Phantom Limb Pain as a Manifestation of Paclitaxel Neurotoxicity

JIHAD KHATTAB, MD; HOWARD R. TEREBELO, DO; AND BASEL DABAS, MD

Paclitaxel is a chemotherapeutic agent with activity directed against several malignancies. It has multiple adverse effects including neurotoxicity. We describe 2 patients with prior amputation who experienced phantom limb pain (PLP) after receiving paclitaxel therapy. A third patient experienced disabling neurotoxicity in the extremity of a prior ulnar nerve and tendon transposition after receiving paclitaxel. This unique syndrome should be identified as a direct causal effect of paclitaxel. In this report, we review the pathophysiology of PLP and treatment options. Physicians should be aware that PLP can occur after initiation of paclitaxel.


PLP = phantom limb pain

Paclitaxel, a natural product obtained from Taxus brevifolia, has antitumor activity by promoting the assembly of microtubules from tubulin dimers and stabilizing them by preventing depolarization. This results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cell functions. Paclitaxel has activity against several malignancies, including breast, ovarian, lung, and bladder lymphomas as well as head and neck cancers.

In this report, we describe 2 patients with prior amputation who experienced severe phantom limb pain (PLP) associated with paclitaxel chemotherapy. An additional patient with a prior tendon and nerve transposition experienced severe disabling pain and weakness in his hand after 1 cycle of paclitaxel.

REPORT OF CASES

Case 1

A 65-year-old woman with a history of insulin-dependent diabetes mellitus and hypothyroidism underwent amputation below the right knee in 1992 because of peripheral vascular disease. She experienced PLP for a few weeks after the amputation. In 1995, she was diagnosed with stage IIB (T2 N1 M0) infiltrating ductal carcinoma of the left breast. She underwent a modified radical mastectomy and was subsequently randomized to Southwest Oncology Group protocol 9410. She was to receive 4 cycles of doxorubicin (Adriamycin) and cyclophosphamide every 21 days, followed by 4 cycles of paclitaxel. She tolerated therapy well until completion of the second cycle of paclitaxel when she complained of severe, intermittent, and disabling PLP in her right leg. Oxycodone was necessary for symptomatic relief. The patient agreed to complete the 4 cycles of paclitaxel in conjunction with narcotics. After she had completed the chemotherapy, the PLP resolved 6 weeks later.

Case 2

A 37-year-old woman underwent surgery in 1970 because of osteogenic sarcoma in her right proximal femur. Amputation above the right knee resulted in successful resection of the localized disease. Prophylactic radiation therapy of 18 Gy was then delivered to her lungs to prevent metastasis. The patient noted PLP at that time, which resolved over 3 months. In 1984, she developed stage I (T1 N0 M0) infiltrating ductal carcinoma of the right breast, which resulted in a right modified radical mastectomy. Two years later, a metachronous stage II (T1 N1 M0) carcinoma of the left breast was detected. Modified radical mastectomy, followed by silicone breast implants, was performed. She then received 6 cycles of cyclophosphamide, doxorubicin (Adriamycin), and fluorouracil adjuvant chemotherapy.

In 1987, the patient had disease metastatic to the lungs. Tamoxifen therapy resulted in a protracted partial response for 6 years. The pulmonary nodules progressed in 1993, and treatment with megestrol acetate failed. Therapy with doxorubicin, 60 mg/m², and paclitaxel, 200 mg/m², every 3 weeks was initiated. The disease stabilized. By the sixth cycle of therapy, the patient described the sensation of PLP at the site of the right above-knee amputation 23 years earlier. The pain was burning, intense, and sharp. She declined further therapy with paclitaxel and required propoxyphene napsylate and acetaminophen for pain relief. The PLP resolved 8 weeks later.
Case 3
A 74-year-old man with a history of coronary artery disease, hypertension, smoking, and excision of a fibrosarcoma, which required tendon and nerve transposition, 30 years earlier presented with stage IIA (T3 N1 M0) squamous cell carcinoma of the right lung. He was treated with brachytherapy, followed by 2 cycles of concurrent radiation therapy combined with etoposide and cisplatin. After a partial response was achieved, consolidation therapy consisting of paclitaxel, 200 mg/m², and carboplatin, 230 mg/m², was initiated. After 1 cycle, he experienced debilitating pain in his right hand at the site of the tendon and nerve transposition. The hand weakened, and lancinating pain was noted in the medial digits of the right hand. The patient was unable to use his right hand and lost all function with this hand. Chemotherapy was discontinued, and he underwent physical therapy to strengthen motor function; after 3 months, improvement was noted. By 9 months, his right hand had returned to baseline function.

DISCUSSION
Taxanes, such as paclitaxel, have increasing indications for use in patients with cancer. Limb amputations in patients with cancer, especially in pediatric patients, are decreasing because of limb preservation surgical techniques and neoadjuvant chemotherapy. However, amputation remains common in patients with peripheral vascular disease and traumatized limbs. Paclitaxel has been accepted as first-line therapy for patients with lung cancer, breast cancer, ovarian cancer, and bladder cancer.

To our knowledge, paclitaxel-associated PLP has not been reported previously. A MEDLINE search from 1990 to 1999 and of Bristol-Myers Squibb Oncology records revealed no reports of this phenomenon.

Other severe events that have been reported after administration of paclitaxel include myelosuppression, mainly in the form of neutropenia (90%); hypersensitivity (31%-36%); mucositis (17%-23%); neurologic complications (46%-70%); and even sudden death. The frequency and severity of the neurologic manifestations are dose dependent, occurring with cumulative dosing and higher doses per cycle, but they are not dependent on the rate of infusion.

In all patients receiving paclitaxel therapy, peripheral neuropathy occurs in 60% and in 52% of those without preexisting neuropathy. The incidence of neurologic symptoms does not increase in patients previously treated with cisplatin. In 1 study, neurologic symptoms were observed after the first course of paclitaxel in 27% of patients and in 34% to 51% of those who had received 2 to 10 courses. These symptoms were due to severe nerve fiber loss, axonal atrophy, and secondary demyelination caused by paclitaxel. Sensory symptoms usually diminish or resolve within several months after discontinuation of paclitaxel.

Phantom limb pain is defined as the phenomenon of a painful sensation perceived in the missing body part or in the part paralyzed by the spinal cord injury or nerve root avulsion or, more simply stated, pain that is experienced in a limb that is no longer present. The sensation and intensity of PLP were first described in the 16th century. Phantom limb pain is most commonly found in the distal portions of the richly innervated distal extremities. The onset of PLP is generally within the first few weeks but may occur several months or even years after amputation. The frequency, duration, and severity of pain episodes decrease during the first 6 months after amputation. A period of quiescence may be interrupted years later by reemergence of PLP. Nathan reported that an application of a noxious stimulant to the residual of a limb amputated years earlier because of a skating injury resulted in recurrence of PLP.

Two types of PLP are commonly described: an intense burning sensation or painful cramping. Either may be continuous or paroxysmal. Phantom limb pain is common and unpredictable, varies in frequency, severity, duration, and character, and stabilizes after a period of up to 6 months; response to aggravation by external or internal stimuli is unpredictable.

There are numerous theories about the cause and pathophysiology of PLP. The neuromatrix concept proposed by Melzack in 1989 and in 1990 describes the neural circuit of a circuitous route from the brain to the extremities and back to the brain. The neuromatrix describes how normal sensation can be felt in the absence of a body part. The injury site is associated with a proliferation of a-adrenergic channels, calcium channels, and stretch-activated channels with nerve severance or nerve blockade. The change in the dorsal horn of the spinal cord that receives central terminus of afferent fibers is described as plasticity. Plasticity is associated with biochemical changes and neuron development within the dorsal horn, which results in activation of excitability amino acid receptors in the dorsal horn (N-methyl-D-aspartate receptors). Substance P release depolarizes pain-specific neurons and sensitizes neurons to excitability amino acid.

Repetitive firing of peripheral nociceptive fibers may result in hyperexcitability of the dorsal and ventral horns, which results in irritability foci over the posterior column. Excitability amino acids and neurokinins are released and induce neural damage. Repeated depolarization leads to chronic changes in the horn. This cascade and irritable focus can account for pain at the spinal level. Drugs targeted at various initiators have a beneficial role in the prevention or treatment of PLP.
Krane and Heller described 45 patients who underwent amputations because of congenital deformities, trauma, infection, and cancer. All their patients experienced PLP. In a significant minority of patients undergoing amputation due to malignancy, PLP can be severe, disabling, and long-standing. Smith and Thompson noted a higher frequency of PLP in pediatric patients with cancer than in other patients who had undergone amputation. Phantom limb pain was reported in 48% of patients with cancer-related amputations compared with 12% of patients with trauma-associated amputations. Among patients with cancer, PLP was reported by 74% who had undergone chemotherapy before or at the time of amputation, 44% who received chemotherapy after amputation, and 12% who never received chemotherapy. Smith and Thompson also noted that pediatric cancer patients who had undergone amputation often experienced PLP during the first or second day of chemotherapy. To our knowledge, studies of adult amputee patients with cancer who received chemotherapy have not described development of PLP.

Treatment of PLP can best be directed toward actions on the spinal level. The earliest report of treatment of PLP involved the ineffective clubbing and pounding of the residual limb with a wooden mallet. Surgical and neurosurgical approaches including sympathectomy, cordotomy, thalamotomy, and gyrectomy all are generally ineffective. N-methyl-D-aspartate inhibitors (ketamine), neuron inhibitors (clonidine), sodium channel blockade (mexiletine), inhibitors of substance P production (capsaicin) or release (narcotics), or local anesthetics have all been reported to be effective treatment interventions in PLP. Short-term calcitonin treatment has demonstrated good to excellent long-term results. The mechanism of analgesia with calcitonin remains uncertain, although it is thought to act by stimulation of serotogenic neurons, which reduces local production of prostaglandins and cytokines.

Paclitaxel-associated PLP was completely reversible in our 3 patients. Patients who experience this neurotoxicity should be reassured. Treatment with calcitonin, tricyclics, neuron inhibitors, and narcotics, along with prompt discontinuation of paclitaxel, is an appropriate course of action in patients with PLP. Patients with prior amputation who receive paclitaxel will probably experience PLP. Administration of amifostine in patients receiving initial and subsequent cycles of paclitaxel chemotherapy may prevent or decrease the incidence of PLP in the amputee patient population at risk.

Other rare, serious neurologic events that have occurred after paclitaxel administration include grand mal seizures, syncope, ataxia, neuroencephalopathy, and paralytic ileus.

REFERENCES