Chemotherapy-induced Neuropathy—Where Are We Now?

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Abstract

Among the most debilitating of chemotherapy-related toxicities is neuropathy, which is associated with several commonly used oncologic agents. The specific characteristics of neurotoxicity vary between inciting drugs, with important differences in symptom characteristics and clinical course. No medications have been found to effectively prevent chemotherapy-induced neuropathy, and investigations of predictors of severe neurotoxicity to date explain only a small part of susceptibility (making it difficult to tailor chemotherapies to individual risk). Treatment has also been challenging. Although duloxetine is modestly beneficial, and Scrambler therapy shows promise in preliminary studies, no other therapies have been proved to be effective.

Keywords

Chemotherapy-related toxicities, neuropathy, chronic peripheral neuropathy, Scrambler therapy

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Chemotherapy-induced neuropathy (CIN), which often results from a number of commonly used oncologic drugs, including taxanes, platinum agents, bortezomib, vinca alkaloids, ixabepilone, and eribulin, is one of the most debilitating symptoms caused by chemotherapy. Most research on this toxicity has focused on paclitaxel and oxaliplatin, both of which are used frequently and can cause severe neurotoxicity.

The most widely recognized and dose-limiting aspect of CIN is a chronic peripheral neuropathy (CIPN), which commonly starts in a stocking glove distribution and is predominantly sensory in nature. These symptoms generally become progressively worse with continued treatment, and numbness and tingling are more prominent than is pain.[1] When many neurotoxic chemotherapy drugs, such as taxanes, are stopped, CIPN generally begins to improve within weeks to months.[2,3] However, with cisplatin and oxaliplatin, a "coasting phenomenon" may be experienced in which the neuropathy worsens during the first months off therapy.[4] In the case of oxaliplatin, the slope of the worsening CIPN after treatment completion mirrors that seen during treatment, suggesting that it is not the stoppage of chemotherapy that causes the worsening symptoms, but rather the continued detrimental effect of the final dose of chemotherapy, which takes about 3 months to be fully manifested. On average, 3 months after finishing oxaliplatin, the neuropathy starts to improve. However, for some patients, CIPN can be a chronic debilitating problem for many years, regardless of the causative agent.

Less problematic is an acute, more reversible CIN that occurs with some neurotoxic agents. Oxaliplatin is the best recognized cause of acute CIN. In contrast to the DNA damage and mitochondrial dysfunction that underlies oxaliplatin-associated chronic neuropathy, acute toxicity has been hypothesized to occur due to calcium chelation, with resultant derangements in activity of neuronal membrane ion channels. In the acute setting, neuropathy is manifested by cold sensitivity, difficulty swallowing cold liquids, throat discomfort, and muscle cramps. The severities of the first three of these symptoms are relatively well correlated in individual patients, but the degree of muscle cramps seems to be experienced as a somewhat separate entity.[5] This type of neuropathy is almost universal among patients receiving oxaliplatin-based chemotherapy, with few patients completely avoiding all four types of symptoms. The severity of these symptoms after the first oxaliplatin dose is usually only half that experienced with the second dose, but symptoms tend to plateau thereafter, without any cumulative drug effect. An individual's severity of acute neuropathy in the first cycle correlates strongly with the severity of acute neuropathy

in subsequent cycles. Although acute CIN commonly peaks at 3 days and then starts to improve, these symptoms persist to a lesser degree between 2-week oxaliplatin repeat doses.[5] Substantial data illustrate that the degree of acute oxaliplatin neuropathy in individual patients predicts the degree of the more bothersome and persistent CIPN.[5]

Paclitaxel has long been known to cause an acute pain syndrome classically characterized as arthralgias or myalgias. However, newer data support classification of the paclitaxel-associated acute pain syndrome (P-APS) as a manifestation of acute neuropathy rather than true joint or muscle pathology.[2,3,6] Although symptom severity also peaks at about 3 days after a dose of paclitaxel, the acute neuropathy symptoms of paclitaxel differ from those of oxaliplatin. The predominant complaint is pain, usually in a trunk/upper leg/hip distribution. As with oxaliplatin, the severity of acute neuropathy symptoms in the first cycle correlates with the severity of symptoms in subsequent cycles.[2,3] However, as is not the case with oxaliplatin, the severity of acute neuropathy symptoms does not worsen with subsequent treatment cycles.[2,3] Some data support the severity of P-APS as a predictor of severity of chronic paclitaxel neuropathy (CIPN), but not to the extent of oxaliplatin.[5]

CIPN susceptibility varies quite substantially from patient to patient, suggesting an underlying genetic predisposition. Patients who have Charcot-Marie-Tooth disease (CMT), a hereditary peripheral neuropathy caused by a specific mutation in one of the more than 50 different "CMT genes," are predisposed to develop severe CIPN when exposed to vincristine[7–10] and occasionally have been diagnosed with CMT only after initiation of chemotherapy.[9–15] CMT is thus a contraindication to neurotoxic chemotherapy. However, CMT is a rare condition, leaving the majority of CIPN cases unexplained. Moderately strong evidence exists at least partially relating these cases to other genetic variants that are not otherwise disease-causing and that were identified by genome-wide association studies[16,17] or, more recently, by next-generation genome sequencing.[18] The effect size of each of these genetic variants appears comparably small, with none currently being clinically actionable.

Recognizing the magnitude of the problem posed by CIPN, extensive efforts have been directed at prevention. Recent American Society of Clinical Oncology (ASCO) guidelines identified 42 randomized controlled trials that investigated agents previously hypothesized to protect against CIPN. Unfortunately, the composite data were unable to establish value for any of the agents tested in these clinical trials, making it imperative that oncology providers closely evaluate patients who receive neurotoxic chemotherapy agents. If a patient develops a moderate or worse neuropathy, it is appropriate to reassess the potential benefits of the offending chemotherapy agent in view of the ongoing toxicity.

Despite efforts to be cognizant of CIPN and to stop chemotherapy in response to worsening symptoms, many patients are left with substantial neuropathy for months to years after cessation of treatment. Recent ASCO guidelines evaluated treatment approaches for established CIPN, identifying six published randomized, controlled trials.[19] The one positive recommendation from the ASCO Guideline Committee was for the use of duloxetine, a drug that has proved more effective than placebo in patients who had substantial neuropathic pain after treatment with paclitaxel or oxaliplatin.[20] However, the magnitude of benefit was quite limited. Subset analyses suggested that duloxetine worked better for neuropathy associated with oxaliplatin than with paclitaxel. An abstract of a subsequent trial, presented after the ASCO guidelines were published, provides additional confirmation that duloxetine decreases CIPN.[21]

In addition to duloxetine, the ASCO guidelines noted three other classes of medications reasonable to try in clinical practice despite no definitive evidence for their efficacy. One of these is the gabapentinoid class (e.g., gabapentin or pregabalin), which has been found to be beneficial for patients having other types of neuropathies. This recommendation was made even though the one placebo-controlled trial of gabapentin for CIPN was convincingly negative.[22] More data are needed regarding the utility of gabapentinoids in this setting. Tricyclic antidepressants (TCAs) were also considered to be reasonable to try for CIPN based on their utility in other neuropathy states, even though only two small trials have looked at such drugs in patients with symptomatic CIPN, each failing to show any substantial improvement in symptoms.[23,24] Last, a topical preparation of baclofen, amitriptyline, and ketamine was presented as a potential option based on results of one placebo-controlled trial that provided evidence suggestive of benefit.[25]

Efforts are ongoing to find alternative means of preventing or treating CIPN. One approach for treating chronic pain (which seems to be caused by a chronic pain signal to the brain from an area that initially was affected with acute pain) uses Scrambler therapy. Scrambler therapy provides cutaneous electrostimulation to nerves that transmit pain to the brain from a particular area of the body. The electrical signals provided by Scrambler therapy are designed to create a "no pain" signal through the affected nerves, inducing the brain to change its interpretation of inputs from those nerves. It has been proposed that Scrambler therapy works similarly to spinal cord stimulation but uses cutaneous nerves to provide the requisite signal noninvasively.

In total, 12 reports of Scrambler therapy have now been published, including more than 700 patients: all 12 of these reports have been encouraging.[26–38] Two relatively small randomized, controlled trials[29,38] (one sham-controlled[38]) reported statistically significant reductions in chronic pain in patients receiving Scrambler therapy. Three nonrandomized trials specifically supported the benefit of Scrambler therapy for treating established chronic CIPN.[27,31,35] While none of the Scrambler trials were large and definitive, they, together with personal experience, suggest that a substantial proportion of patients who have chronic CIPN may benefit from this approach.

New research approaches are certainly needed to prevent or treat CIN. Improved ability to identify who will be at risk for severe neuropathy from a given chemotherapy drug would help tailor oncologic regimens and initiate early symptom management to optimize quality of life. ■

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