Chemotherapy-Induced Neuropathic Pain

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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The advancement of chemotherapy has prolonged survival for many cancer patients. However, treatment with chemotherapeutic agents has left cancer survivors with many long-term sequelae and new and challenging problems, such as pain, sensory deficits, and motor weakness (Stillman & Cata, 2006).

Unfortunately, the nervous system bears the brunt of most of these toxicities. Chemotherapy-induced peripheral neuropathy (CIPN) has become a common neurologic toxicity, particularly in patients with preexisting baseline peripheral neuropathy and those over the age of 65 years (Hile, Fitzgerland, & Studenski, 2010). Among chemotherapeutic agents, platinum-based compounds (e.g., cisplatin, oxaliplatin [Eloxatin]) are most commonly associated with CIPN (Quant, Plotkin, & Wen, 2010). In addition, the administration of plant alkaloids, taxanes, thalidomide (Thalomid), lenalidomide (Revlimid), and bortezomib (Velcade) is associated with CIPN (Visovsky, 2010).

Quick recognition and swift management of CIPN is important, as is either dose reduction or discontinuation of the agent to prevent long-term irreversible injury (Quant et al., 2010). Without proper management, peripheral neuropathy can have a significantly negative impact on the patient's quality of life and physical and emotional functioning.

Pathophysiology

Symptoms of CIPN result from injury to the peripheral nervous system, although the exact mechanism of action is not entirely understood (Visovsky, 2010). The toxic effects of chemotherapy target the structures and functions of the peripheral nervous system, including the axon, the myelin sheath, the neuronal cell body, and the supporting glial structures (Stillman & Cata, 2006). According to Quant et al. (2010), chemotherapeutic agents may cause toxicity directly by acting upon the nervous system or indirectly by causing metabolic abnormalities or cerebrovascular disorders. Most toxic neuropathies affect axons, resulting in axonopathy and distal, symmetric, sensory-predominant neuropathy. The distal branches are most affected by axonal transport flow disruption, causing the stocking-and-glove pattern of sensory loss (Stillman & Cata, 2006).

Definition and Assessment

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.3 defines peripheral motor and sensory neuropathy as disorders characterized by inflammation or degener-

ation of the peripheral motor or sensory nerves, respectively (National Cancer Institute [NCI], 2010). The CTCAE base these definitions on the degree of symptomatology as well as the effect on activities of daily living. Neuropathic pain caused by chemotherapy is often distinguished by a cluster of symptoms that include spontaneous pain that is both constant and intermittent, loss of sensation, and motor symptoms (Tofthagen, 2010). It is very common for patients to experience both persistent burning pain and superimposed episodes of shooting, lancinating discomfort, as well as paresthesias that are spontaneous or stimulus-independent. Many patients describe the sensation as a limb having "fallen asleep," as well as varying sensations such as burning, stabbing, stinging, squeezing, aching, cramping, shooting, and freezing. Motor symptoms of CIPN may cause painful arthralgias or muscle weakness (Tofthagen, 2010). Symptoms generally begin in the toes and fingers and spread proximally to affect the legs and arms (Quant et al., 2010).

There is no gold standard clinical or laboratory test to diagnose CIPN (Visovsky, 2010). The diagnosis itself is primarily based upon symptoms reported by the patient and findings on physical examination. A grading system developed by the CTCAE is used to identify the severity of the neuropathy, with a score of 1 representing mild symptoms and 5 being equivalent to death (Table 1; NCI, 2010). In addition, the patient should be screened for comorbid conditions (e.g., diabetes) that are associated with neuropathic pain syndromes (Visovsky, 2010).

A thorough evaluation is essential to ensure adequate pain management. Assessment strategies are outlined in Table 2 (National Comprehensive Cancer Network, 2010).

Management

Currently, there are no evidence-based recommendations for the prevention or treatment of CIPN (Visovsky, 2010). Management of CIPN is primarily based upon controlling symptoms, and it should include both pharmacologic and nonpharmacologic therapies (Table 3; Paice, 2009). According to Velasco and Bruna (2010), early recognition of symptoms and dose reduction or discontinuation of therapy are the best ways to minimize the development of long-term complications of CIPN. Multiple agents—including chemoprotectants, vitamins, electrolyte infusions, opioids, antidepressants, and antiepileptic drugs (AEDs)—have been tested for possible efficacy for preventing or improving CIPN (Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). However, many of these agents have had limited success in clinical studies (Visovsky et al, 2007).

Chemoprotectants, such as amifostine, have little effect on peripheral neuropathy outcomes. The use of vitamins has resulted in modest improvements in CIPN. In studies examining the cytoprotective properties of vitamin E, groups of patients who received vitamin E supplementation had a lower incidence of neurotoxicity than did control groups, suggesting a relationship between cisplatin neurotoxicity and vitamin E deficiency

Table 1. Common Terminology Criteria for Adverse Events Reporting: Peripheral Motor and Sensory Neuropathy (Version 4.3)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistance device indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Note. ADL = activities of daily living. A semicolon indicates "or" in the grade description. Adapted from the National Cancer Institute (2010).

Table 2. Assessment tools for neuropathy

Comprehensive history	Comprehensive pain assessment/ patient report	Physical examination
Cancer diagnosis and past/current treatments Review patients past and current chemotherapeutic agents, specifically those commonly associated with neurotoxicity (e.g., vincristine, paclitaxel, cisplatin, oxaliplatin, thalidomide) Review preexisting conditions/ comorbidities that may be associated with peripheral neuropathy (i.e., diabetes, HIV infection, alcoholism, spinal cord injuries)	Screening for pain If pain is present (pain score > 0), have patient quantify pain intensity (numerical pain-rating scale or the faces pain-rating scale) Perform comprehensive pain assessment: type and quality of pain, pain history, pain intensity, location, referral pattern, radiation of pain, exacerbating/relieving factors, current pain management plan, response to therapy, prior pain therapies, and psychosocial effects of pain/interfering with quality of life Probe for key characteristics: Sensory: paresthesias, numbness and tingling, burning, sharp, shooting. Motor: muscle weakness, gait and/or balance disturbance, difficulty with fine motor skills (e.g., buttoning clothing, writing).	Sensory, motor, reflex, and autonomic testing Diminished or absent proprioception, vibratory sensation, cutaneous sensation, sense of discrimination between sharp and dull

Note. HIV = human immunodeficiency virus. Adapted from the National Comprehensive Cancer Network (2010).

Table 3. Management of chemotherapy-induced neuropathy

Assessment	Pharmacologic interventions	Nonpharmacologic interventions
Initiate therapy for any patient rating pain > 4 or ≥ grade 2 and with symptoms interfering with ADL	Initiate opioids *and* AEDs/TCAs: Start with a low dose and increase every 3–5 days if tolerated or lengthen interval up to 14 days Consider topical agents (lidocaine patch 5%)	***Physical modalities*** Bed, bath, and walking support Physical therapy Energy conservation, pacing of activities Massage Acupuncture/acupressure ***Cognitive modalities*** Imagery/hypnosis Distraction Active coping training Cognitive behavioral training Spiritual care

Note. ADL = activities of daily living; AEDs = antiepileptic drugs; TCAs = tricyclic antidepressants. Adapted from Paice (2009).

(Visovsky et al., 2007). Retrospective studies of electrolyte replacement with magnesium and calcium also have shown improvements of acute neurotoxicity in patients receiving platinum-based therapies (Visovsky et al., 2007). However, further randomized, controlled trials are needed to further evaluate the role of chemoprotectants, vitamins, and electrolyte replacement in preventing and treating CIPN.

Opioids are an important element in the treatment of CIPN. Opioids relieve neuropathic pain by blocking the release of neurotransmitters into the spinal cord (Paice, 2009). Agents such as codeine, hydrocodone, oxycodone, morphine, hydromorphone, and oxymorphone can be used to treat CIPN effectively (Table 4; NCCN, 2010; Chang, Janjan, Jain, and Chau, 2006; Gimbel, Richards, and Portenoy, 2003). In a double-blind, placebo-controlled, crossover trial involving 76 patients with neuropathic pain, patients receiving a combination of tricyclic antidepressants (TCAs) and opioids had better pain control than did those given placebo (Gimbel, Richards, & Portenoy, 2003).

In addition to opioids, AEDs, TCAs, and topi-

Table 4. Opioids: Drugs and dosing

Drug	Dosage
Codeine	100 mg PO every 3 hours, as needed
Hydrocodone	15 mg PO every 4 hours, as needed
Oxycodone	5–10 mg PO every 2–3 hours, as needed
Morphine	15 mg PO every 4 hours, as needed
Hydromorphone	4 mg PO every 4 hours, as needed
Oxymorphone	10 mg PO twice daily; titrate upward, as needed

Note. Opioid dosing has no ceiling and can be titrated up as needed for pain control. Adapted from NCCN (2010); Chang, Janjan, Jain, and Chau (2006); Gimbel, Richards, and Portenoy (2003).

cal anesthetics have proven to be effective modes of treatment for CIPN, both anecdotally and in case reports (Paice, 2009). However, the results of randomized, controlled trials have not supported anecdotal reports. Due to the lack of supporting evidence, an empirical approach to prescribing AEDs has been suggested (Table 5; Carceni, et al., 2004; Galer, Rowbothan, Perander, & Friedman, 1999; Max, Lynch, Muir, Shoaf, Smoller, & Dubner, 1992; Visovsky, et al., 2007). Gabapentin, currently the most widely used AED, generally is well tolerated (Finnerup, Otto, McQuay, Jensen, & Sindrup, 2005). Carbamazepine also has been tested for preventing CIPN in a nonrandomized pilot study of patients with advanced colorectal cancer receiving oxaliplatin, folinic acid, and fluorouracil (Paice, 2009). Grade 2 to 4 neuropathy was absent in patients given carbamazepine and occurred in 30% of the control group.

Use of TCAs may cause an analgesic effect by ameliorating neuropathic symptoms (Visovsky et al., 2007). At one time, amitriptyline was the most widely used TCA, but it has dose-limiting sedative and anticholinergic side effects (Levy, 1996). Nortriptyline and desipramine (Norpramin) cause fewer side effects, and their dosages can be titrated upward based upon need (Max et al., 1992). Nortriptyline blocks the reuptake of serotonin and norepinephrine in the pain-modulating system of the central nervous system (Visovsky et al., 2007). However, further studies are needed to establish the effectiveness of TCAs in reducing symptoms associated with CIPN.

Table 5. Nonopioid pharmacotherapy: Drugs and dosing

Drug	Dosage
Antiepileptics	
Gabapentin	100–1,200 mg/day PO in 3 divided doses
Carbamazepine	100–400 mg PO twice daily
Pregabalin (Lyrica)	100–600 mg/day PO in 2–3 divided doses
Tricyclic antidepressants	
Amitriptyline	50–150 mg/day PO
Nortriptyline	10–150 mg/day PO
Desipramine (Norpramin)	50–200 mg/day PO
Venlafaxine (Effexor)	37.5–225 mg/day PO in 2–3 divided doses
Duloxetine (Cymbalta)	30–60 mg/day PO
Topical therapy	
Lidocaine patch 5%	Apply up to 3 patches topically at one time, for up to 12 hours within a 24-hour period
Lidocaine and prilocaine cream	Apply a thin layer topically to intact skin in the affected area and apply an occlusive dressing

Note. Opioid dosing has no ceiling and can be titrated up as needed for pain control. Adapted from Carceni et al. (2004); Galer et al. (1999); Max et al. (1992); Visovsky, et al. (2007).

Topical anesthetics, such as transdermal lidocaine patches, are another noninvasive, cost-effective method of treating neuropathic pain and are particularly useful for pain flare-ups (Galer, et al., 1999; Paice, 2009). Lidocaine 5% has been approved by the US Food and Drug Administration to treat neuropathic pain (Table 5). Overall pain relief should be achieved in 2 to 4 weeks after initiating therapy. The topical eutectic mixture of lidocaine and prilocaine (EMLA) cream also can be used as a topical treatment for CIPN (Table 5).

Nonpharmacologic treatments are also important to consider when managing CIPN and can be helpful during pain flares by enhancing management of discomfort (Paice, 2009). Behavioral modification techniques (e.g.,

relaxation, guided imagery, distraction, cognitive reframing, support groups) are helpful, as are physical techniques such as heat, cold, or massage therapy. Physical activity, particularly strengthening exercises, has also been moderately effective in reversing losses in muscle strength related to diabetic neuropathy, but trials in patients with CIPN are lacking (Visovsky, 2009).

Role of the Advanced Oncology Practitioner

The advanced oncology practitioner plays a crucial role in educating patients about the potential side effects of chemotherapy and providing continual assessment and monitoring of patients at risk for CIPN. Early and continual assessment, along with appropriate intervention, is necessary. Referrals to physical therapy or pain management are also appropriate. The advanced oncology practitioner also must be vigilant about monitoring the severity of symptoms and must intervene if modification or discontinuation of therapy is warranted.

DISCLOSURES

The author has no potential conflicts of interest to disclose.

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