiety, depression, and central sensitization of pain, a holistic treatment concept is therefore mandatory.

## Conclusion

Considering the increasing prevalence of cancer, wider scope of chemotherapy drugs, and long-term side effects, patients with polyneuropathy will present with many issues and not only physical findings. In view of the large scale of patient numbers and prevalence, polyneuropathy as an important side effect of antineoplastic treatments must be addressed as a so far unmet need. Quality of life issues and rehabilitation concepts for long-term functional deficits will be future directions for research.


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