

Mechanisms and Management of Neuropathic Pain in Cancer

Judith A. Paice, PhD, RN, FAAN

Neuropathic pain is a common syndrome seen in persons treated for cancer. The underlying mechanisms of such pain are poorly understood. Consequently, treatment is often inadequate, and patients suffer needlessly. Knowledge regarding the pathophysiology of cancer-related neuropathic pain, expertise in appropriate assessment techniques, awareness of the more common neuropathic pain syndromes seen in those with cancer, and attention to new pharmacologic interventions will lead to improved pain relief. Furthermore, rehabilitation of persons with neuropathic pain should be considered to limit functional impairment and to address safety factors so as to reduce accidents resulting from the sensory loss common to a variety of neuropathic pain states in cancer.

Neuropathic pain is defined as “pain initiated or caused by a primary lesion or dysfunction in the nervous system” [1]. The exact prevalence of neuropathic pain is unknown, particularly in the cancer population. However, several extrapolations can be drawn to suggest the enormity of the problem. For instance, nearly 20% of patients with herpes zoster, a common phenomenon in cancer, will develop postherpetic neuropathy, and up to 80% of people with limb amputation suffer phantom pain [2].

Neuropathic pain can be of peripheral origin, such as postherpetic or chemotherapy-induced neuropathy, or from a central etiology, such as pain after stroke or involvement of the spinal cord with a tumor. The prevalence of neuropathic pain seems to be increasing, due, in part, to the aging population (as with postherpetic neuropathy), as well as the increasing use of neurotoxic agents in the management of life-threatening illness, such as paclitaxel

Abstract Neuropathic pain is a common syndrome in people with cancer. The pathophysiology of such pain in cancer is not fully understood, often leading to poor management and needless suffering. Knowledge regarding the *potential* mechanisms of neuropathic pain, skill in appropriate history-taking and physical-assessment techniques, and awareness of the more common neuropathic pain syndromes and their etiologies, as well as familiarity with the role of new pharmacologic interventions, will allow healthcare professionals to provide better relief of neuropathic pain. At present, a variety of agents are used to treat neuropathic pain situations. Rehabilitation of persons with neuropathic pain should be part of overall management and should address functional impairment and safety factors to prevent accidents resulting from sensory loss.

(Taxol), thalidomide (Thalomid), anti-retrovirals, and other agents. Because neuropathies are so common in patients with cancer, all health professionals caring for these patients should have a basic understanding of the mechanisms—and a *thorough* knowledge of the management—of this often difficult to manage pain syndrome.

Pathophysiology of Neuropathic Pain

Neuropathic pain represents a diverse set of syndromes, and, as a result, one mechanism or etiology cannot explain the underlying pathology. Changes may occur in the peripheral, central, and autonomic nervous system, and each can contribute to the development of chronic neuropathic pain. In fact, multiple mechanisms may well be involved in most neuropathies.

In the peripheral nervous system, several mechanisms have been proposed to explain the generation of neuropathic pain [3, 4], including abnormal nociceptor sensitization and ectopic impulse generation. After nerve injury, regenerating axons discharge spontaneously, and the threshold to various noxious stimuli is lowered. Thus, the neuron becomes more sensitive to any stimulation, leading to spontaneous pain and hyperalgesia. Another putative

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peripheral mechanism for neuropathic pain is the increased sensitivity of afferent neurons to sympathetic nervous system activation and noradrenergic agonist receptor binding. In addition, various neuropeptides, such as the cytokine tumor necrosis factor- α , are released in response to inflammation, specifically macrophage activation. These cytokines are believed to generate spontaneous ectopic activation of nociceptors. Other hypothesized peripheral mechanisms include the development of ephaptic conduction between sensory neurons and alterations in ion-channel expression, including down-regulation of Na^+ channels and loss of N-type Ca^{++} channels.

SOME PROBLEMS SPECIFIC TO ONCOLOGY

Unique to oncology is the role of chemotherapy-induced damage to peripheral sensory neurons. The precise mechanisms are unknown and likely vary with the chemotherapeutic agent administered. However, recent advances in the laboratory provide some information regarding the damage incurred to the nervous system. For example, paclitaxel administered to rats produces symptoms of peripheral neuropathy similar to those seen in humans, including hyperalgesia (an increased response to stimuli that are usually painful) and allodynia (pain due to light touch or other stimuli that are not usually painful) [5]. Although no degeneration was seen in the dorsal root ganglia or dorsal horns, endoneural edema was seen on electron microscopic examination of the sciatic nerve.

In studies of vincristine-induced peripheral neuropathy in the rat, the animals experienced hyperalgesia to touch, and conduction velocities in sensory fibers were slowed [6]. In other studies involving vincristine, large-diameter sensory neurons became swollen, and neurofilaments in the cell bodies and axons increased in number, suggesting impaired anterograde axonal transport [7].

Central nervous system changes also contribute to the development of neuropathic pain. In the spinal cord, neuropathic pain is associated with central sensitization of nociceptive neurons [8, 9]. Central sensitization refers to changes in the primary afferent and spinal neurons that alter nociceptive responses. Hyperalgesia, where the patient will describe severe pain to a stimulus that in most situations is only mildly painful (eg, a pinprick), is believed to be one result of this process. Central sensitization is mediated, in part, through neuro-

peptides, such as substance P, and excitatory amino acids that activate the N-methyl-D-aspartate (NMDA) receptor, including glutamate. Reorganization of primary afferent input within the dorsal horn of the spinal cord may also contribute to the central mechanisms of neuropathic pain. As peripheral nerve damage occurs, C-fiber terminals within the dorsal horn of the spinal cord degenerate. The resulting vacancy allows sprouting of $\text{A}\beta$ -mechanoreceptors into lamina II, creating the opportunity for innocuous stimuli, such as touch, to activate central nociceptors. The clinical expression of this may be tactile allodynia, where light touch is perceived as pain, a phenomenon often seen in neuropathic pain states.

Decreased inhibitory pain pathways, including decreased levels of gamma-aminobutyric acid (GABA) receptors in the spinal cord and decreased blood and cerebrospinal fluid levels of adenosine may also add to the phenomenon of neuropathic pain [10]. Finally, cortical changes have been described as a consequence of chronic neuropathic pain [11]. Better understanding of the peripheral and central mechanisms of neuropathic pain in cancer will eventually lead to improved therapeutic options.

Common Neuropathic Pain Syndromes in Oncology

Painful neuropathies are common in people with cancer and may arise from the tumor itself, from treatment of the cancer, or may be totally unrelated to the cancer [12–14]. Common cancer-related and non-cancer-related neuropathic pain syndromes are listed in Table 1. Of the many etiologies of neuropathies in cancer, chemotherapy-induced neuropathic pain is particularly troublesome, and the use of agents known to produce peripheral neuropathy is increasing. Thus, patients enjoy improved life expectancies, yet reduced quality of life due to significant pain and impaired function.

Although many chemotherapeutic agents have been implicated, cisplatin (Platinol), ifosfamide (Ifex), paclitaxel, and vincristine in particular are known to consistently cause peripheral neuropathies [15]. In addition, oxaliplatin (Eloxatin) administered parenterally produces an initial, acute, cold allodynia, sometimes within minutes of beginning the infusion. Patients experience this as painful numbness when picking up a cold drink or when they leave the clinic to face cold temperatures. This may be followed by a persistent neuro-

Table 1**Common Neuropathic Pain Syndromes**

Cancer-related
Brachial plexus neuropathies
Chemotherapy-induced neuropathy
Cisplatin
Oxaliplatin
Paclitaxel
Thalidomide
Vincristine
Vinblastine
Cranial neuropathies
Postherpetic neuropathy
Post-radiation plexopathies
Surgical neuropathies
Phantom pain
Post-mastectomy syndrome
Post-thoracotomy syndrome
Non-cancer-related causes of neuropathies
Alcohol-induced neuropathy
Brachial plexus avulsion (trauma)
Carpal tunnel syndrome
Complex regional pain syndrome
Diabetic neuropathy
Fabry's disease
Failed-back syndrome
Guillain-Barré syndrome
HIV-associated neuropathy
Viral involvement
Antiretrovirals
Post-stroke pain
Trigeminal neuralgia
Vitamin deficiencies

pathy, similar to that induced by other chemotherapeutic agents [16]. Intrahepatic infusion of oxaliplatin also has been shown to cause peripheral neuropathy [17]. Most chemotherapy-induced neuropathies are dose-related, and regimens that include concomitant administration of implicated agents increase the risk of developing peripheral neuropathy.

Cancer patients with preexisting peripheral neuropathy due to other conditions, such as diabetes, ischemic vascular disease, or nutritional deficiencies, may be at greater risk for the development of peripheral neuropathies after chemotherapy. Medications such as ciprofloxacin (Cipro), ethambutol (Myambutol), gentamicin, isoniazid, metronidazole, phenytoin, and the statins can also increase risk.

Diagnosis

The diagnosis of neuropathy begins with a thorough history and continues with a comprehensive physical examination [18]. During the history, patients often use terms such as "burning," "tingling," "electrical," "stabbing," or "pins and needles" to describe neuropathic pain. They may describe tactile allodynia, or pain as a result of light touch. A common complaint is the inability to tolerate clothing touching the skin or the movement of air from a fan or an air-conditioning vent blowing on the affected area. The patient also may describe painful paresthesias in the affected area.

The location of the pain is critical in determining the underlying etiology. The location may be in a stocking or glove distribution, as seen in diabetic or chemotherapy-induced neuropathy, or along a single dermatome as a result of postherpetic neuropathy. Central pain after stroke or some brain tumors can occur diffusely throughout the body. In general, the distribution of neuropathic pain follows a nerve, plexus, root, or the cord. The pain may have a temporal pattern, worsening at different times during the day or night and is often exacerbated by activity, such as movement or walking. Patients should be questioned regarding changes in gait, including frequent falls, as this may be a result of decreased sensation and motor weakness. Another indicator of decreased sensation associated with neuropathy is the report of frequent bruises in the affected region.

Because the autonomic nervous system may be affected, patients may report dizziness, constipation or other changes in bowel function, urinary retention, and impotence. Careful questioning is indicated to differentiate whether these symptoms are due to autonomic nervous system dysfunction, dehydration, poor compliance with a laxative/softener regimen, or depression.

PHYSICAL EXAMINATION

A comprehensive physical evaluation is crucial, with particular attention to the neurological examination, including the sensory, motor, and autonomic systems. Sensory evaluation can differentiate large-fiber vs small-fiber damage. Reduced sensation to vibration or an altered ability to sense proprioception suggests large neuronal fiber damage, as seen with cisplatin. Changes in temperature sensation in the affected region and altered response to a pinprick are

common indicators of small-fiber dysfunction. Although vincristine produces both large- and small-fiber damage, small sensory fibers are affected to a greater extent.

The evaluation of tactile allodynia includes lightly stroking the area with a brush or cotton ball. Holding a cool or warm item lightly against the skin can test for thermal allodynia. Reflexes, too, should be tested, particularly in the affected areas; often they are found to be reduced or absent. Standard motor evaluation should include observation of gait, as well as assessment of strength and tone. A slapping gait and foot drop are common in neuropathies, and safety measures may be indicated to prevent falls.

ADDITIONAL STUDIES THAT MAY BE INDICATED

In some cases, additional diagnostic studies, such as CT, MRI, or electromyography, may be indicated. The primary purpose of the history, physical, and diagnostic evaluation is to establish the diagnosis, rule out potentially treatable causes, and establish a baseline upon which to gauge the efficacy of analgesic therapy.

Pharmacologic Management

Although few studies of neuropathic pain have been conducted in people with cancer, a variety of pharmacologic therapies have been shown to be effective in relieving nonmalignant neuropathic pain. See Figure 1. An important recommendation in initiating pharmacologic therapy for neuropathic pain is to introduce one drug at a time, with gradual upward titration, based upon the patient's response. Prescribing several agents at one time precludes determination of the most effective agent or, if side effects occur, the agent responsible for the complications.

NON-OPIOIDS

Non-opioids, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, have limited usefulness in the management of neuropathic pain [19]. However, some patients do report relief, so a trial may be indicated. Many patients have concomitant neuropathic and nociceptive pain, which may respond to non-opioids.

OPIOIDS

In the past, neuropathic pain was often referred to as "opioid-nonresponsive pain," but more recent

studies suggest that opioids may indeed be effective in relieving this type of pain [20, 21], though higher doses of opioids may be needed. Scheduled dosing is preferred to prn dosing, beginning with a low dose and gradually titrating upward. Due to the wide variability in response to the opioids, failure to respond to one opioid should not eliminate them as a possible treatment, but rather rotation—switching—to another opioid should be considered [22]. As with any use of opioids, attention must be given to prevention and management of potential side effects, particularly constipation.

ADJUVANTS

Corticosteroids. Although there have been no randomized clinical trials, corticosteroids have long been used to treat a variety of neuropathic pain states, particularly those related to cancer [13, 23]. Dexamethasone has the least mineralocorticoid effect, and, due to the long duration of effect, dosing can be scheduled once per day. This dosing schedule fosters adherence and prevents sleep disturbances that may result from the stimulant effects of this drug when administered in the afternoon or evening. Unfortunately, immunosuppressant and endocrine effects limit long-term use. Proximal muscle wasting also can occur after 4–6 weeks of therapy.

Anticonvulsants. Older anticonvulsants, particularly carbamazepine, phenytoin, or valproate, have been used extensively to treat neuropathic pain, yet potential adverse effects require careful monitoring, particularly for neutropenia and megaloblastic anemia. The newer anticonvulsant, gabapentin (Neurontin), approved for treatment of complex partial seizures, has been shown to have analgesic properties in both animal and human models of neuropathic pain. Two well-designed, randomized, controlled, multicenter studies evaluated the efficacy of gabapentin in postherpetic neuropathy and diabetic neuropathy [24, 25]. Using doses of up to 3,600 mg/day, mean daily pain-intensity scores decreased significantly and other secondary outcome measures, such as sleep and mood, improved when compared with the placebo groups. The most common side effects, dizziness and somnolence, appear to be reduced with more gradual upward dose titration. As a result of gabapentin's efficacy and limited adverse effects, it has become the first-line therapy in most neuropathic pain states.

Tricyclic antidepressants. Tricyclic antidepressants block the reuptake of biogenic amines,

including serotonin and norepinephrine [23]. Because of the anticholinergic effects of agents such as amitriptyline, they may not be well tolerated, particularly in the elderly. Alternative agents, with fewer adverse effects, include nortriptyline (Aventyl, Pamelor) and desipramine (Norpramin, Pertofrane) [26]. Patients with preexisting conduction abnormalities should have a baseline electrocar-

diogram, as the tricyclic antidepressants can alter cardiac conduction. In all patients, start at a low dose, usually at bedtime, and titrate every 3–7 days, based on the patient's response. Recent studies conducted in cancer patients demonstrate only slight analgesic effects from amitriptyline and nortriptyline [27, 28]. Newer agents, such as venlafaxine (Effexor), a serotonin and norepinephrine

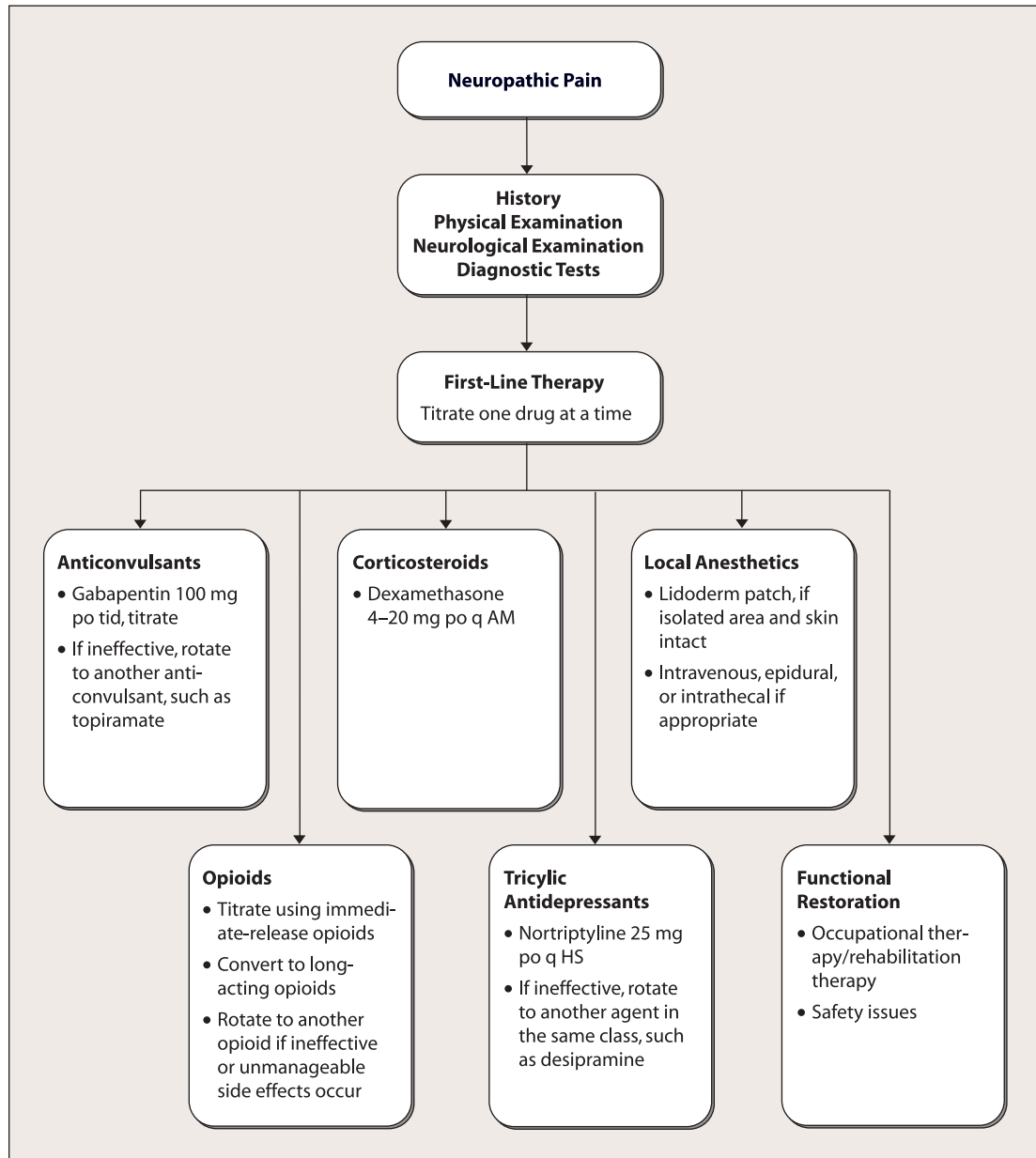


Figure 1 Algorithm for Management of Neuropathic Pain

If these first-line therapies are ineffective, consider other agents, such as GABA-B agonists (baclofen) or NMDA antagonists (such as ketamine). Nerve blocks may be indicated in certain patients. Cancer therapies, such as radiotherapy, may be helpful to reduce tumor size and compression against nerve roots.

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reuptake inhibitor, may be more effective in ameliorating neuropathies in cancer patients [29, 30]. Serotonin selective reuptake inhibitors, such as fluoxetine (Prozac), appear to have little efficacy in relieving neuropathic pain [26].

Local anesthetics. Local anesthetics inhibit pain primarily by blocking sodium channels and are particularly useful in neuropathic pain syndromes. Lidocaine (Lidoderm) (5%) patches have been found to reduce pain related to postherpetic neuropathy, without any significant accumulation of drug in plasma levels after application of up to three patches [31]. Oral lidocaine analogs, such as mexiletine (Mexitil), have been shown to be

effective in some patients. Intravenous lidocaine infusions are gaining acceptance in a variety of pain-management settings, including pain clinics, hospices, and palliative-care centers [32]. A bolus intravenous dose of lidocaine (1–2 mg/kg) is given over 15–30 minutes. If this is effective, it may be followed by a continuous infusion of 1–2 mg/kg/h. In some patients, the effects can be quite prolonged, giving up to weeks of relief. An early warning sign of potential toxicity is perioral numbness. Hepatic dysfunction and significant cardiac conduction abnormalities may be contraindications to treatment, depending upon the patient's prognosis and goals of care. Epidural or

PEER VIEWPOINT

Commentary by Nessa Coyle, PhD, NP, FAAN

Chronic neuropathic pain resulting from injury to the peripheral or central nervous system remains a significant problem for cancer patients. Despite advances in understanding the pathophysiology and molecular biology of neuropathic pain, as outlined by Dr. Paice, management remains suboptimal at best [1]. Anticonvulsant and antidepressant therapies provide partial relief for some patients, but are effective in less than half of patients half of the time [2]. Opioid therapy has been shown to provide additional relief for some patients with neuropathic pain syndromes [3–5], with opioid responsiveness greater in patients with peripheral neuropathic pain [6]. In addition, most patients with cancer have a mixed pain syndrome, that is, a combination of both nociceptive and neuropathic pain, and frequently require combination drug therapy for their pain.

OTHER NEUROLOGICAL PAIN SYNDROMES

Dr. Paice briefly discusses selective neuropathic pain syndromes. However, in addition to those discussed, there are a variety of other common and well-described neurological pain syndromes with which physicians and nurses need to be familiar. These syndromes are associated with both direct tumor involvement and cancer therapy but can also be unrelated to cancer or to its therapy. Early diagnosis is essential to prevent or minimize neurological damage.

The neurological pain syndromes associated

with direct tumor involvement include:

1. Those involving tumor infiltration of the bone, such as metastases to the base of the skull, jugular foramen syndrome, clivus metastases, sphenoid sinus metastasis, and fracture of the odontoid process.

2. Those involving tumor infiltration of nerve, plexus, and meninges, such as peripheral nerve, brachial plexopathy, lumbosacral plexopathy, and leptomeningeal metastases.

Metastases to the base of the skull are most commonly seen in patients with nasopharyngeal tumors but can occur with any type of tumor that metastasizes to bone. Pain is the earliest complaint and may precede neurological signs and symptoms by weeks or months. Early treatment is associated with the greatest improvement in neurological function [7]. Jugular foramen syndrome is associated with occipital pain referred to the vertex of the head and the ipsilateral shoulder and arm and is exacerbated by head movement. Signs and symptoms vary with the cranial nerves involved but may include hoarseness, dysarthria, dysphagia, neck and shoulder weakness, and ptosis.

The presenting symptom for clivus metastases is typically a vertex headache made worse by neck flexion. Lower cranial nerve dysfunction, first unilateral and then bilateral, follows [7].

Sphenoid sinus metastases are characterized by bifrontal headache radiating to both temples, a feeling of fullness, and intermittent retro-orbital pain.

Fracture of the odontoid process in patients with cancer is most often secondary to destruction of the atlas. Typically, patients com-

intrathecal administration of a local anesthetic, alone or in conjunction with an opioid, may provide relief in patients who are not candidates for systemic delivery.

NMDA antagonists. Ketamine (Ketalar) and dextromethorphan are NMDA receptor antagonists that are being explored for use in relieving neuropathic pain. However, despite promising case reports, ketamine often produces adverse effects, such as dissociative reactions and hallucinations, which have limited its use [23]. Methadone is believed to bind not only to opioid receptors but to be an antagonist to the NMDA receptor as well. As a result, this opioid is often selected when treat-

ing neuropathic pain. Magnesium, known to block the NMDA channel, has been given intravenously to patients with neuropathic pain due to cancer and has been reported to provide relief [33]. However, additional studies are needed.

Others. Baclofen (Lioresal) is an antispasmodic that may have some benefit in relieving neuropathic pain, although there have been no studies in cancer patients [34]. Although one study of postsurgical neuropathic pain supports the use of topical capsaicin (Zostrix), other studies in non-cancer patient populations suggest that the pain associated with application of this drug precludes its use [35, 36]. Recent studies in rodents suggest

plain of severe neck pain and neck stiffness without signs of epidural cord compression. The pain frequently radiates over the posterior aspect of the skull to the vertex and is made worse by neck movement, especially neck flexion. Pain is almost always the earliest symptom. If it is not diagnosed early, irreversible neurological damage may occur, and the patient may go on to develop paraplegia or quadriplegia [7].

PAIN DUE TO TUMOR INFILTRATION OF NERVE

The pain associated with tumor infiltration of nerve, plexus, and meninges may be caused by direct tumor infiltration of the nerve, compression or metastatic fracture of bone adjacent to a nerve or nerve root. The peripheral nerve is most commonly infiltrated by tumors that invade the intercostal, paravertebral, or retroperitoneal space. Constant burning pain with dysesthesia in an area of sensory loss is the usual clinical picture. The pain is radicular and tends to be unilateral [7].

Pancoast syndrome represents an example of a specific problem of tumor infiltration of the brachial plexus and is most commonly seen in patients with breast cancer, lymphoma, and lung cancer. Pain is the initial symptom in the majority of patients and is characterized by an aching sensation in the shoulder and paraspinal region. Tumor can infiltrate all levels of the brachial plexus, and associated symptoms are dependent on the level of infiltration. Fifty percent of patients with Pancoast tumor go on to develop epidural cord compression during the course of their illness. Early diagnosis and aggressive treatment

are essential for optimal results. Successful therapy is associated with dramatic relief of pain [7]. In patients who complained of increasing pain after radiation therapy or surgery, recurrent tumor was the cause of the pain in 98% of the cases [7].

Lumbosacral plexopathies associated with pelvic tumors can cause incapacitating pain, as well as leg weakness and associated decreased mobility. They are often seen in the setting of advanced disease, when tumor-directed chemotherapy is no longer effective. The pain is characterized as aching and pressure-like in quality and may be difficult to manage without the use of a combination of epidural opioids and local anesthetics.

In the case of leptomeningeal metastases, pain occurs in about 40% of individuals, with the two most common types of pain being constant headache, with or without neck stiffness, and back pain, usually localized to the lower back and buttocks [7].

NEUROLOGICAL PAIN SYNDROMES DUE TO THERAPY

The neurological pain syndromes associated with cancer therapy include:

1. Post-surgical pain syndromes, such as those following radical neck dissection, mastectomy, thoracotomy, nephrectomy, and limb amputation (different from phantom limb pain).
2. Post-chemotherapy pain syndromes, such as peripheral neuropathy, steroid pseudo-rheumatism, aseptic necrosis of the bone, and post-herpetic neuralgia.
3. Post-radiation therapy pain syndromes, such as radiation fibrosis of the brachial plexus,

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that zoledronic acid (Zometa) has analgesic efficacy in experimental models of peripheral neuropathy and inflammation (pamidronate [Aredia] and clodronate [Bonefos] were not effective) independent of the bone-preserving effect of this bisphosphonate [37].

Ablative procedures, such as nerve blocks, may be of benefit in some patients. An example of a highly effective block is the celiac plexus block used to relieve pain due to pancreatic cancer [38]. However, a recent systematic literature review of chemical sympathectomy for neuropathic pain revealed an inability to draw conclusions regarding the efficacy of this

therapy, due to poor reporting of outcomes [39]. Extradural cortical stimulation, a technique developed in the early 1900s to ascertain the functional role of various cortical areas of the brain, has been reported to be of benefit in neuropathic and central pain syndromes [40], but additional research is indicated.

PREVENTION

A potentially promising area is prevention of neuropathy. For example, both laboratory and clinical studies are under way to evaluate the use of glutamine and glutathione to prevent chemotherapy-induced peripheral neuropathies

PEER VIEWPOINT

radiation fibrosis of the lumbosacral plexus, radiation myelopathy, and radiation-induced peripheral nerve tumors [7].

These post-treatment pain syndromes are of two types. The first type commonly occurs within weeks after a specific course of therapy, and the associated pain is self-limiting. The second type occurs several weeks to months later, and occasionally even years following the completion of treatment. Late occurrence presents the clinical problem of whether the pain is a complication of therapy or a sign of recurrent disease. In post-thoracotomy cancer patients, the recurrence or persistence of pain in the distribution of the thoracotomy scar is commonly associated with recurrent tumor [7].

Pain after limb amputation is of two types and is different from the almost universally occurring phantom limb sensation. Phantom limb pain usually occurs in patients who reported pain at the same site prior to surgery. After amputation, the pain may initially escalate and then slowly diminish. Stump pain is pain that occurs at the site of the surgical scar several months to years following the amputation. It results from the development of a traumatic neuroma. The pain is described as a burning, dysesthetic sensation. The recurrence of pain in a phantom limb alerts the clinician to the possibility of more proximal disease, such as in the pelvis [7].

POSTRADIATION PAIN SYNDROMES

Finally, neurological pain syndromes following radiation therapy are an important group with which to conclude this brief and selective

review (for a more comprehensive review, see Foley [7]). Post-radiation therapy pain syndromes include radiation fibrosis of the brachial and lumbar plexus, radiation myelopathy, and radiation-induced peripheral tumors. Pain in the distribution of the brachial plexus following radiation therapy may occur as much as 6 months to 20 years after such treatment. Thus, differentiating radiation fibrosis from recurrent tumor is difficult. Typically, the patient first complains of numbness or paresthesias in the hand, usually in a C5-C6 distribution. Pain occurs late and is often described as diffuse arm pain; in addition, lymphedema in the arm is often present [7]. The patient may progress to having a painful, useless, swollen extremity. When a patient has no evidence of disease, yet is left with a painful, heavy, useless arm, the level of suffering and demoralization experienced is enormous. Psychological and rehabilitation measures are a critical component of the patient's care.

Radiation fibrosis of the lumbosacral plexus, although far less common than involvement of the brachial plexus, can also lead to significant disability associated with progressive motor and sensory dysfunction [7].

SOME IMPORTANT POINTS

In summary, in patients with a neurological pain syndrome, pain is often the most common presenting symptom, without any initial evidence of neurological damage. Taking into consideration the type of cancer, the treatment history, and the location of the pain, the onset of pain in a patient with cancer should make the clinician think, for exam-

[41, 42]. Other areas that are theoretically interesting, but require further investigation, include the use of local anesthetic blockade or other analgesics prior to or during cancer surgery to preemptively relieve neuropathic pain.

Psychological Therapies

Pain, depression, and anxiety are highly interrelated, greatly impairing quality of life in those with cancer. Studies in non-cancer patients suggest that painful neuropathies often are associated with mood and activities of daily living, such as work, recreation, socializing, and sleep [43]. Therapies such as distraction,

imagery, expressive arts, hypnosis, relaxation, prayer, and other techniques may provide a sense of control, can improve mood, and increase positive coping behaviors [44]. These should be employed as adjuncts to pharmacologic therapies, rather than as a replacement for analgesics. These cognitive-behavioral techniques can be particularly useful during episodes of breakthrough or escalating pain while waiting for medications to provide relief.

Finally, patients and their family members may gain some sense of control by learning more about their condition. Numerous resources are available (Table 2).

ple, that it might be a symptom of brachial or lumbosacral plexopathy or cranial nerve infiltration. An early diagnosis in these situations is critical so that treatment can be initiated promptly in an attempt to prevent neurological damage as well as to avoid development of a chronic neuropathic pain syndrome. This is extraordinarily important in the care of these patients, because:

1. The degree of neurological deficit with which a patient presents at time of diagnosis is usually the degree of neurological deficit that remains.

2. The treatments available to manage neuropathic syndromes remain suboptimal at best. If it is at all possible to prevent neurological damage and the development of chronic neuropathic pain through early diagnosis of a neurological pain syndrome, a great service will have been done to the patient, and the potential for significant suffering will have been avoided.

Suffering associated with chronic neuropathic pain is due not only to the severity of the pain, its chronicity, and the loss of function that may result from the underlying pathophysiology, it is also associated with the *meaning* of the pain. Pain that signifies disease progression in the patient's mind has a different suffering component than pain that occurs as a result of treatment or is unrelated to cancer or its treatment. Patients need to be asked directly what they think is causing the pain and what the pain means to them. Such an exploration can give significant information to the attending physician or nurse about the suffering component of pain, which can then be addressed and perhaps ameliorated.

Because the sensations associated with neuro-

pathic pain are often unfamiliar, the patient may not have the language to describe the pain. This leaves the individual feeling alone, isolated, and not understood. Patients express enormous relief when they are given an explanation of the mechanisms underlying the pain sensations they are experiencing. That knowledge alone can lessen the severity and suffering component of the pain.

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Neuropathic Pain

Table 2

Consumer Resources for Information on Neuropathic Pain

American Chronic Pain Association

P.O. Box 850
Rocklin, CA 95667
Tel: 800-533-3231
www.theacpa.org

American Pain Foundation

201 N. Charles Street, Suite 710
Baltimore, MD 21201-4111
Tel: 888-615-7246
www.painfoundation.org

National Cancer Institute

Cancer Information – PDQ
(see Supportive Care Summaries)
NCI Public Inquiries Office
Suite 3036A, 6116 Executive Boulevard, MSC 8322
Bethesda, MD 20892-8322
Tel: 800-422-6237
www.cancer.gov/cancerinfo/pdq/

Neuropathy Association

60 East 42nd Street, Suite 942
New York, NY 10165-0999
Tel: 212-692-0662
www.neuropathy.org

Ovarian News Group

“Conversations”
P.O. Box 7948
Amarillo, TX 79114-7948
Tel: 806-355-2565
www.ovarian-news.org

VZV Research Foundation (for research on varicella zoster and postherpetic neuropathy)

40 East 72nd Street
New York, NY 10021
Tel: 212-472-3181
www.vzvfoundation.org

Numb Toes and Other Woes: More on Peripheral Neuropathy

By J.A. Senneff
San Antonio: MedPress, 2001

Rehabilitation and Safety Factors

Since these syndromes often include paresthesias and motor changes, rehabilitation and safety factors are essential considerations in the man-

agement of neuropathic pain. Regardless of the patient's prognosis, rehabilitation may enhance function, and attention to safety factors may avoid serious accidents.

Rehabilitation begins with assessment of the patient's functional dependence—their ability to walk, dress, prepare meals, and perform other activities. Assistive devices may be useful when there is impairment in any of these activities. Physical therapy can increase the strength of involved muscles as well as accessory muscles, which can improve coordination and sensory integration. Physical activity also maintains muscle and ligament length, preventing later deformities. Ankle-foot orthotics (AFO)-type braces, which fit easily within a standard shoe, can help prevent falls when patients experience a slapping gait or foot drop.

Safety factors are of significant concern for patients with peripheral neuropathies. Practical measures include advising patients who are insensitive to heat to test the temperature of water in their home to avoid scalding. Patients should be advised to wear gloves while working in the garden or while washing dishes and to use oven mitts or pot holders when cooking. Walkways in the home should be clear, with no throw rugs that could lead to falls. Well-lit hallways and the use of nightlights, especially with the elderly patient, may prevent falls. Non-skid shower and tub mats will also help prevent falls while bathing.

Conclusion

Neuropathic pain is a chronic, complex pain problem that is often refractory to treatment. Skilled assessment and awareness of the various neuropathic pain syndromes will lead to improved diagnosis and more rapid initiation of treatment. Present treatment strategies rely heavily upon pharmacotherapy. Research is needed to identify new techniques and therapies that will not only relieve pain and suffering, but also help prevent neuropathy.

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Ricardo A. Cruciani, MD, PhD, Belinda Lobban, NP, and David Lussier, MD.

This review of the management of neuropathic pain syndromes by Judith Paice, PhD, provides an excellent summary of the clinical presentation, physiology, diagnosis, and treatment of neuropathic pain in the cancer patient. As indicated by the author, painful neuropathies are common among patients undergoing chemotherapy. The intensity of the symptoms and poor response to treatment may require discontinuation of the chemotherapy agent or compel the physician to switch to another chemotherapeutic agent. In addition to chemotherapy, compression, and damage to or direct invasion of the neural tissue also can cause neuropathies. Depending on the structure involved, they can present as mononeuropathies, polyneuropathies, radiculopathies, or plexopathies [1]. An early and thorough assessment is imperative to devise an optimal treatment plan.

Painful peripheral mononeuropathy results from a lesion to a single nerve. When a lesion occurs in the base of the skull, the syndrome may have characteristic symptoms of the cranial nerve involved. Occasionally, however, more than one cranial nerve can be compromised when the lesion is localized at the level of a foramina shared by more than one cranial nerve. Rapid recognition of the condition may allow early radiation therapy or decompression of the structures. The same phenomena can be observed in nerves in other regions of the body.

Metastatic disease to the vertebral bodies or to a rib may result in single nerve injury and symptoms of painful mononeuropathy. When a patient presents with these symptoms a differential diagnosis of herpetic or post herpetic neuralgia has to be considered because the treatment of the two entities—rib lesion and herpetic syndrome—is different. Post herpetic neuralgia, a chronic pain condition that extends more than 3 months after the original herpetic lesion, may require steroids and nerve block, whereas a metastatic lesion to the rib may respond to radiation.

Painful polyneuropathies present when more than one nerve is involved and in unrelated parts of the body. These symptoms are more commonly seen in the non-cancer population

(eg, as diabetic neuropathy). In cancer patients, polyneuropathies can be seen in paraneoplastic syndromes or leptomeningeal disease. Radiculopathies can also be seen in this patient population. The recognition of these conditions is very important because they are so often overlooked, resulting in late diagnosis. Radiculopathies are commonly caused by direct tumor compression or as a complication of a vertebral collapse.

Plexopathies may result from direct invasion of the plexus, such as in patients with lymphoma. The symptoms will vary with the plexus involved and whether the pain and neurological deficit involve more than one root. A common diagnostic mistake is to image the spinal cord rather than the plexus [1].

ROLE OF OPIOIDS IN MANAGING NEUROPATHIC PAIN

Dr. Paice has nicely summarized the clinically-relevant information on adjuvant therapy for cancer-related pain. The role of adjuvants in the treatment of cancer pain has been well recognized for many years, and they have become the cornerstone for the treatment of neuropathic pain.

On the other hand, the role of opioids in the management of neuropathic pain has been controversial. For many years opioids were excluded from the treatment of any type of neuropathic pain syndrome because it was believed that such pain was resistant to this form of treatment. Then, in the early 1990s, the opioids were reexamined in relation to neuropathic pain, and trials by Portenoy and colleagues showed that up to 50% of patients with certain types of neuropathic pain might respond to opioids [1].

The current recommendations by the World Health Organization—the so-called “ladder” approach—have proven to be an excellent guide to the selection and titration of opioids in the treatment of all kinds of pain, including neuropathic pain [2]. The philosophy is to start treating pain with the least potent medications (i.e., non-steroidal agents) and then climb up the ladder to more potent types of opioids, either alone or combined with adjuvants, depending on the response to treatment and tolerability of side effects. This approach is interesting because dosing is not limited by potency and efficacy of the drug, but rather by its side effects and tolerability. In this context, opioids with different potencies can still achieve an equal effect in a particular

Neuropathic Pain

patient. An opioid with lower potency might be better tolerated than another opioid with higher potency, allowing higher dosing. With this paradigm, the opioid is customized to a particular patient.

One opioid in particular that has come under the spotlight recently is methadone. This drug, originally developed in Germany as an analgesic, was introduced in the sixties as the treatment of choice for opioid addiction. Since then, many Methadone Maintenance Treatment Programs (MMTP) have opened and the stigma of drug addiction has become associated with this drug. However, in recent times, due to its good analgesic properties and low cost, methadone has been recognized as an important player in the treatment of both nociceptive and neuropathic pain.

One needs to monitor patients on methadone carefully because, due to its peculiar pharmacokinetics (the half-life ranges between 4 and 150 hours), it may accumulate in the system unless titration is done carefully. The recommendation is to adjust the dose no sooner than every 3–4 days. In patients with neuropathic pain and a comorbidity of drug addiction, who are currently enrolled in a MMTP program, methadone can be prescribed for the treatment of pain in addition to the maintenance dose for addiction. This strategy obviously requires coordination with the patient's counselor at the addiction program. The patient would continue in the program, where he receives his addiction dose on a daily or weekly basis, with the pain practitioner prescribing methadone solely for the treatment of pain. This additional amount of methadone can be titrated to pain and side effects, independently of the maintenance dose, which may remain constant.

NEW STRATEGIES FOR THE TREATMENT OF HYPERALGESIA.

In the early nineties, Trujillo and Akil recognized the role of excitatory amino acids in hyperalgesia and the development of tolerance to opioids [3]. In addition, Mao and coworkers explored the benefits of simultaneous administration of opioids and dextromethorphan in an animal model [4]. Based on these observations, several clinical trials were designed utilizing a variety of N-methyl-D-aspartate (NMDA) antagonists alone or in combination with opioids, but the results were disappointing. More recently, Crain and Shen observed that ultra-low doses of naltrexone (an opioid antagonist that is used to revert opioid overdose), can potentiate the effect of many

opioids that they tested [5, 6]. This so-called bimodal effect is the result of the simultaneous activation of opioid-mediated excitation (caused by ultra-low doses of opioids) and inhibition (elicited by the "pharmacological" dose of the same opioids). Thus, excitation (hyperalgesia) can be blocked with ultra-low doses of an antagonist, resulting in potentiation of the inhibition. Cruciani and Pasternak [7] suggested that the mechanism is mediated by G_{α} protein via intrathecal administration of antisense oligonucleotides directed against the G_{α} mRNA. These results are in agreement with *in vitro* experiments by Crain and Shen [5]. The notion of two systems mediating hyperalgesia in neuropathic pain suggests that successful intervention will occur only if both systems are shut down simultaneously. Clinical trials focusing on concomitant blockade of NMDA receptors and ultra-low doses of opioid antagonists will test this model.

CONCLUSION

As indicated by Dr. Paice, the pathophysiology of neuropathic pain may involve a diversity of etiologies that may vary with the evolution and progression of the disease. These observations support the notion of polypharmacy for the treatment of these conditions. The combination of drugs with completely different mechanisms of action (alpha-2 agonists, Ca^{++} or Na^{+} channel blockers), may be the optimal approach. Polypharmacy within the same group of agents also might be beneficial. Indeed, in the animal model, it has been observed that the simultaneous administration of certain opioids can result in synergistic analgesia rather than simply an additive effect.

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OBSERVATIONS

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Hemoglobin levels in the control group dropped significantly—an average of >1 g/dL by week 4 and > 2 g/dL by week 8 (with a mean hemoglobin level of 10.8 g/dL for the group overall). However, hemoglobin levels were maintained in the epoetin alfa group (mean hemoglobin level of 12.9 g/dL for the group). The patients in the control group who crossed over to epoetin alfa benefited (with a mean overall level of 11.5 g/dL), "...but many never quite came back to their original level," Dr. Crawford said. Significantly more patients in the crossed-over group needed dose escalations, and more patients in the control group needed blood transfusions during the study (21.0% versus 12.3% in the group receiving epoetin alfa).

Differences between groups for various Quality of Life scales were not significant, although trends did favor epoetin alfa. Also, tumor response trended in favor of epoetin alfa (29% versus 22%). Slightly greater disease severity at baseline in the epoetin alfa group and the expected high rates of progressive disease (35%–41%) in this population, Dr. Crawford speculated, may account for the lack

of significant advantage. "We know that patients with progressive disease tend to have a blunted quality of life," he said. Side effects and discontinuations for side effects were similar between groups.

The findings, Dr. Crawford concluded, confirm that hemoglobin levels can be maintained in patients with advanced-stage NSCLC. "We have some data that outcomes including response and possibly survival in radiation patients may be improved when hemoglobin is preserved. Now we can look at stage III NSCLC populations receiving chemoradiation and assess survival," he added.

In another presentation at ASCO, Jeffrey Patton, MD, of Tennessee Oncology in Nashville, described a pilot study among 20 anemic patients (mean age 60.1 years) receiving myelosuppressive chemotherapy for a nonmyeloid malignancy. The study tested two hypotheses:

1. Hemoglobin response rates would increase with a higher initial epoetin dose (60,000 U once weekly).

2. Increasing the maintenance dose to 120,000 U would allow the dosing interval to be lengthened to coincide with

every 3-week chemotherapy regimens.

After the initial 60,000 U dose, if at ≥ 8 weeks hemoglobin had increased by ≥ 2 g/dL from baseline, maintenance therapy of 120,000 U weekly was instituted. The primary outcome measures for the ≤ 24-week study were hematologic response over time (defined as ≥ 2 g/dL increase in hemoglobin level or achievement of hemoglobin ≥ 12 g/dL at any point without transfusion). Analysis showed that by week 8, 86% of patients had a hemoglobin increase of ≥ 2 g/dL. Mean hemoglobin increase was 1.0 g/dL by week 4 and 2.9 g/dL by week 8. Among 13 patients receiving the higher maintenance dose, 2 required dose reductions to 100,000 U weekly and 10 completed the study. Hemoglobin levels of 13.0 g/dL were sustained in this group. There were no adverse safety events, and three deaths in the overall group were attributed to disease progression.

In an interview with *The Journal of Supportive Oncology* after his presentation, Dr. Patton said that both hypotheses were confirmed. "Many chemotherapy regimens are based on Q3 weeks administration. For patients not to have to come in every week for epoetin alfa is helpful," he commented. Larger trials of the higher dose regimens are underway, he said.