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Chemotherapy-Induced Peripheral Neuropathy

A review of strategies to reduce and manage common symptoms.

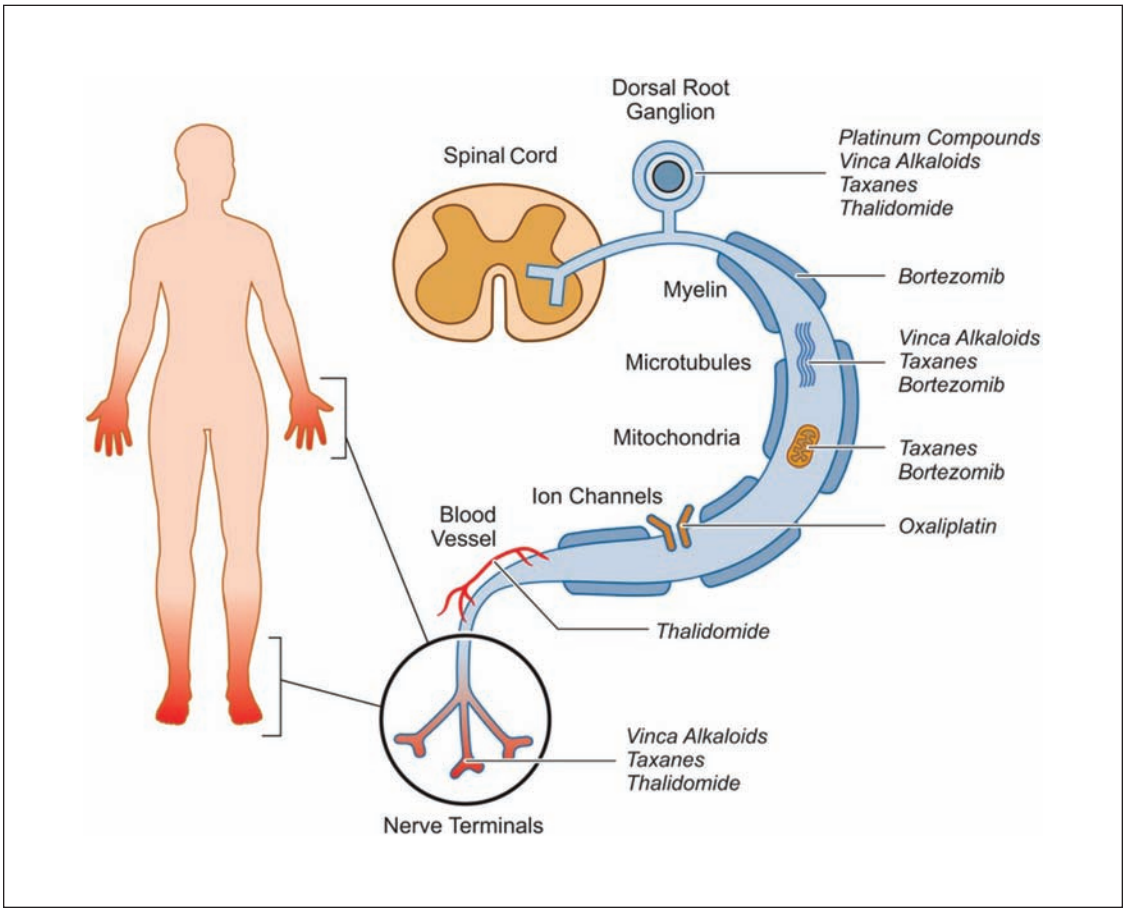
ABSTRACT: Chemotherapy-induced peripheral neuropathy (CIPN) occurs in more than 68% of patients receiving the neurotoxic chemotherapy agents commonly used to treat breast, gastrointestinal, gynecologic, and hematologic malignancies. CIPN, often experienced initially as numbness, tingling, or pain in the upper or lower extremities, may progress to the point where the resultant decline in physical function requires a reduction in the chemotherapy dose. This article provides nurses with strategies to use in assessing, managing, and educating patients who are at risk for or who are already experiencing CIPN. Currently, the American Society of Clinical Oncology endorses only one treatment for CIPN: duloxetine 60 mg/day. Discussing CIPN with patients before chemotherapy is initiated and throughout the course of treatment promotes its early identification and management, which may minimize its impact on physical function and chemotherapy dosing, reducing the patient's risk of experiencing chronic symptoms after chemotherapy ends.

Keywords: chemotherapy-induced adverse effects, chemotherapy-induced peripheral neuropathy, neurotoxic chemotherapy, oncology nursing, peripheral nervous system dysfunction

More than 68% of patients receiving neurotoxic chemotherapy report chemotherapy-induced peripheral neuropathy (CIPN) within a month of completing this treatment with such agents as taxanes, platinums, vinca alkaloids, proteasome inhibitors, and antiangiogenic drugs.[1] CIPN may manifest as numbness, tingling, or shooting pain in the bilateral upper or lower extremities following neurotoxic chemotherapy administration. CIPN can occur as early as the first chemotherapy infusion and persist for 12 months or more after treatment is completed.[2] As CIPN symptoms become more severe throughout the course of chemotherapy, patients and clinicians may face the dilemma of choosing whether to reduce chemotherapy, or even stop it altogether, to prevent worsening CIPN.[3] It's a difficult choice between either receiving less than the optimal chemotherapy dose to treat the cancer, thus increasing the risk of death, or potentially contributing to long-lasting, debilitating CIPN, which may reduce physical function and increase the risk of falling,[4] thereby compounding patients' health care costs and possibly impeding their return to work.

Despite the published evidence demonstrating the detrimental effects of CIPN on chemotherapy dosing and physical function, documentation of CIPN assessment and management is infrequently integrated into provider workflow. A review of 48 electronic health records revealed that breast oncology NPs and physician assistants providing care to women receiving neurotoxic chemotherapy documented numbness or tingling in approximately 58% of the records reviewed.[5] Notably, the providers adhered to the National Comprehensive

Figure 1. Progression and Potential Causes of CIPN Symptoms



The typical distal to proximal progression of CIPN symptoms, such as those starting in the hands and feet, results from various mechanisms of chemotherapy-induced damage to putative targets in the peripheral nervous system—from the dorsal root ganglion, axon, and axonal components (myelin, microtubules, mitochrondria, ion channels, and blood vessels), to the distal nerve terminals. Reprinted with permission from Park SB, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. *CA Cancer J Clin* 2013;63(6):419-37.

Cancer Network guidelines for the management of nonpainful CIPN for only six of the 12 patients reporting it.[5]

Nurses are uniquely positioned to positively influence patients' CIPN symptom experience because they frequently interact both with patients to assess symptoms and teach them about symptom management and with other clinicians to generate treatment recommendations based on symptom presentation. This article provides nurses with a variety of strategies for assessing and managing CIPN, and for teaching patients about this frequent complication of chemotherapy—before, during, and after neurotoxic chemotherapy is administered.

COMMON SYMPTOMS OF CIPN

The symptom presentation of CIPN is complex and varies with the specific chemotherapy agent used. Generally, neurotoxic chemotherapy is thought to cause CIPN by inducing a progressive distal to proximal ("dying-back") axonal degeneration, though the mechanism by which neurotoxic agents induce this degeneration (through altered axonal transport, intracellular calcium^{2+} dynamics, or mitochondrial dysfunction, for example) varies.[6] Consistent with the proposed underlying pathophysiology, CIPN symptoms begin in the fingers or toes and progress proximally (see Figure 1). In addition to sensory symptoms, including numbness, tingling, or pain, the platinum compounds (oxaliplatin, cisplatin, or car-

boplatin) and the vinca alkaloids (vincristine or vinblastine) may produce motor symptoms such as muscle weakness or cramping. Moreover, autonomic symptoms such as dizziness or hearing difficulties may follow the administration of either the vinca alkaloids or the antiangiogenesis agents (thalidomide and lenalidomide).[7] As a result of its multifaceted nature, CIPN is difficult to assess and quantify.

STANDARDIZED TOOLS FOR ASSESSING CIPN

While there is a plethora of standardized CIPN measures, none is currently considered the gold standard. In both research and clinical practice, common toxicity criteria scales, such as the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), the Eastern Cooperative Oncology Group criteria, the Ajani scale, and the World Health Organization neurotoxicity scale, are most often used to assess CIPN but such scales have demonstrated poor interrater reliability.[8] For this reason, they should not be the first choice for CIPN measurement.

There are at least 16 different CIPN patient-reported outcome measures, though there is no consensus as to which is optimal, and the more comprehensive patient-reported outcome measures may not be feasible to administer in practice because of the number of questions and the burdensome scoring procedures.[8]

The Total Neuropathy Score (TNS), which takes into account not only objective measures, including reflex, vibration sensibility, and strength, but also subjective findings, such as sensory and motor symptoms, has demonstrated strong reliability and validity.[8,9] Administration, however, is time consuming and involves special tools (a vibrameter and nerve conduction studies), which require training.[8] Simplified variants of the original 10-item TNS have been developed to facilitate CIPN assessment in routine practice. These include the TNS reduced version (TNSr), which does not require vibrameter use, and the TNS clinical version (TNSc), which eliminates both vibrameter use and nerve conduction studies.[8]

After a systematic review of 117 CIPN assessment tools, the six highest scoring of these—three patient-reported outcome assessments: the CIPN Assessment Tool, the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) subscale, and the Patient Neurotoxicity Questionnaire (PNQ); as well as three clinician-administered measures: the GOG toxicity criteria, the TNSc, and the TNSr—were included in a Delphi survey of 24 physicians, six oncology nurse consultants, and two consumers. The PNQ and the TNSc received the highest survey ratings of the patient-reported outcome assessments and the clinician-administered measures, respectively.[10]

SIMPLE CIPN ASSESSMENT STRATEGIES

In the absence of a gold standard for assessing CIPN, nurses working in an oncology setting may use the following approaches.

Screen for related sensory impairments. Ask patients whether they have experienced any numbness, tingling, pain, "pins and needles," or sensations resembling burning or electric shock, and whether they have felt that their hands or feet were ice cold or had "fallen asleep." Using a number of neuropathic descriptors may help patients identify related symptoms because patients with CIPN may have difficulty describing how it feels.

Assess physical function related to CIPN. Ask patients if they have any difficulty completing tasks of daily living, such as buttoning a shirt; using a fork, knife, or pen; typing; opening a jar; or walking.

Screen for motor-related impairments. Assess hand grip, wrist extension, ankle dorsiflexion strength, and gait.

Screening standardization may be improved by using measures that have demonstrated clinical feasibility, such as the numbness and tingling items of the patient-reported outcomes version of the CTCAE (PRO-CTCAE), which asks patients to rate the severity of these CIPN symptoms and the degree to which they have interfered with daily activities over the past seven days.[11] PRO-CTCAE numbness and tingling items have demonstrated strong concurrent validity with more comprehensive CIPN outcome measures,[12] such as the FACT/GOG-Ntx.[13] The PRO-CTCAE is available for free download on the NCI website (see https://healthcaredelivery.cancer.gov/pro-ctcae). Furthermore, electronic administration of PRO-CTCAE items has been shown to be feasible in oncology practice.[14]

PRECHEMOTHERAPY ASSESSMENT

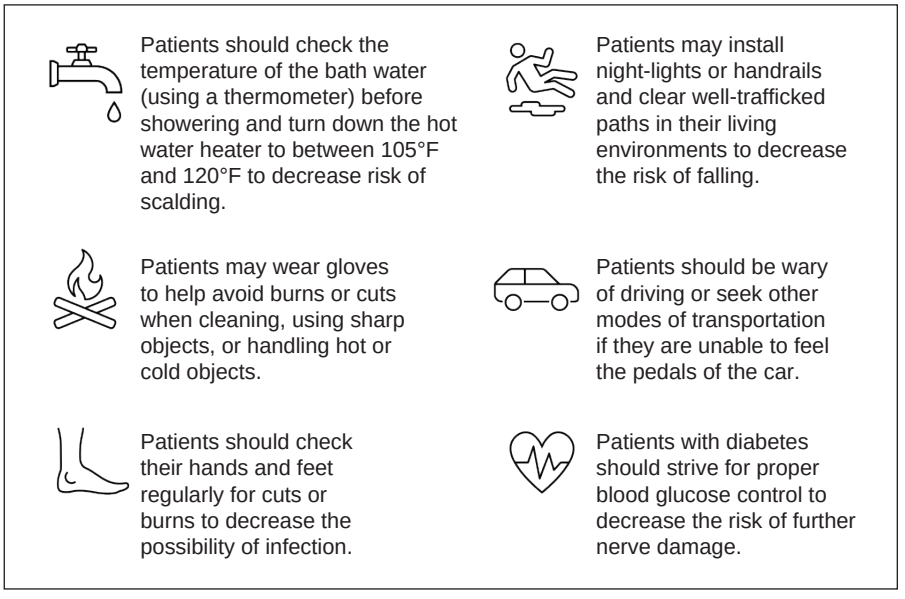
To establish a baseline, patients should be assessed for peripheral neuropathy before neurotoxic chemotherapy is initiated. Specifically, they should be evaluated for neuropathy from other causes, such as diabetes; prior CIPN or neurotoxic chemotherapy exposure; nutritional deficits; and such factors as advanced age, heavy alcohol use, and high body mass index, all of which may increase patients' risk of developing CIPN.[7] Patients whose medical history includes CIPN risk factors should be closely monitored during chemotherapy.

ASSESSMENT THROUGHOUT CHEMOTHERAPY

Once treatment begins, patients should be assessed for CIPN at every visit associated with neurotoxic chemotherapy administration, as the cumulative dose of a neurotoxic agent is the most important predictor of chronic CIPN. CIPN symptoms tend to increase in duration and severity following each neurotoxic chemotherapy infusion, with specific

agents associated with sensory or motor symptoms. For example, in the days following oxaliplatin infusion, patients frequently experience acute neurotoxicity, which may manifest as muscle cramping or ice-cold sensations in the mouth, throat, or extremities when drinking or touching cold items.[15]

Figure 2. Safety Tips for Patients with CIPN[20]



POSTCHEMOTHERAPY ASSESSMENT

CIPN assessment should continue even after the completion of neurotoxic chemotherapy. Approximately 30% of patients who receive neurotoxic chemotherapy experience chronic CIPN six months or more after the completion of treatment.[1] Patients receiving platinum-based chemotherapy or vincristine may experience the phenomenon known as "coasting," in which CIPN symptoms increase in severity or frequency in the months following the final neurotoxic chemotherapy treatment.[15, 16]

PHARMACOLOGICAL MANAGEMENT OF CIPN

Currently, duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is the only first-line treatment recommended by the American Society of Clinical Oncology (ASCO) for managing painful CIPN,[3] though the U.S. Food and Drug Administration has not approved painful CIPN as an indication for duloxetine use.

The evidence for the ASCO recommendation of duloxetine for managing CIPN-related pain stemmed from a randomized, double-blind, placebo-controlled crossover trial that was conducted at eight NCI-funded cooperative research networks and included 231 patients in which duloxetine resulted in greater pain reduction than placebo.[17] ASCO clinical practice guidelines suggest that duloxetine may be used off-label for moderate-to-severe CIPN-related pain occurring during or after neurotoxic chemotherapy treatment.[3]

CAN CIPN BE PREVENTED?

There is no strong evidence to support the use of any interventions for CIPN prevention, such as vitamin B, alpha lipoic acid, gabapentin, venlafaxine, acetyl-L-carnitine, or calcium and magnesium infusions.[3] Although the anticonvulsant gabapentin is often prescribed for CIPN,[18] it is not recommended for CIPN management by the ASCO clinical practice guidelines as there is no evidence from large clinical trials to suggest that gabapentin reduces CIPN severity.[3]

Chemotherapy dose reductions. Clinicians often reduce doses of neurotoxic chemotherapy when patients begin to experience moderate-to-severe CIPN-related pain or functional impairment to prevent worsening of CIPN. Nurses may consider referring such patients to physical or occupational rehabilitation.[19] If concerned that a patient may be at increased risk for CIPN before even starting neurotoxic chemotherapy because of CIPN risk factors such as diabetes, HIV, kidney disease, or previous neurotoxic chemotherapy exposure, nurses may recommend reducing the dose of the neurotoxic chemotherapy agent or seeking a potential alternative to the therapy while closely monitoring and managing coexisting conditions known to increase CIPN risk.

HELPING PATIENTS MANAGE CIPN

Patients with CIPN are at an increased risk for injury due to a loss of sensation or strength in their upper or lower extremities. Loss of sensation in the feet may make it hard for patients to feel the ground when walking, whereas loss of sensation in the hands may make it difficult to feel hot temperatures or sharp objects (see Figure 2[20]).

Benefits of exercise. Although no clinical practice guidelines recommend nonpharmacological or self-management modalities for preventing or managing CIPN,[3] emerging evidence supports the benefits of exercise, particularly balance and aerobic exercises, for patients with CIPN.[21] While clear evidence supporting exercise for CIPN remains limited, exercise is generally safe and can be highly beneficial for most cancer survivors. In addition, strong evidence suggests that exercise may positively affect other common cancer treatment–related adverse effects, such as depression, anxiety, reduced quality of life, fatigue, and decline in physical function.[22] Before

beginning a structured exercise program, patients with CIPN should undergo a medical evaluation by a physician or nurse.

DISCUSSING CIPN WITH PATIENTS

Because of the lack of effective CIPN treatments, communicating with patients to help them identify changes in CIPN throughout neurotoxic chemotherapy treatment plays an important role in helping patients manage its early signs and symptoms, preventing the development of chronic CIPN, and reducing patients' risk of CIPN-related injury. ▼

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REFERENCES

1. Seretny M, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain* 2014;155(12):2461-70.
2. Pachman DR, et al. Comparison of oxaliplatin and paclitaxel-induced neuropathy (Alliance A151505). *Support Care Cancer* 2016;24(12):5059-68.
3. Loprinzi CL, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. *J Clin Oncol* 2020;38(28):3325-48.
4. Winters-Stone KM, et al. Falls, functioning, and disability among women with persistent symptoms of chemotherapy-induced peripheral neuropathy. *J Clin Oncol* 2017;35(23):2604-12.
5. Knoerl R, et al. Chemotherapy-induced peripheral neuropathy: use of an electronic care planning system to improve adherence to recommended assessment and management practices. *Clin J Oncol Nurs* 2018;22(5):E134-E140.
6. Fukuda Y, et al. A mechanistic understanding of axon degeneration in chemotherapy-induced peripheral neuropathy. *Front Neurosci* 2017;11:481.
7. Kanzawa-Lee GA. Chemotherapy-induced peripheral neuropathy: nursing implications. *J Infus Nurs* 2020;43(3):155-66.
8. Park SB, et al. Overview and critical revision of clinical assessment tools in chemotherapy-induced peripheral neurotoxicity. *J Peripher Nerv Syst* 2019;24 Suppl 2:S13-S25.
9. Cornblath DR, et al. Total neuropathy score: validation and reliability study. *Neurology* 1999;53(8):1660-4.
10. McCrary JM, et al. Optimal clinical assessment strategies for chemotherapy-induced peripheral neuropathy (CIPN): a systematic review and Delphi survey. *Support Care Cancer* 2017;25(11):3485-93.
11. Basch E, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst* 2014;106(9).
12. Knoerl R, et al. Electronic versus paper-pencil methods for assessing chemotherapy-induced peripheral neuropathy. *Support Care Cancer* 2017;25(11):3437-46.
13. McCrary JM, et al. Optimizing clinical screening for chemotherapy-induced peripheral neuropathy. *J Pain Symptom Manage* 2019;58(6):1023-32.
14. Kennedy F, et al. Electronic patient reporting of adverse events and quality of life: a prospective feasibility study in general oncology. *JCO Oncol Pract* 2020:OP2000118.
15. Staff NP, et al. Platinum-induced peripheral neurotoxicity: from pathogenesis to treatment. *J Peripher Nerv Syst* 2019;24 Suppl 2:S26-S39.
16. Islam B, et al. Vinca alkaloids, thalidomide and eribulin-induced peripheral neurotoxicity: from pathogenesis to treatment. *J Peripher Nerv Syst* 2019;24 Suppl 2:S63-S73.
17. Smith EM, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013;309(13):1359-67.
18. Gewandter JS, et al. Chemotherapy-induced peripheral neuropathy (CIPN) and its treatment: an NIH collaboratory study of claims data. *Support Care Cancer* 2020;28(6):2553-62.
19. Knoerl R, et al. Proactive rehabilitation for chemotherapy-induced peripheral neuropathy. *Semin Oncol Nurs* 2020;36(1):150983.
20. American Cancer Society. *Managing peripheral neuropathy*. Atlanta; 2019 Nov 1. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/peripheral-neuropathy/managing-peripheral-neuropathy.html.
21. Kanzawa-Lee GA, et al. Exercise effects on chemotherapy-induced peripheral neuropathy: a comprehensive integrative review. *Cancer Nurs* 2020;43(3):E172-E185.
22. Campbell KL, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exerc* 2019;51(11):2375-90.