Management of Chemotherapy-Induced Peripheral Neuropathy

Meghna S. Trivedi, MD, Dawn L. Hershman, MD, MS, Katherine D. Crew, MD, MS

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of several commonly used cancer treatments, including taxanes, platinum agents, and vinca alkaloids. Sensory symptoms in the hands and/or feet, typically in a "stocking-glove" pattern, are common, and manifested as pain, numbness, and/or tingling. CIPN can result in chemotherapy dose reduction or discontinuation, and can also have long-term effects on quality of life. The course of CIPN can be unpredictable: while symptoms may resolve after chemotherapy is discontinued, they can also continue for years. There are several methods available to assess CIPN: objective measures include physical examination and neurophysiological testing and subjective measures include the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale and patient-reported outcome measures. While many interventions have been studied for CIPN prevention and treatment, only duloxetine has proven efficacy for treatment. Given the clinical implications of CIPN, there is great interest in better understanding its pathophysiology, standardizing evaluation, and developing effective treatments.

Key words: Chemotherapy-induced peripheral neuropathy, prevention, treatment, outcomes measures.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of many anticancer drugs, such as platinum analogs, antitubulins (eg, taxanes and vinca alkaloids), bortezomib, and thalidomide.[1] It can present as sensory symptoms in the hands and/or feet, typically in a "stocking-glove" pattern; pain, numbness, or tingling; or motor symptoms, manifested as weakness, cranial nerve deficits, or autonomic neuropathy.[2] In a recent meta-analysis of 31 CIPN studies involving 4179 patients, the aggregate prevalence of CIPN was 48%.[3] Within the first month of completing chemotherapy, the prevalence of CIPN was 68.1%; after 6 or more months of completing chemotherapy, the prevalence of CIPN decreased to 30.0%.[3] The course of CIPN can be unpredictable, and although some symptoms may improve with time, others may persist or worsen as a result of permanent nerve damage.[1] There are limited data on the natural history of CIPN in long-term cancer survivors, who are beyond 1 year of completing chemotherapy. Patients with breast cancer, who received taxane-based adjuvant chemotherapy, had neuropathy symptoms up to 2 years after completing treatment,[4] and patients with colon cancer receiving oxaliplatin-based adjuvant chemotherapy had numbness or tingling of hands and feet up to 6 years from starting treatment.[5]

One of the challenges in managing and preventing CIPN is that the exact pathophysiology is not well understood. The hypothesized mechanisms of taxane-induced neuropathy include the disruption of the axonal microtubule structure and a deficit in axonal energy supply from the toxic effect of chemotherapy on mitochondria in primary afferent neurons.[2,6] CIPN due to vinca alkaloid therapy is thought to be due to alterations in the neuronal cytoskeleton that cause axonal degeneration.[2,6] Platinum agents are thought to cause CIPN by exerting damage in the dorsal root ganglion through mitochondrial dysfunction and neuronal apoptosis, either by DNA crosslinking or oxidative stress.[2,6]

Despite investigations leading to hypotheses of several mechanisms of CIPN, none has resulted in clinically relevant therapeutic interventions.[7] Several studies have attempted to identify risk factors for CIPN development, which also vary with different chemotherapeutic agents. Some of the clinical factors implicated in the development of CIPN include baseline neuropathy,[8,9] the presence of diabetes,[9] smoking history,[10] and decreased creatinine clearance.[10] In addition, there is interest in pharmacogenomics and identifying genes that may play a role in the development of CIPN. Although numerous genes have been investigated, such as *GSTP1, CYP2C8,* and *AGXT*, there have been no conclusive findings.[11]

One of the clinical implications of CIPN is that the symptoms can result in treatment dose reduction or discontinuation, which may ultimately affect overall survival.[2] In a retrospective single-institution study of 123 patients with breast cancer receiving tax-

ane-based adjuvant or neoadjuvant chemotherapy regimens, 17% received chemotherapy dose reductions specifically due to CIPN that developed during treatment.[12] In addition, for cancer survivors, CIPN symptoms can significantly impact quality of life.[1,7,13]

This review article will discuss the methods used to assess CIPN and review the trials investigating its management. The American Society of Clinical Oncology (ASCO) recently published a systematic review of 48 randomized controlled trials providing guidelines on prevention of and treatment approaches to CIPN,[14] which will be summarized here.

Practical Application

- CIPN is a common adverse effect of several chemotherapy agents that can affect patient quality of life and adherence to cancer treatment.
- Although there are many methods to assess and grade CIPN, a standardized method has not been established.
- Duloxetine is the only intervention with efficacy for the treatment of CIPN demonstrated from a randomized, double-blind, placebo-controlled trial.

Assessment of CIPN

There are several methods available to assess CIPN; however, there is no consensus on *the* best method. There are objective assessments, such as clinical or neurophysiological examinations, and subjective assessments, such as the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale and patient-reported outcome measures. Other causes of neuropathy (ie, diabetic neuropathy) should also be entertained in a patient with symptoms.

The objective assessments can be either invasive or noninvasive. Noninvasive methods to assess CIPN include neurological assessment on physical examination to identify sensory and motor deficits and vibration sensation measurement.[1] Nerve conduction studies are an invasive method and will typically reveal a reduction in the amplitude of the sensory nerve action potentials (SNAPs).[2] However, this procedure can cause discomfort to the patient without providing additional clinical information.[1] In addition, nerve conduction studies detect abnormalities in large-diameter nerve fibers, not the small-size fibers that are involved in painful CIPN.[1]

NCI-CTCAE Version 4.03 is a subjective method to evaluate CIPN: it is performed by a healthcare professional, who grades adverse events that include peripheral sensory or motor neuropathy, dysesthesia, paresthesia, and neuralgia on a scale of 1 to 5, depending on the severity.[15] The advantage of the NCI-CTCAE is that the assessment is quick and easy for providers to perform.[16] However, it is limited by the subjectivity of interpretation; lack of detail about location, type, and severity of impairment; and a narrow scoring range.[1]

There are several patient-reported outcome measures that can be used to assess CIPN, and there is evidence that these measures are more accurate and sensitive at reporting patients' symptoms compared with such physician-reported measures as the NCI-CTCAE.[4,17] Postma et al[18] developed a CIPN subscale as part of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30 (QLQ-30), the QLQ-CIPN20 module. The instrument contains 20 questions evaluating sensory, motor, and autonomic symptoms, and has been validated as an assessment tool for CIPN.[19] Another patient survey used to assess CIPN is the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire.[20] This validated and reliable tool uses 11 questions to evaluate the severity of neuropathy and its impact on patient quality of life.

Composite scales that combine invasive and noninvasive objective measures, as well as subjective measures, are also available, with the most frequently used scale being the Total Neuropathy Score (TNS).[1,21] The TNS includes subjective provider-scored sensory, motor, and autonomic symptom measures; noninvasive objective measures of pin sensibility, vibration sensibility, strength, tendon reflexes, and quantitative sensory testing; and invasive objective measures of sural and peroneal nerve conduction studies.[21] In a single-institution study of 60 women with CIPN secondary to cisplatin and paclitaxel, the TNS results correlated well with those obtained from the NCI-CTCAE scales.[21] The disadvantages of the TNS are that it is time-consuming to administer, requiring approximately 1 hour, and requires specialized instrumentation.[16,21] There is a version of the TNS that does not use quantitative sensory testing, known as the TNS-reduced (TNSr) scale, and a version that uses only the clinical evaluation of symptoms and signs, known as TNS-clinical (TNSc) scale.[16] A study by Cavaletti et al[22] demonstrated that the TNS and TNSc are more sensitive than the NCI-CTCAE and provide more accurate grading of CIPN. The challenge is how to incorporate these CIPN measures into clinical practice and standardize this approach across multiple centers.

Prevention of CIPN

The recently published ASCO guidelines on the prevention of CIPN, based on a systematic review of 42 randomized controlled trials investigating 18 agents, found that there are no agents that have shown consistent, clinically meaningful benefits for CIPN prevention.[14] Investigations of intravenous calcium/magnesium for oxaliplatin-induced neuropathy[23] and oral vitamin E[24] have shown no benefit in prevention of CIPN. Two agents have actually been shown to worsen CIPN compared with placebo: acetyl-L-carnitine (ALC) and nimodipine.[25,26] ALC is a natural compound that has been shown to improve sensory neuropathy and reduce the severity of neuropathy development in a rat model.[27] In a single-arm study by Bianchi et al[28] of 25 patients with established CIPN due to paclitaxel or cisplatin, there was improvement in sensory and motor neuropathy with 3-times-dai-

TABLE. Phase 3 Randomized, Placebo-Controlled CIPN Treatment Trials

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
Antidepressant	Amitriptyline 10 mg daily with dose escalation of 10 mg/week up to target maximum dosage of 50 mg daily for 8 weeks	Kautio et al, 2008[39]	Total: 33 Placebo: 16 Amitriptyline: 17 Double-blind study	Vinca alkaloids, platinum agents, or taxanes	• Global improvement as assessed by numeric scales (scale, 0-10) in diary data: no significant difference in mean score between groups (3.4±3.6 vs 1.9±3.1 in placebo arm; *P* = NS). • Global improvement at final visit assessed by verbal rating scale (scale, complete relief-symptoms worse): no significant difference between groups (47% vs 31% in placebo arm; *P* = NS).	Negative	Tiredness Tachycardia
	Nortriptyline (N) 25 mg daily with dose escalation of 25 mg/week up to target maximum dosage of 100 mg during treatment period	Hammack et al, 2002[38]	Total: 51 Group A (N/PL): 26 Group B (PL/N): 25 Double-blind crossover study after 4 weeks	Cisplatin	• Paresthesia as assessed by visual analog scale: in first treatment period, no significant reduction in paresthesia (49 vs 55 [scale, 0-100] in placebo arm; *P* = .78).	Negative	Dry mouth Dizziness Constipation
	Venlafaxine 50 mg 1 h prior to oxaliplatin infusion and 37.5 mg extended-release twice daily on days 2 through 11	Durand et al, 2012[40]	Total: 48 Placebo: 24 Venlafaxine: 24 Double-blind study	Oxaliplatin	• Full relief of acute neurotoxicity: 31.3% vs 5.3% in placebo arm (*P* = .03).	Positive	Grade 1-2: nausea and vomiting, asthenia, somnolence
	Duloxetine (D) 30 mg daily for 1 week, then 60 mg daily for 4 weeks during treatment period	Smith et al, 2013[46]	Total: 220 Group A (D/PL): 109 Group B (PL/D): 111 Double-blind crossover study after 5 weeks	Paclitaxel, docetaxel, nanoparticle albumin-bound paclitaxel, cisplatin, oxaliplatin	• Reduction in average pain as measured by BPI-SF: in initial treatment period, larger mean reduction in BPI-SF pain score in duloxetine group than placebo group (1.06 vs 0.34 [scale, 0-10]; *P* = .003) with moderately large effect size (0.513).	Positive	Fatigue (7%) Insomnia (5%) Nausea (5%)

ly dosing of 1 g of ALC for 8 weeks with little toxicity. However, when studied in a large randomized, double-blind, placebo-controlled trial of 409 patients with breast cancer initiating adjuvant taxane-based chemotherapy, ALC was found to significantly increase CIPN.[25] Also, nimodipine was found to have a neuroprotective effect against cisplatin in a rat model,[29] and when studied in a small randomized, placebo-controlled trial of 51 patients, it exacerbated neurotoxicity in patients receiving cisplatin for treatment of ovarian cancer.[26]

Glutathione is a natural compound composed of the 3 amino

TABLE. Phase 3 Randomized, Placebo-Controlled CIPN Treatment Trials *(continued)*

Drug Class	Pharmacologic Agent and Dosage	Authors and Year of Publication	Number of Patients and Study Design	Drug Causing CIPN	Primary Study Outcome Measure and Results	Overall Results	Adverse Effects of Intervention
Antiepileptic	Gabapentin (G) 300 mg with dose escalation of 300 mg to a target maximum dosage of 2700 mg daily for 6 weeks during treatment period	Rao et al, 2007[36]	Total: 115 Group A (G/PL): 57 Group B (PL/G): 58 Double-blind crossover study after 6 weeks	Vinca alkaloids, taxanes, or platinum agents	• "Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline, 6 weeks, or 14 weeks between groups.	Negative	No significant differences in toxicities between groups
	Lamotrigine 25 mg at bedtime for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then 100 mg twice daily for 2 weeks, then 150 mg twice daily for 2 weeks	Rao et al, 2008[37]	Total: 125 Placebo: 62 Lamotrigine: 63 Double-blind study	Vinca alkaloids, taxanes, or platinum agents	• "Average" pain by NRS and ENS: no difference in NRS or ENS score at baseline or 10 weeks between groups.	Negative	No significant differences in toxicities between groups
Topical	Baclofen, amitriptyline, and ketamine gel, 1.31 g of compounded gel containing 10 mg baclofen, 40 mg amitriptyline HCL, and 20 mg ketamine twice daily for 4 weeks	Barton et al, 2011[41]	Total: 203 Placebo: 102 BAK gel: 101 Double-blind study	Vinca alkaloids, platinum agents, taxanes, or thalidomide	• EORTC CIPN sensory subscale mean neuropathy change from baseline to 4 weeks: 8.1 vs 3.8 in placebo arm (P = .053).	Negative	No significant differences in toxicities between groups
	Amitriptyline and ketamine (AK) cream 4 g twice daily for 6 weeks	Gewandter et al, 2014[42]	Total: 458 Placebo: 231 AK: 227	Taxanes or nontaxanes	• Mean pain, numbness, and tingling score at week 6: no significant reduction in mean score (P = .363)	Negative	No significant differences in toxicities between groups

BPI-SF indicates Brief Pain Index-Short Form; CIPN, chemotherapy-induced peripheral neuropathy; EORTC, European Organisation for Research and Treatment of Cancer; ENS, ECOG Neuropathy Scale; NRS, Numerical Rating Scale.

acids glutamic acid, cysteine, and glycine that has been extensively studied for CIPN prevention—but with mixed results.[30] In mouse studies, when glutathione was given with cisplatin, the platinum concentration in the dorsal root ganglia was lower and sensory nerve conduction velocity decreased less compared with mice that received only cisplatin.[31] And there have been several small placebo-controlled trials which have shown that intravenous administration of glutathione with platinum-based chemotherapy regimens can decrease the incidence of neurotoxicity without diminishing the effect of chemotherapy.[32-35] Leal et al[30] studied the use of glutathione with carboplatin and paclitaxel and found no improvement in neurotoxicity symptoms, suggesting that glutathione may not help in taxane-induced CIPN.

Treatment of CIPN

Eight agents have been studied in randomized controlled trials for the treatment of CIPN, but there has been limited success. The characteristics and results of these studies are summarized in the **Table**. Clinical trials of the antiepileptic agents gabapentin[36] and lamotrigine[37] and the antidepressants nortriptyline[38] and amitriptyline[39] have all been negative.

In the EFFOX study,[40] Durand et al investigated the EFFicacy of venlafaxine for prevention and relief of OXaliplatin-induced acute neurotoxicity. In this small placebo-controlled trial of 48 patients, venlafaxine was shown to provide relief of recurrent acute neurotoxicity and decrease the incidence of cumulative permanent neurosensory toxicity following completion of oxaliplatin treatment. The mechanism of efficacy for venlafaxine was

thought to be through a protective effect against oxaliplatin-induced oxidative stress.[40]

A topical mixture of baclofen, amitriptyline, and ketamine (BAK) was developed by Barton et al[41] to treat CIPN in a group of patients who had numbness, tingling, or pain associated with peripheral neuropathy while receiving or after having received neurotoxic chemotherapy. The investigators hypothesized that since there may be several complex pathways resulting in CIPN, a combination of drugs with unique but complementary mechanisms of action may be beneficial in treatment. The patients applied the topical treatment twice daily for 4 weeks. Compared with placebo, the topical treatment resulted in an improvement in motor neuropathy and a trend toward improvement in sensory neuropathy; however, the overall effect was modest.[41] Gewandter[42] studied the use of topical amitriptyline and ketamine twice daily for 6 weeks and found no significant reduction in the pain, numbness, or tingling score at the end of topical treatment.

Duloxetine is a neuronal serotonin and norepinephrine reuptake inhibitor that has been shown to be effective in the treatment of diabetic neuropathy.[43-45] A phase 3, randomized, double-blind, placebo-controlled crossover trial evaluated the use of duloxetine in the treatment of painful CIPN.[46] Forty percent of patients in this study received paclitaxel, and 59% of patients received oxaliplatin as the neurotoxic agent. The study used the Brief Pain Inventory-Short Form (BPI-SF) as the primary outcome measure in patients with established CIPN, and found that duloxetine use resulted in a greater mean reduction in pain (scale, 0-10) of 1.06 compared with 0.34 in the placebo arm (effect size, 0.513; $P = .003$).[46] Based on the results of this study, the ASCO clinical practice guidelines give a moderate recommendation for the use of duloxetine in patients with cancer experiencing CIPN.[22]

Future Directions in Treatment of CIPN

Clinical trials investigating complementary and alternative medicine in the treatment of CIPN, such as acupuncture (NCT02129686) and massage therapy (NCT02221700), are under way. A few small trials have investigated the use of Scrambler therapy, a device that provides noninvasive cutaneous electrostimulation, to treat CIPN and found efficacy with no toxicity.[47-49] A randomized, double-blind trial to evaluate Scrambler therapy is under way (NCT02111174) now. The use of topical menthol for CIPN is also being investigated in a placebo-controlled, randomized trial (NCT01855607) after the encouraging results of a phase 1 study showing improvement in CIPN pain and function with a 6-week course of twice-daily application of 1% topical menthol to affected areas.[50]

Conclusions

CIPN is a frequent complication of cancer treatment that can not only affect a patient's response to treatment, due to the need for dose reduction or discontinuation, but also quality of life. Although treatment and prevention options for CIPN are limited at present, the use of duloxetine for painful CIPN can be recommended based on the results of a positive phase 3 trial. It is also reasonable to try tricyclic antidepressants, gabapentin, or topical BAK after discussing the limited evidence, risks, and benefits with the patient. However, patients undergoing treatment with causative agents should undergo assessment by their treating physician for CIPN symptoms, using NCI-CTCAE criteria and clinical examination, and perhaps validated patient-reported outcome measures. Understanding the pathophysiology of CIPN and the ability to accurately and consistently assess CIPN are 2 major challenges in the treatment of CIPN. There is great interest in not only the investigation of interventions to treat CIPN, but also in investigations to better understand and characterize this treatment-related adverse effect.

Affiliations: Drs Trivedi, Hershman, and Crew are from the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY. Drs Hershman and Crew are from the Department of Epidemiology, Mailman School of Public Health, and the Herbert Irving Comprehensive Cancer Center, Columbia University.

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Address correspondence to: Katherine D. Crew, MD, MS, Assistant Professor of Medicine and Epidemiology, Herbert Irving Comprehensive Cancer Center, Columbia University, 161 Fort Washington Ave, 10-1072, New York, NY 10032. Phone: 212-305-1732; fax: 212-305-0178; e-mail: kd59@cumc.columbia.edu.

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