CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Determine three of the most common causative agents for chemotherapy-induced peripheral neuropathy
- Describe the most common symptoms of chemotherapy-induced peripheral neuropathy
- Discuss the management options for chemotherapy-induced peripheral neuropathy

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CIPN: Treatment preservation and prevention are the goals

Colleen H. Erb, MSN, ACNP-BC, AOCNP

STATEMENT OF NEED/PROGRAM OVERVIEW

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, serious side effect that can lead to dose reductions or early discontinuation of chemotherapy, reducing the efficacy of cancer treatments. It can cause debilitating symptoms and also significantly impacts the patient's quality of life. This activity is designed to give an overview of the causes of CIPN, its symptoms, and possible prevention and treatment strategies. To date, no medications are approved for treatment or prevention of CIPN; therefore, this overview presents the most common agents currently under investigation.

CE INFORMATION

Title: CIPN: Treatment preservation and prevention are the goals
Release date: October 15, 2011
Expiration date: October 15, 2013
Estimated time to complete this activity: 1.25 hours

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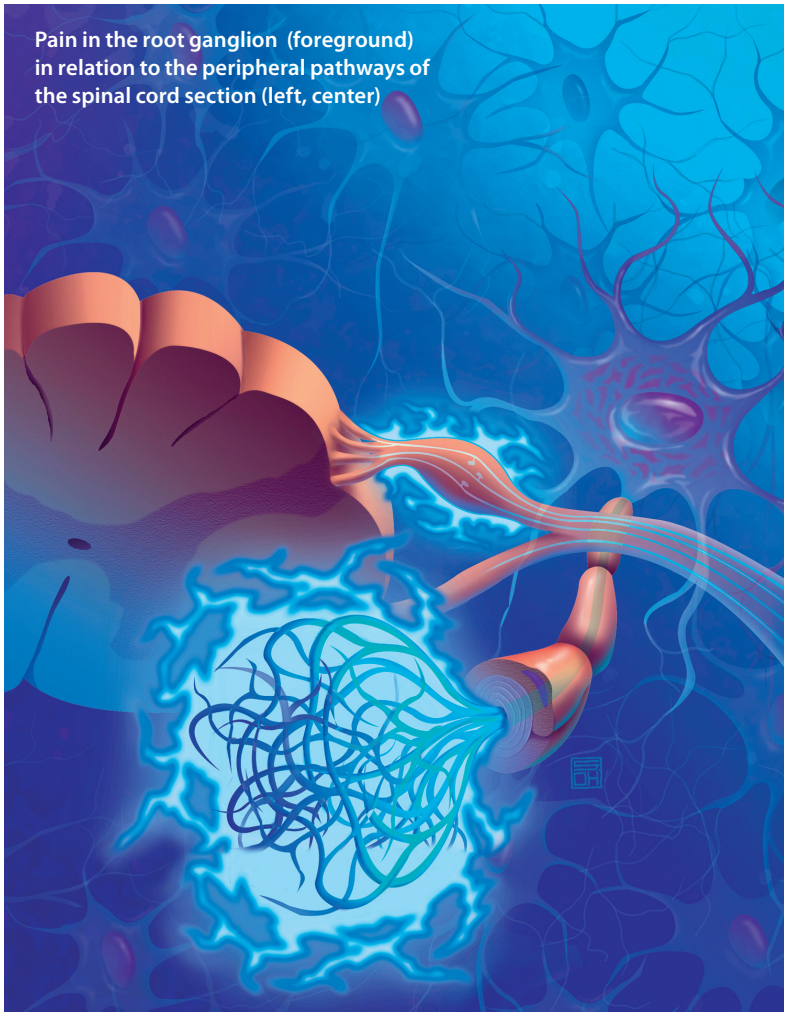
CIPN: Treatment preservation and prevention are the goals

Chemotherapy-induced peripheral neuropathy can lead to reduced doses that hinder treatment effectiveness or early discontinuation of therapy.



Pain in the root ganglion (foreground) in relation to the peripheral pathways of the spinal cord section (left, center)

COLLEEN H. ERB, MSN, ACNP-BC, AOCNP

Peripheral neuropathy is a serious side effect experienced by many patients receiving chemotherapy, and may lead to dose reductions or early discontinuation of treatment. It also significantly impacts the patient's quality of life. The overall incidence of chemotherapy-induced peripheral neuropathy (CIPN) is believed to be 30% to 40% but can vary depending on the chemotherapy agents used.[1] Many prescription medications and supplements have been investigated for the prevention of CIPN and for symptom management of the condition, but none are currently approved for this indication. This article presents the most common agents under investigation.

UNDERSTANDING CIPN AND ITS CAUSES

Peripheral neuropathy is caused by nerve damage resulting in both sensory and motor nerve impairment. Manifestations are relative to which neurons—autonomic, motor, or sensory—are disrupted (**Table 1**);[2] the resultant pain can be severe and lead to functional disability.

Patient age, dose intensity, cumulative dose of administered chemotherapy agent, use of more than one neurotoxic chemotherapeutic agent, and other preexisting comorbidities are other contributing factors to CIPN.[3] The specific manifestations of neuropathy vary depending on

the type of drug used. Severity of CIPN is measured according grading scales that determine a need for intervention or discontinuation of neurotoxic agents (**Table 2**).[4,5] The most common offending agents are the vinca alkaloids, taxanes, and platinum-based drugs, but neuropathy is also caused by many other agents as well (**Table 3**).[1,6]

Platinum-based agents These drugs, especially cisplatin and oxaliplatin (Eloxatin, generics), frequently cause sensory neuropathy symptoms. Although carboplatin can cause symptoms as well, manifestation is less common. Cisplatin-related CIPN is dose dependent. Patients receiving cisplatin experience decreased vibratory sense, a loss of deep tendon reflexes, and paresthesias. A unique finding in patients receiving cisplatin is neurosensory high-frequency hearing loss and tinnitus.[1] Oxaliplatin, unlike other platinum-based agents, causes unique paresthesias and muscle cramping enhanced by exposure to cold, including shortness of breath and difficulty swallowing due to cold-related pharyngolaryngeal dysesthesia. These symptoms usually begin within a few hours after infusion.[1,3]

Taxanes Higher cumulative doses of taxanes are strongly associated with increased incidence of CIPN. In comparison, docetaxel (Docefrez, Taxotere, generics) is less neurotoxic than paclitaxel (Abraxane, generics) at high doses.[3] The most common symptoms are paresthesias and dysesthesias manifesting within 24 to 72 hours after infusion. Manifestations usually begin as proximal weakness, myalgias/arthralgias specifically in the knees and shoulders, and, less often, nocturnal leg cramps. These symptoms often resolve 4 to 7 days after infusion. Over time, more than 70% of patients receiving taxanes develop persistent distal extremity numbness, tingling, and burning pain.[1]

Vinca alkaloids These agents cause pain and paresthesias in the feet and hands as well as the loss of deep tendon reflexes; however, findings of autonomic neuron disruption are unique to this class of drug.[1] Vincristine frequently causes constipation, ileus, and erectile dysfunction. Therefore, assessment of bowel function prior to starting vincristine is essential.[3] Both vincristine and vinblastine can affect the cranial nerves, leading to vocal cord paralysis, jaw pain, or optic neuropathy (rare).[1]

Motor neurons are located in the spinal cord, which offers more protection to these neurons, making motor neuropathy less common.

TABLE 1. Manifestations based on affected neurons[2]

Autonomic	
• Anhidrosis	• Ileus
• Blurred vision	• Orthostasis
• Changes in taste	• Overflow incontinence
• Constipation	• Sexual impotence
• Dizziness	• Tinnitus
• Hearing loss	• Urinary retention
Motor	
• Cramps	• Spasms
• Difficulty with fine motor activities (writing or dialing a phone)	• Tremors
• Gait disturbances	• Weakness
• Paralysis	
Sensory	
• Burning	• Hypersensitivity to touch
• Decreased or absent pain sensation	• Numbness
• Decreased or absent touch sensation	• Tingling
• Electric-shock sensations	

Other risk factors Preexisting sensory neuropathy should be documented to ensure that providers can distinguish CIPN from the patient's preexisting condition. Other causes of sensory neuropathy include diabetes, HIV, congenital neuropathy, alcohol abuse, and other medications the patient may be taking. Sensory neuropathy may also be a symptom of the diagnosed disease itself. Those with preexisting neuropathy should be monitored closely as their neuropathy can worsen quickly.[1]

PATHOPHYSIOLOGY OF CIPN

The peripheral nervous system (PNS) is very sensitive to the effects of certain chemotherapy agents. Unlike the central nervous system (CNS), the PNS is not protected by a vascular barrier (eg, the blood-brain barrier). The nerves of the PNS exit the vertebral bodies and subsequently innervate specific areas called *dermatomes*. Each PNS neuron consists of a single axon surrounded by a myelin sheath, a cell body, and dendrites. The sensory neurons are bundled together in the dorsal root ganglia. Motor neurons are located in the spinal cord itself, which offers more protection to these neurons, making motor neuropathy less common.[7]

In almost all cases, CIPN is symmetrical and begins distally (ie, at the toes or fingertips), and if not corrected, progresses

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Illustration of neuropathy: pain sensation due to neuromatous or ganglion cell sources. Pain in the root ganglion (foreground) is shown in relation to the peripheral afferent and efferent pathways of the spinal cord section (left, center). Pathologic conditions that may contribute to this type of pain sensation include amputation and peripheral nerve injury.

TABLE 2. Grading scales for CIPN[4,5]

Functions	Grade 1	Grade 2	Grade 3	Grade 4
NCI CTCAE				
Motor	• Asymptomatic • Detected on examination	• ADLs not effected • Weakness that interferes with function	• Interference with ADLs • Needs assistance to walk • Weakness	• Paralysis
Sensory	• Asymptomatic • Loss or decrease in DTR or mild sensory alteration	• Sensory alterations that interfere with function with no effect on ADLs	• Any alteration that interferes with ADLs	• Debilitating
ECOG CTC				
Motor	• Subjective weakness	• Mild weakness on examination • No impairment of function	• Weakness with impairment of function	• Paralysis
Sensory	• Loss of DTR • Mild paresthesias	• Mild to moderate objective sensory loss	• Interference with function • Severe objective sensory loss	

Key: ADLs, activities of daily living; CIPN, chemotherapy-induced peripheral neuropathy; DTR, deep tendon reflexes; ECOG CTC, Eastern Cooperative Oncology Group common toxicity criteria; NCI CTCAE, National Cancer Institute common terminology criteria for adverse events.

proximally in a stocking-glove distribution.[1] Most cases of CIPN resolve slowly over time when the offending chemotherapy agent is reduced or stopped; however, CIPN may be irreversible in cases of severe damage or neuronal death. Patients can also experience *coasting,* wherein symptoms worsen even after cessation of the causative agent.[1]

PREVENTIVE MEASURES

Prevention is the best option for patients receiving neurotoxic agents. The only widely accepted treatment for CIPN is dose modification based on the extent of interference in the patient's daily life and the impact on quality of life.[3] Patients with preexisting neuropathy are at greatest risk of developing CIPN; therefore, a careful history should be obtained before starting therapy. Extremely close monitoring is essential if the patient has preexisting neuropathy.

A later review of CONcePT showed numerically higher response rates and lower incidence of high-grade CIPN in patients who received CaMg.

Supplements and medications have been tested in clinical trials for their CIPN-preventive properties (**Table 4**);[3,6] however, results are mixed. Although some agents appear promising, clinical trials have not produced adequate evidence for recommending one agent over another.[8] An investigation of vitamin E showed very promising results with a decrease in CIPN.[9] A second trial, however, showed no significant differences between vitamin E and placebo in regard to grade 2 or greater CIPN, time to onset, chemotherapy dose reductions due to CIPN, or patient-reported symptoms.[10] Despite these conflicting results, vitamin E is a promising CIPN preventive, and other clinical trials to determine its efficacy are ongoing.

Investigators hypothesized that intravenous administration of calcium gluconate and magnesium sulfate (CaMg) may lessen CIPN in patients with oxaliplatin-induced neuropathy. One study showed intravenous CaMg before and after oxaliplatin infusions produced significant reductions in CIPN with no effect on treatment efficacy.[11] The Combined Oxaliplatin Neurotoxicity Prevention Trial (CONcePT) initially revealed significantly lower disease response to therapy and closed early; however, a later review of this trial demonstrated numerically higher response rates and lower incidence of high-grade CIPN in patients who received CaMg.[12] At this time, data that support the use of CaMg infusions is insufficient.

Glutathione has been studied by European investigators. The hypothesis behind its proposed effectiveness is it may inhibit accumulation of platinum-based agents in the dorsal root ganglia. In a randomized, double-blind, placebo-controlled study from Italy, a lower incidence of grade 3 or

greater CIPN with little impact on tumor response was seen in patients who received IV glutathione before oxaliplatin therapy.[13] Although this study was promising, it had a very small sample size. Other trials, although not as rigorous, have also shown lower incidence of grade 3 to 4 CIPN.[14]

TREATMENT STRATEGIES

The effectiveness of many treatment options is anecdotal because the data are limited by a lack of well-conducted, large, randomized trials. However, resolution of symptoms may be achieved with tricyclic antidepressants (TCAs), anticonvulsants, opioids, or a topical analgesic in some patients.

Tricyclic antidepressants, such as amitriptyline, desipramine (Norpramin, generics), and imipramine (Surmontil, Tofranil, generics) are known to modulate the sodium channels and inhibit reuptake of norepinephrine and serotonin, thereby decreasing pain. Adverse effects associated with TCAs include anticholinergic effects, cardiac effects, and sedation, and patients with significant cardiac disease should not use these agents.[1]

Anticonvulsants, particularly gabapentin (Gralise, Neurontin, generics), are used quite often and have been investigated without any true recommendation for use. In a randomized trial, gabapentin treatment failed to show any reduction of symptom severity.[15]

Opioids have been used to treat CIPN-related pain and can be titrated to achieve maximal reduction of pain. Once maximal relief is achieved, the preferred modality is a long-acting opioid analgesic with short-acting opioids used for breakthrough pain. Adding a TCA or an anticonvulsant may lower the total dose of opioid needed in some patients.[1]

Topical analgesics may be effective. A study presented at the 2009 American Society of Clinical Oncology (ASCO) general meeting demonstrated modest but not statistically significant improvement in motor symptoms with baclofen/amitriptyline/ketamine (BAK) gel.[16] The other well-studied topical agent is capsaicin (Qutenza), which has had results ranging from significant pain reduction to worsening pain and burning.[1]

Some nonpharmacologic interventions may produce a benefit, including transcutaneous nerve stimulation, relaxation techniques, and exercise. None of these have been extensively studied, and no true recommendation is available. A referral to physical therapy or rehabilitation may be appropriate to increase functional status for patients with functional impairment or a balance problem.[1]

A referral to physical therapy or rehabilitation may be appropriate to increase functional status or resolve a balance problem.

TABLE 3. Chemotherapeutic agents that can cause CIPN[1,6]

Epothilones
Ixabepilone (Ixempra Kit)
Less common agents
Arsenic trioxide (Trisenox)
Cytarabine (Cytosar-U, Depocyt, generics)
Etoposide
Hexamethylmelamine (altretamine [Hexalen])
Ifosfamide (Ifex, generics)
Methotrexate (Trexall, generics)
Procarbazine (Matulane)
Novel agents
Bortezomib (Velcade)
Thalidomide (Thalomid)
Platinum-based agents
Carboplatin
Cisplatin
Oxaliplatin (Eloxatin, generics)
Taxanes
Docetaxel (Docefrez, Taxotere, generics)
Paclitaxel (Abraxane, generics)
Vinca alkaloids
Vinblastine
Vincristine

Key: CIPN, chemotherapy-induced peripheral neuropathy.

CONCLUSION

The discovery of new therapy combinations and medications that lead to longer patient survival has made the care of patients with cancer more complex. Although some promising CIPN-preventive measures are being investigated, no standard treatment modalities have been established. A comprehensive patient history and thorough neurologic assessment with early dose reduction are the most effective interventions. The evidence for prevention and treatment using other substances, including vitamin E, CaMg, and glutathione,

TABLE 4. Agents investigated for CIPN-preventive properties[3,6]

Acetyl-L-carnitine
Alpha-lipoic acid
Amifostine (Ethyol, generic)
Amitriptyline
Baclofen/amitriptyline/ketamine (BAK) gel
Calcium gluconate and magnesium sulfate (CaMg)
Capsaicin (Qutenza)
Desipramine (Norpramin, generics)
Erythropoietin
Glutamate
Imipramine (Surmontil, Tofranil, generics)
Insulin-like growth factor
Lidocaine topical (Lidoderm, generics)
Nerve growth factor
Nimodipine
Oxcarbazepine (Trileptal, generics)
Venlafaxine (Effexor, Pristiq, generics)
Vitamin B complex
Vitamin E

is inconsistent. Trials for their use are ongoing (www.clinicaltrials.gov); until these trials are completed, there are no definitive recommendations for their use. ■

Colleen Erb is a hematology-oncology nurse practitioner at Fox Chase Cancer Center, Philadelphia, Pennsylvania.

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