Peripheral neuropathy (PN) is characterized as any injury, inflammation, or degeneration of the peripheral nerve fibers (Armstrong, 2000). Loss of motor and sensory nerve function results from an insult to the peripheral nerve fibers. As many as two million Americans may be unaware that they have PN (Mayo Clinic, 2000). When a patient receives certain chemotherapy agents, such as cisplatin, vinca alkaloids, and taxanes, chemotherapy-induced PN (CIPN) may occur. Patients with preexisting PN may experience exacerbated PN when these chemotherapeutic agents are administered. The neurologic side effects of CIPN range from interference with normal daily function to life-threatening neurologic damage. Oncology nurses can effect the detection and treatment of CIPN; therefore, oncology nurses must be aware of the potential impact of CIPN, the pathophysiology of the peripheral nervous system, how chemotherapy can induce PN, and what interventions are used to manage CIPN.

Pathophysiology of Peripheral Nerves

The peripheral nervous system functions to communicate signals between the central nervous system and the periphery of the body. With the exception of cranial nerves (CNs) I and II, the CNs are part of the peripheral nervous system (Seidel, Ball, Dains, & Benedict, 1999). Anatomically, the peripheral nerves arise from the spinal cord or CNs. Peripheral nerve fibers made of axons and dendrites are arranged in nerve bundles called fascicles. Fascicles are covered by the epineurium, perineurium, and endoneurium. These three layers of covering serve several important functions. They provide structural support, blood supply, and interstitial electrolyte storage compartments to the human body. Electrolytes are essential for nerve impulse conduction. The peripheral nerves conduct impulses to the skin and muscles of the limbs from the spinal nerve roots and follow a dermatome pattern. The CNs arise from the brain stem and innervate specific anatomic structures (Sugerman, 2001).

The peripheral nerve fibers are categorized as either motor or sensory in function. The axons are covered with Schwann cells, which produce and maintain the myelin sheath.

The distinction between motor or sensory fibers comes from whether the fiber is myelinated or unmyelinated. Motor fibers are larger, myelinated fibers ranging in diameter from 2–20 µm and conduct action potentials at a high rate of speed. Motor fibers are responsible for vibration sense, strength, movement, and proprioception (Vallat & Vallat-Decouvelaere, 2001). Sensory fibers are the smaller, unmyelinated fibers with an average diameter of 2 µm. Sensory fibers conduct action potentials at a velocity slower than motor fibers. Four to six times more sensory fibers exist than motor fibers. Sensory fibers are responsible for the transduction of pain and temperature signals (Vallat & Vallat-Decouvelaere). In
addition to pain and temperature signals, the small fibers carry autonomic system signals (Corse & Kunel, 1999). Motor and sensory fibers are contained within the fascicles.

Classifications of Peripheral Neuropathy

PN can have multiple causes that produce motor, sensory, or autonomic dysfunction. The type of nerve fiber affected and location of the lesion classify the disorder but not the etiology of the disorder (Chalk & Dyck, 2000). Mononeuropathy involves lesions of the nerve root or peripheral nerve fiber. Symptoms generally are caused by compression or trauma to the nerve and are asymmetrical. Polyneuropathy generally is caused by a disease process that affects many peripheral nerves; therefore, symptoms are symmetrical. Damage to the peripheral nerve can occur at the axon or the myelin sheath. The longer fibers generally are involved first. Symptoms of neuropathy initially begin at the feet and progress to the hands, hence the term “stocking-glove syndrome” (Corse & Kunel, 1999). CIPN generally is a polyneuropathy.

Causes and Clinical Features

PN commonly is associated with other disease states and often is unrecognized. Figure 1 summarizes the major causes of PN. Administering chemotherapy agents that cause PN in patients with preexisting PN or those who have risk factors for PN increases the likelihood that chemotherapy will induce PN (Armstrong & Gilbert, 2002). Because of these compounding problems, oncology nurses should be aware of the symptoms associated with this disorder. The symptoms of PN are the result of which nerve is involved, the etiology of the disorder, and the length of time the syndrome has been present. Major symptoms include weakness, pain, muscle atrophy, loss of sensation, and loss of deep tendon reflexes. If the autonomic nerves are involved, symptoms might include urinary incontinence, constipation, impotence, and orthostatic hypotension (Corse & Kunel, 1999). Table 1 describes the various types of pain associated with PN.

Chemotherapy Agents Associated With Peripheral Neuropathy

CIPN is a dose-limiting toxicity (Armstrong & Gilbert, 2002). The possibility of severe PN occurring when receiving one of the PN-inducing chemotherapy agents is 3%–7%. When receiving more than one agent at a time, the risk of PN increases (Cavaletti & Zanna, 2002).

Cisplatin

Cisplatin is the chemotherapy agent most commonly associated with PN. It causes demyelination and axonal damage in the dorsal root ganglia that may be irreversible (Voss & Wilkes, 1999). Cisplatin affects the large fiber neurons and causes problems with proprioception and vibration (e.g., foot drop resulting from the loss of deep tendon reflexes). Demyelination of the spinal cord nerves is responsible for Lhermitte’s sign, which is the occurrence of a sudden, shock-like sensation when the neck is flexed (Voss & Wilkes). PN associated with cisplatin is dose related and generally occurs when patients receive a cumulative dose of 300 mg/m² or more (Almadrones, Armstrong, Gilbert, & Schwartz, 2002). Some patients may not notice symptoms until therapy is completed. These symptoms slowly progress and may become permanent (Posner, 2001).

Vinca Alkaloids

Vinca alkaloids include vincristine, vinorelbine, vinblastine, and etoposide. These agents disrupt the microtubules and cause degeneration of the axon cytoskeleton. Although both types of fibers can be affected, primarily small fibers are affected. Symptoms of PN caused by vinca alkaloids include paresthesia, loss of deep tendon reflexes, orthostatic hypotension, and slowed gastrointestinal motility. These symptoms are reversible. Paralytic ileus and bowel perforation are complications of autonomic nervous system neuropathy (Voss & Wilkes, 1999). Vincristine frequently is associated with constipation related to autonomic nervous system damage; therefore, patients who receive vincristine need to monitor their bowel patterns and report any changes to a nurse or physician.

Taxanes

Paclitaxel and docetaxel cause damage to the microtubules and injury to the axon and myelin sheath that can result in mixed sensory and motor neuropathies. PN associated with paclitaxel is dose related. Doses greater than 250 mg/m² of paclitaxel may cause sensory neuropathy that can be complicated by ataxia and muscle weakness (Posner, 2001). Neuropathy associated with docetaxel is less severe and less frequent than neuropathy associated with paclitaxel. Symptoms associated with taxane-derived PN are paresthesia and loss of deep tendon reflexes, proprioception, vibration sense, and fine motor skills. Symptoms may begin within 24 hours after administration of the drug and may last as long as six months after therapy is completed (Voss & Wilkes, 1999).

Miscellaneous Agents

Other chemotherapeutic agents can cause PN, including methotrexate, high-dose cytarabine, procarbazine, and oxaliplatin. Other drugs used in oncology, such as interferons, thalidomide, and corticosteroids, also can cause neurotoxicities. When chemotherapy agents are combined with other agents that cause PN, or when patients have preexisting PN, the risk of

| TABLE 1. TERMS FOR THE TYPES OF PAIN ASSOCIATED WITH PERIPHERAL NEUROPATHY |
|-----------------|----------------------------------|
| **TERM**       | **DESCRIPTION OF PAIN**          |
| Allodynia  | Pain induced by a stimulus that usually does not cause pain, such as a light touch |
| Anesthetic | A lack of sensation               |
| Causalgia   | Burning type of pain              |
| Dysesthesia | An unpleasant abnormal sensation |
| Hyperesthesia| An increase in sensation           |
| Paresthesia | A sensation of numbness, tingling, or prickling |

*Note: Based on information from Armstrong, 2000; Pett, 2001.*
CIPN dramatically increases (Armstrong, 2000). Knowledge of side effects of chemotherapy and patients’ histories can assist oncology nurses in prevention, detection, and treatment of CIPN.

**Assessment**

Patients receiving chemotherapy agents that can cause PN should be screened for the presence of PN prior to initiating treatment. After treatment is initiated, patients need to be assessed routinely for the onset of CIPN (Armstrong & Gilbert, 2002). Assessment for the presence of PN includes testing CNs, evaluating cerebellar function and proprioception, assessing sensory function, and testing deep tendon reflexes (Seidel et al., 1999). Table 2 summarizes the assessment procedures used in evaluating for PN.

**Pharmacologic Interventions**

Most of the current treatments used for CIPN are aimed at symptom control. However, prevention of CIPN is being incorporated into the clinical setting. Although not approved by the U.S. Food and Drug Administration for this indication, amifostine frequently is used to prevent neurotoxicities associated with cisplatin, paclitaxel, and carboplatin. The dose used is 740 mg/m² administered via IV over 15 minutes. Side effects of the infusion may include hypotension, severe nausea, and vomiting. Patients must be pretreated with an antiemetic, dexamethasone, and IV hydration. To decrease the possibility of adverse effects, patients must be kept supine prior to, during, and immediately following the infusion. Because of the possibility of hypotension during the infusion, monitoring the blood pressure is warranted (Voss & Wilkes, 1999). If CIPN occurs despite preventive pharmacologic efforts, measures to control symptoms should be initiated.

Analgesics may be used for symptom relief of CIPN. However, they do not prevent or treat the underlying neuropathy. In 2002, the ONS Foundation and the Purdue Frederick Company funded a multidisciplinary team to address evidence-based practice standards for CIPN. The team developed a treatment algorithm for CIPN that was modeled after the World Health Organization’s tiered pain relief algorithm. Pharmacologic intervention for CIPN begins at level one and progresses to level three (Smith, Whedon, & Bookbinder, 2002).

**Table 2. Assessment Skills Used to Evaluate the Neurologic System**

<table>
<thead>
<tr>
<th>Function</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar and proprioception</td>
<td>• Evaluate rapid alternating movements of the hands.</td>
</tr>
<tr>
<td></td>
<td>• Observe for accurate movement of the extremities.</td>
</tr>
<tr>
<td></td>
<td>• Evaluate balance using the Romberg test: Have the patient stand with feet together and arms at the sides with his or her eyes open and closed. Slight swaying is normal.</td>
</tr>
<tr>
<td></td>
<td>• Observe the patient’s gait for stride and stance.</td>
</tr>
<tr>
<td></td>
<td>• Test for response to touch and pain.</td>
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<tr>
<td></td>
<td>• Check for vibration sense using a tuning fork.</td>
</tr>
<tr>
<td></td>
<td>• Evaluate position sense: Move a finger or great toe up and down while patient’s eyes are closed; have the patient identify the position of the digit.</td>
</tr>
<tr>
<td></td>
<td>• Assess for discrimination between sharp and dull sensation.</td>
</tr>
<tr>
<td></td>
<td>• Evaluate the ability to distinguish the body part being touched.</td>
</tr>
<tr>
<td></td>
<td>• Evaluate for stereognosis, the ability to distinguish a common object such as a coin.</td>
</tr>
<tr>
<td></td>
<td>• Evaluate for graphesthesia, the ability to identify a common letter or number drawn on the hand.</td>
</tr>
<tr>
<td>Sensory function</td>
<td>• Test for deep tendon reflexes (biceps, brachioradial, triceps, patellar, Achilles).</td>
</tr>
<tr>
<td></td>
<td>• Check for clonus.</td>
</tr>
<tr>
<td>Deep tendon reflexes</td>
<td>• Test for deep tendon reflexes (biceps, brachioradial, triceps, patellar, Achilles).</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Seidel et al., 1999.

**Level One**

In the first level of intervention for CIPN, over-the-counter (OTC) pain relievers are used to treat mild symptoms. OTC drugs recommended for use with CIPN are acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). The recommended doses are extended-relief acetaminophen at 1,300 mg three times a day or an NSAID, such as ibuprofen, of 800 mg three times a day (Smith et al., 2002). However, these medications are contraindicated in patients with impaired hepatic or renal function and those with duodenal ulcers (Paice, 1996). Patients should be instructed to take these medications with food. Because of the potential for hepatic necrosis with large doses of acetaminophen, patients should not exceed a daily dose of 4 g or 4,000 mg (Paice).

**Level Two**

Level two management includes the moderately potent drug classifications of neuroleptics and tricyclic antidepressants (Smith et al., 2002). Antidepressants such as amitriptyline, imipramine, and nortriptyline, with dosages of 25–75 mg at bedtime, are used to treat burning, shooting, or tingling pain. Side effects of antidepressant medications include dizziness, dry mouth, drowsiness, weakness, weight gain, and constipation (Mayo Clinic, 2000).

Anticonvulsant medications such as gabapentin, phenytoin, and carbamazepine are used for jabbing pain (Mayo Clinic, 2000). The starting dose of gabapentin is 300 mg daily, and it can be titrated slowly to a maximum daily dose of 3,600 mg (Backonja et al., 1998). Gabapentin can be used as an alternative to amitriptyline in people unable to tolerate the antidepressant, such as the elderly or people at risk for cardiac arrhythmias (Kupecz, 2001). However, gabapentin causes drowsiness; patient teaching should include advising patients to take this drug at bedtime. Patients taking gabapentin in divided doses throughout the day should be advised to avoid driving or operating equipment. The dosing of phenytoin is 300–500 mg per day to achieve a serum level of 15–20 mcg/ml. Carbamazepine is given at a dose of 200–1,000 mg per day in two to three divided doses to maintain a serum level of 8–12 mcg/ml (Corse & Kune, 1999). Side effects of anticonvulsant medications include drowsiness and confusion. When using phenytoin and carbamazepine, periodic laboratory testing is required to monitor serum levels of the drugs. The cost and inconvenience of extra laboratory testing should be considered when using these anticonvulsant medications. The action of the antidepressants and anticonvulsants is a result of interference with neurotransmitters in the brain (Mayo Clinic).

**Level Three**

Level three management involves the use of potent opioids. Similar to the pain relief ladder, the CIPN ladder can involve combinations of drugs from all levels to achieve the maximum benefit in reducing the symptoms of PN (Smith et al., 2002).

A paucity of research addresses interventions for CIPN. Therapeutic interventions for CIPN are borrowed from other PN intervention studies, such as interventions used with diabetes and HIV. Apfel et al. (2000) studied the use of nerve growth factor in diabetic patients with polyneuropathy. Nerve growth factor is involved with the survival mechanisms that prevent the growth of pathological nerve fibers.
of the small fiber sensory neurons. The effects associated with PN to these neurons include pain and temperature changes. The objective of the study was to determine the effects and safety of nerve growth factor used for one year in diabetic patients with PN. A total of 1,019 men and women diagnosed with diabetes and sensory polyneuropathy were entered into a randomized, double-blind study. Patients were assigned to receive subcutaneous injections of either nerve growth factor (n = 504) or a placebo (n = 515) three times a week for 48 weeks. Patients were evaluated qualitatively using the Neuropathy Impairment Score, Neuropathy Symptoms and Change, and a monofilament test prior to being enrolled in the study and again at 12, 24, and 48 weeks after enrollment. Quantitative testing for sensory symptoms used nerve conduction testing, cooling detection threshold, vibratory detection threshold, and heating pulses. The tests were conducted at baseline and at the completion of the study. Adverse events were reported as pain at site of injection, myalgia, and peripheral edema. Qualitatively, 45% of the recipients of the nerve growth factor reported an improved quality of life and ability to complete activities of daily living. Quantitative testing did not demonstrate any benefit of nerve growth factor over the placebo. The researchers concluded that use of nerve growth factor in sensory polyneuropathy associated with diabetes was safe to administer but failed to show any statistical benefit (Apfel et al.). Only further studies will provide data on whether the use of nerve growth factor could have a statistical clinical benefit when used with CIPN.

Current research efforts specifically devoted to CIPN are limited. According to the U.S. National Library of Medicine (2002), clinical trials involving the use of either gabapentin or Neotrofin™ (AIT-082, letrazim potassium, NeoTherapeutics, Inc., Irvine, CA) are under way. To keep up to date on clinical trials addressing CIPN, access the National Institutes of Health Web site at http://clinicaltrials.gov.

In addition to the prescriptive and OTC pharmacologic interventions used for CIPN, nutritional supplements also are being investigated. Glutamine is an amino acid that has been explored as a supplement in managing the side effects of chemotherapy (Armstrong & Gilbert, 2002; Decker, 2002). Vahdat et al. (2001) conducted a nonrandomized cohort study to determine whether glutamine reduced PN associated with administration of paclitaxel. The first group of patients (n = 33) did not receive glutamine, whereas the second group of patients (n = 12) received 10 g of glutamine three times a day for four days, starting 24 hours after receiving paclitaxel. Patients received a baseline neurologic examination that included a grading of PN symptoms. The examination was repeated two weeks after paclitaxel was administered. Nerve conduction studies were completed on 39 of the 45 patients. Patients using glutamine after receiving paclitaxel had a reduction in dysesthesia, numbness, and motor weakness and had increased ability to complete activities of daily living. The study findings are not generalizable because of the small sample size and study design. The researchers recommended a larger, randomized, placebo-controlled study (Vahdat et al.).

Nonpharmacologic Interventions

Drug-free therapies and interventions have been used to treat PN. Nurses have the opportunity to assist patients in the use of nondrug interventions alone or in conjunction with medication. One nondrug intervention is transcutaneous electronic nerve stimulation (TENS). TENS is used to block the conduction of the nerve signal to the brain through the use of electrical impulses. TENS is safe and painless.

Nurses can teach relaxation techniques, another safe and painless nondrug intervention that can reduce muscle tension that increases pain. Common relaxation techniques include deep-breathing exercises, yoga, meditation, and visual or guided imagery. Patients can be referred to other practitioners for hypnosis, biofeedback, and acupuncture.

Exercise also may be beneficial in reducing neuropathic pain (Mayo Clinic, 2000). In addition to reducing pain, exercise may improve balance in patients with sensory PN (Richardson, Sandman, & Vela, 2001). To determine the effects of exercise on balance, a study randomized 20 subjects to two study groups. The experimental group exercised daily for three weeks (Richardson et al.). The exercises included a warm-up phase involving range of motion to the ankle followed by heel and toe raises, inversion and eversion of the feet, wall slides, and balancing on one foot. At the conclusion of the three weeks, the intervention group had improved balance as measured by unipedal stance, tandem stance, and functional reach. Patients with deficits in two of the three balance measurements were at risk for falls. Limitations of the study included the small sample size, short duration of the intervention, and lack of a double-blind research design (Richardson et al.). If patients have significant deficits in walking, dressing, or toileting as a result of CIPN, a referral to a physical or occupational therapist may be warranted.

OTC topical creams have been recommended for pain relief associated with PN (Huebscher, 2000). Capsaicin cream applied three or four times a day may alleviate pain in a limited area. The cream’s primary ingredient comes from chili peppers and works by depleting substance P, which is involved in the transmission of pain signals (Huebscher). Patients should be cautioned to wear gloves when applying the cream and should immediately wash their hands. They may experience stinging or burning at the application site. These symptoms will resolve with continual use of the product (Huebscher). Figure 2 presents a summation of the pharmacologic and nonpharmacologic interventions used to treat CIPN.

Educating patients and identifying safety issues are important aspects of interventions by nurses. Suggestions include providing adequate lighting in the home, keeping floors clear of clutter and throw rugs, and keeping hot water heater temperature below 110°F (Almadrones & Arcot, 1999). Almadrones and Arcot published a patient education tool titled “Patient Guide to Peripheral Neuropathy.” The article guides nurses in providing practical tips for patients and caregivers to use in the home. Addressing the safety needs of patients includes a discussion about whether patients should drive. Deficits caused by CIPN can interfere with...
the ability to feel the pedals and grasp the steering wheel. Nurses are in an ideal position to assess, educate, and provide decision-making guidance for patients concerning this safety issue.

Summary

CIPN is a phenomenon encountered by oncology healthcare providers. Knowledge of its etiology, symptoms, and treatment is imperative to oncology nurses. Armed with this information, oncology nurses are in a position to positively impact patients’ quality of life. Nurses can have a major impact on outcomes for patients receiving chemotherapy that causes PN. All of these factors together have an impact on what oncology nursing is all about—providing the best care for patients.

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References


Rapid Recap

Updating Your Peripheral Neuropathy “Know-How”

• Presenting symptoms of chemotherapy-induced peripheral neuropathy (CIPN) are related to the fibers affected.

• CIPN is a dose-limiting toxicity.

• Preexisting conditions, such as diabetes or pernicious anemia, increase the likelihood of developing CIPN.

• Causative agents include cisplatin, vinca alkaloids, and taxanes.

• Patients need to be assessed for peripheral neuropathy prior to initiating chemotherapy and routinely throughout treatment.

• Safety recommendations should be incorporated into patient education for all patients receiving chemotherapy agents that may cause CIPN.