Hand Problems Related to Chemotherapeutic Agents

Beatrice L. Grasu, MD,* Dawn M. LaPorte, MD*†

With the increasing use of powerful chemotherapeutic agents, the impact of their associated toxicity has also increased. It is important for hand surgeons to recognize and manage complications in the hand caused by chemotherapy. The most commonly used therapies that may be associated with these complications are bleomycin, platinum, taxol, and vinca agents that are used to treat lymphoma, testicular, breast, and prostate cancers. These therapies may extravasate and cause local soft tissue damage in the hand (incidence varies from 0.01% to 7%) but other more systemic adverse hand reactions such as chemotherapy-induced peripheral neuropathy (CIPN), hand–foot syndrome, and Raynaud phenomenon must also be recognized and addressed (incidence varies in the acute setting from 68% to 9.9% and 37%, respectively).[1–5]

ADVERSE EFFECTS

Peripheral neuropathy

Chemotherapeutic agents can cause substantial systemic complications such as bone marrow suppression and renal toxicity. These complications frequently require antitumor therapy termination or modification. Another reason to adjust chemotherapy is the neurotoxic side effect known as CIPN, which can adversely affect the patient's quality of life.[6] Antineoplastic agents used to treat lymphoma, testicular, breast, and prostate cancer are known to cause CIPN (Table 1).[2,3] Pain, burning, tingling, numbness in the hands, difficulty with fine motor activities or coordination, hyperesthesia, hyporeflexia, and muscle atrophy may develop because the agents are neurotoxic to the spinothalamic tract (small fiber axons for pain and temperature) and dorsal column tract (large fiber axons for vibration and proprioception).[6] Neurotoxicity depends on the total cumulative dose and type of drug used. An example of these agents is platin: doses above 400 mg/m^2 have been reported to result in axonal damage.[7] Neuropathy assessment relies on clinical examination because electrodiagnostic studies are often inconclusive for determining early stages of CIPN. The Pressure-Specified Sensory Device (Sensory Management Services, LLC, Baltimore, MD) is better tolerated by patients than are electrodiagnostic studies. Two metal probes gently touch the skin and can identify CIPN before axonal loss occurs, using computer analysis of neurosensory testing (Fig. 1).[7–9] Full recovery often occurs once the medication is discontinued, usually within 6 months, but some patients with CIPN may have irreversible persistent symptoms.[7,10]

Although similar in presentation to diabetic peripheral neuropathy in a stocking-glove distribution, treatments that improve diabetic neuropathy symptoms do not seem to help patients with CIPN.[10] Neuropathic drugs, such as gabapentin, and analgesics may be prescribed to relieve pain. There are also several investigational studies evaluating pharmaceutical agents to treat CIPN, such as antidepressants, duloxetine, and venlafaxine; topical muscle relaxants such as baclofen; and analgesics such as ketamine.[11] To prevent the onset of CIPN in patients receiving oxaliplatin, one trial used intravenous calcium and magnesium, which reduced CIPN symptoms by half compared with placebo.[10,11] Unfortunately, intravenous calcium and magnesium are not routinely used because of concerns regarding decreased chemotherapy efficacy. Gluthalione has also shown promising results by binding to heavy metals such as platinum-based chemotherapeutic agents. In addition, duloxetine has been found to be more effective than placebo in treating oxaliplatin- or paclitaxel-induced CIPN and should be considered a first-line treatment

*From the *Curtis National Hand Center, MedStar Union Memorial Hospital; and the †Department of Orthopaedic Surgery, Johns Hopkins University, Baltimore, MD.*

Received for publication August 20, 2015; accepted in revised form October 1, 2015.

No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

Corresponding author: Dawn M. LaPorte, MD, c/o Anne Mattson, Curtis National Hand Center, MedStar Union Memorial Hospital, 3333 North Calvert St., Baltimore, MD; e-mail: anne.mattson@medstar.net.

0363-5023/15/4012-0028$36.00/0
http://dx.doi.org/10.1016/j.jhsa.2015.10.001

TABLE 1. Chemotherapeutic Medications That Cause Peripheral Neuropathy

Platinum Agents	Vinca Alkaloids	Taxanes	Epothilones	Newer Agents
Cisplatin	Vincristine	Paclitaxel	Ixabepalone	Bortezomib
Carboplatin	Vinblastine	Docetaxel		Thalidomide
Oxaliplatin				Lenolidamide

FIGURE 1: Neurosensory testing with the Pressure-Specified Sensory Device to determine peripheral neuropathy. (Photo courtesy of Dolf R. Ichtertz, MD.)

option for CIPN.[10] Vitamin E was also effective in 47 patients receiving cisplastin compared with placebo; however, larger randomized controlled clinical trials are required to make more concrete conclusions.[10] Finally, in patients with a positive Tinel sign at the site of anatomic entrapment, surgical decompression of the peripheral nerve frequently results in resolution of symptoms. In one study of 9 patients with CIPN who had received cisplatin or paclitaxel, patients underwent surgical decompression 0.5 to 4.5 years after cessation of chemotherapy and the preoperative visual analog scale pain level was 9.57, whereas after surgery it was 1.14 ($P < .001$).[7]

Hand–foot syndrome

Hand–foot syndrome (HFS), also known as plantar erythrodysesthesia, chemotherapy-associated acral erythema, and Burgdorf reaction, is a cutaneous toxicity associated with chemotherapeutic agents.[12] Causative chemotherapeutic agents affect not only the palm but also the dorsal surface of the hand in severe cases (Table 2).[12,13] Usually about 2 to 12 days after drug administration, paresthesias and palmoplantar dysesthesia occur followed by burning pain, symmetric erythema, and edema. Blistering, desquamation, and ulceration occur with varying grades of severity (Table 3).[14] After withdrawal of the chemotherapy agent, symptoms usually resolve within a few weeks.[12] Multikinase inhibitors have more variable effects: Hand–foot syndrome may present a few months after therapy initiation, worsen significantly within days, and affect local pressure points such as the fingertips.[13] Multikinase inhibitor-associated HFS is more painful and has callus-like thickening of the horny layer of the epidermis, termed "palmoplantar epidermal hyperplasia."[13]

Mechanical stresses on the skin, such as pressure and friction, and heat should be avoided. Regularly applied moisturizing lotion may alleviate symptoms. Topical salicylic acid or urea may be used for hyperkeratosis whereas topical steroids such as mometasone may be given for inflammation.[13] Use of oral steroids and pyridoxine is not supported by randomized controlled trials.[12] One study investigated the efficacy of cryotherapy for docetaxel-induced hand and fingernail toxicity and found no significant difference.[15] Ultimately the tumor therapy dose should be modified or discontinued.

Vasospastic conditions

Chemotherapy-induced Raynaud phenomenon is another adverse reaction associated with cancer medications. Characterized by episodic pallor and cyanosis, it often occurs in testicular cancer patients who receive bleomycin, and appears 3 to 6 months after initiation (Fig. 2). The exact pathophysiology is uncertain. Hand arteriograms visualize diffuse arterial narrowing and abrupt vessel cutoffs in cases of Raynaud phenomenon associated with digital occlusive arterial disease (Fig. 3).[16] There has been discussion regarding whether bleomycin and vincristine directly injure vascular endothelium or impair autoregulation causing hyperreactivity to terminal arterioles in response to cold. Regardless of the mechanism, Raynaud phenomenon occurs as a dose-dependent response.[16,17]

Fortunately, chemotherapy-induced Raynaud phenomenon rarely causes substantial functional impairment and often resolves spontaneously once the medication is discontinued; however, it tends to recur with subsequent administration.[18] This adverse

In Brief