

FAST FACTS AND CONCEPTS #197

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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Background Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity for many anti-cancer agents. The incidence of CIPN can be variable, but more common figures are 30–40% of chemotherapy treated patients (1). This *Fast Fact* will review the clinical features and treatment of CIPN.

Etiology & Risk Factors Several mechanisms have been postulated to cause CIPN (2). Antineoplastic agents known to cause neuropathies are vinca alkaloids, taxanes, platinum-derived compounds, protease inhibitors (bortezomib), antibodies (brentuximab vedotin), aromatase inhibitors (anastrozole and exemestane), thalidomide, lenalidomide, ixabepilone and interferon alpha. The risk of CIPN is higher in patients previously exposed to chemotherapy, patients over 50 years old, heavy alcohol users, patients with renal or hepatic insufficiency, and those with preexisting neuropathies (4).

Clinical Characteristics The onset of symptoms can be sudden or slowly progressive. Sensory symptoms generally improve many months after drug discontinuation, *but not in all patients*. Motor symptoms are less likely to improve over time.

- Sensory symptoms frequently include tingling, numbness and pain. Motor symptoms include foot drop, wrist drop, and difficulty with fine motor skills, such as buttoning a shirt or holding a pen. Autonomic symptoms include diarrhea, constipation and difficulty breathing.
- Pain is often reported as burning, freezing, lancinating or electric shock-like. Normal touch can be perceived as painful (allodynia) and sensations that would normally be painful can be experienced as excruciating (hyperpathia).
- Signs include symmetrical glove and stocking sensory deficit, foot or wrist drop, symmetric motor weakness, loss of deep-tendon reflexes, low blood pressure, and irregular heartbeat.
- The most common pattern of CIPN is an asymptomatic loss of deep tendon reflexes progressing to a sensory and finally motor neuropathy (1). The severity of neuropathy usually increases with treatment dose and duration and then decreases after cessation of treatment. A notable exception is the platinum agents, for which symptoms may progress for weeks to months after treatment completion. This is called the “*coasting effect*” (3).
- Oxaliplatin can cause both an acute and chronic neuropathy. The acute process can begin during the drug infusion and include cold-induced paresthesias of the hands, feet, throat, and perioral area. The chronic form is a dose-dependent sensory neuropathy similar to other CIPNs (4).
- *Vincristine* can cause pharyngeal myalgias (sore throat) and autonomic neuropathy manifested by constipation, in addition to a typical axonal neuropathy.

Diagnosis The diagnosis is largely based on history and neurological examination. Clinicians should consider other than axonal-neuropathies in their differential (e.g. mass lesion causing a radiculopathy), as well as non-chemotherapy causes of a neuropathy (paraneoplastic; non-neoplastic) (3). Nerve conduction studies are helpful when the diagnosis is unclear, but do not have 100% sensitivity or specificity.

Prevention Many agents have been proposed for preventing neuropathy caused by antineoplastic drugs. The mechanisms by which most of these drugs may minimize neuropathy are based on limited preclinical data and informed opinion. There are small clinical trials showing positive results with calcium and magnesium infusion, N-acetyl cysteine, glutamine oxycarbamazepine, omega-3-fatty acid and ganglioside-monosialic acid (GM1). Larger randomized controlled trials are needed to further evaluate whether or not the above agents are truly chemoprotective (5). Recent clinical trials with vitamin E, xaliproden, amifostine, org 2766, nimodipine, recombinant-human leukemia inhibiting factor and diethyldithiocarbamate lack positive results (2). One recent randomized, double-blind, placebo-controlled trial of venlafaxine showed a significant reduction of oxaliplatin induced acute neurosensory toxicity (6). Other prevention strategies consist of chemotherapy dose reduction or lower dose intensities, particularly in those patients who are at higher risk to develop CIPN. Non-drug protective measures include hand and feet protection from extremes of temperature (wearing socks, using gloves while cooking), routine inspection for cuts or abrasions, and fall prevention education.

Symptomatic Treatment Overall the symptomatic treatment of CIPN remains empiric. Small clinical trials have shown positive results with a topical amitriptyline/baclofen/ketamine gel (2). Pregabalin, gabapentin, lamotrigine, alpha lipoic acid, acetyl-L-carnitine, and nortriptyline have not shown efficacy in controlled trials (7-12). One randomized, double-blind, crossover trial showed a small but significant improvement in pain control with duloxetine 60 mg per day compared with placebo (13). Non-pharmacological options, including exercise, acupuncture, and neurostimulation currently lack appropriate evidence to support their efficacy (3). Opioids are empirically recommended as a short-term treatment while waiting for an adjuvant to work or for moderate to severe pain despite the use of an adjuvant.

References

1. Windebank A, Grisold W. Chemotherapy-induced neuropathy. *J Peripheral Nervous System*. 2008; 13: 27-46.
2. Pachman D, Barton J, Watson E, et al. Chemotherapy-induced peripheral neuropathy: prevention and treatment. *Clin Pharmacology & Therapeutics*. 2011; 90:377-97.
3. Stubblefield M, Burstein H, Burton A, et al. NCCN Task Force Report: Management of neuropathy in cancer. *J National Comprehensive Cancer Network*. 2009; 7:S1-S26..
4. Argyriou A, Bruna J, Marmiroli P, et al. Chemotherapy-induced peripheral neurotoxicity (CINP): an update. *Critical Reviews in Oncology/Hematology*. 2012; 82:51-77.
5. Albers JW, Chaundry V, Cavaletti G, Donehower RC. Interventions for preventing neuropathy caused by cisplatin and related compounds. *Cochrane Database Syst Rev*. 2014 Mar 31; 3:CD005228. doi: 10.1002/14651858.CD005228.pub4.
6. Durand J, Deplanque G, Montheil V, et al. Efficacy of venlafaxine for the prevention and relief of oxaliplatin-induced acute neurotoxicity: results of EFFOX, a randomized, double-blind, placebo-controlled phase III trial. *Annals of Oncology*. 2012; 23:200-5.
7. Wasif M, Syrigos K, Kaley D, et al. Role of pregabalin in treatment of oxaliplatin-induced sensory neuropathy. *Anticancer Research*. 2010; 30:2927-34.
8. Rao R, Michalak J, Sloan J, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy. A phase 3 randomized, double blind, placebo-controlled, crossover trial (N00C3). *Cancer*. 2007; 110:2110-18.
9. Rao R, Flynn P, Sloan J, et al. Efficacy of lamotrigine in the management of chemotherapy-induced peripheral neuropathy. *Cancer*. 2008; 112:2802-8.
10. Guo Y, Jones D, et al. Oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. *Supportive Care in Cancer* 2014; 22:1223-1231.
11. Callander N, Markovina S, et al. Acetyl-L-carnitine (ALCAR) for the prevention of chemotherapy-induced peripheral neuropathy in patients with relapsed or refractory multiple myeloma treated with bortezomib, doxorubicin and low-dose dexamethasone: a study from the Wisconsin Oncology Network. *Cancer chemotherapy and pharmacology* 2014; 74:875-882.
12. Hammack J, Michalak J, Loprinzi C, et al. Phase III evaluation of nortriptyline for alleviation of symptoms of cisplatin-induced peripheral neuropathy. *Pain*. 2002; 98:195-203.
13. Lovoie E, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy. A randomized clinical trial. *JAMA*. 2013; 309(13):1359-67.

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