Chemotherapy-Induced Peripheral Neurotoxicity: A Critical Analysis

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With a 3-fold increase in the number of cancer survivors noted since the 1970s, there are now over 28 million cancer survivors worldwide. Accordingly, there is a heightened awareness of long-term toxicities and the impact on quality of life following treatment in cancer survivors. This review will address the increasing importance and challenge of chemotherapy-induced neurotoxicity, with a focus on neuropathy associated with the treatment of breast cancer, colorectal cancer, testicular cancer, and hematological cancers. An overview of the diagnosis, symptomatology, and pathophysiology of chemotherapy-induced peripheral neuropathy will be provided, with a critical analysis of assessment strategies, neuroprotective approaches, and potential treatments. The review will concentrate on neuropathy associated with taxanes, platinum compounds, vinca alkaloids, thalidomide, and bortezomib, providing clinical information specific to these chemotherapies. CA Cancer J Clin 2013;63:419–437. © 2013 American Cancer Society, Inc.

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Introduction

As a consequence of advances in cancer diagnosis and treatment, there are now an estimated 28 million cancer survivors worldwide. As such, long-term quality of life is an increasingly important issue, with 67% of U.S. cancer patients surviving at 5 years. Addressing the long-term toxicities of cancer treatment is critical due to their potential impact on cancer survivorship. Accordingly, there has been a gradual shift in focus toward postchemotherapy recovery and survivorship, with an awareness of the importance of the individual patient experience, patient-reported outcomes, and the long-term effects of treatment. Of particular importance is chemotherapy-induced peripheral neuropathy (CIPN), which can lead to permanent symptoms and disability in up to 40% of cancer survivors. CIPN can be a significant disability following the treatment of many types of cancer, including breast, colorectal, testicular, and hematological malignancies, and have an impact on quality of life. As such, there is a critical need to understand pathophysiological mechanisms, optimize clinical assessment, and develop neuroprotective strategies to prevent neuropathy. This review will address the challenge of CIPN, highlighting treatment-related neuropathy caused by some of the most commonly used chemotherapeutic agents (such as taxanes, platinum compounds, vinca alkaloids, thalidomide, and bortezomib), and provide recommendations regarding assessment strategies, management, and follow-up.

Search Strategy and Review Structure

The search strategy for the present review involved the National Center for Biotechnology Information (NCBI)/PubMed database, American Society of Clinical Oncology Annual Meeting abstract library, and the Cochrane Library. Databases

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Peripheral neuropathy is a broad term that refers to peripheral nerve damage. CIPN may develop as a consequence of treatment with multiple chemotherapy agents (Table 1), including platinum compounds (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vinblastine), thalidomide, and bortezomib. Most commonly, large sensory nerves are affected, leading to symptoms of paresthesias (“pins and needles”), dysesthesias, and numbness in the hands and feet.5 Sensory loss in a “glove-and-stocking”-type distribution (Fig. 1) is typically associated with a reduction or absence of deep tendon reflexes. From the perspective of a clinical examination, perception of touch, vibration, and proprioception may also be impaired. Typically, the nerve endings in the extremities of the hands and feet are affected earliest by toxicity in a symmetrical, length-dependent manner. Large sensory nerve fibers are most commonly affected, with damage to smaller sensory fibers occurring only rarely with select chemotherapies. Sensory nerve dysfunction is more common than motor involvement. However, motor and autonomic neuropathic symptoms may also develop, depending on the chemotherapy. Symptoms such as sensory ataxia, pain, and severe numbness can be disabling, and interfere with functional ability and quality of life. Neuropathic symptoms may also interfere with treatment, leading to a dose reduction or the early cessation of chemotherapy, thereby potentially impacting patient survival. Symptoms may continue to worsen even after treatment has ceased, a process referred to as the “coasting” phenomenon. While the overall clinical presentation of CIPN is similar among the different chemotherapies, there are important differences in the risk profile and underlying mechanisms of neurotoxicity between the different drugs.

Different chemotherapies affect distinct components of the nervous system, from the level of the sensory cell bodies in the dorsal root ganglion (DRG) to the distal axon (Fig. 1). The DRG is a prominent target as it is less protected by the blood-nerve barrier and more vulnerable to neurotoxic damage,6 potentially explaining the predominance of sensory involvement in patients with CIPN. Platinum compounds accumulate in the DRG,7,8 with platinum-DNA adducts leading to cell death in sensory neurons.9,10 Taxanes, vinca alkaloids, thalidomide, and bortezomib have also been associated with neuronal DRG damage.11-14 Disruption of microtubule dynamics is another common mechanism of neurotoxicity. Microtubules are central to axonal transport processes, and critical for energy and

| TABLE 1. Chemotherapies Associated With Peripheral Neuropathya |
|--------------------------|------------------------|-----------------|------------------------|------------------------|------------------------|
| TYPE | CLASS | THRESHOLD DOSE | SENSORY NEUROPATHY | MOTOR NEUROPATHY | AUTONOMIC NEUROPATHY |
| Paclitaxel | Taxane | >300 mg/m² | Predominantly sensory neuropathy | At higher doses, myalgia and myopathy | Rare |
| Docetaxel | Taxane | >100 mg/m² | Predominantly sensory neuropathy | At higher doses, myalgia and myopathy | Rare |
| Oxaliplatin | Platinum | >550 mg/m² | Acute sensory symptoms and chronic sensory neuropathy | Acute cramps and fasciculations | Rare |
| Cisplatin | Platinum | >350 mg/m² | Predominantly sensory neuropathy | Rare | Rare |
| Vincristine | Vinca alkaloid | >2-6 mg/m² | Sensory neuropathy | Muscle cramps and mild distal weakness | Yes |
| Thalidomide | Immunomodulatory/ antiangiogenic agent | >20 g | Sensory neuropathy | Mild distal weakness and cramps | Yes |
| Bortezomib | Proteasome inhibitor | >16 mg/m² | Painful, small-fiber sensory neuropathy | Rare | Yes |

*Treatments associated with chemotherapy-induced peripheral neuropathy and details of clinical presentations are shown, with an indication of the frequency of the presentation in sensory, motor, and autonomic neuropathy categories.
material delivery. Taxanes bind to β-tubulin components of microtubule assemblies, producing overpolymerization and interference with normal microtubule dynamics, which has been linked to the disruption of axonal transport.\textsuperscript{15,16} Vinca alkaloids bind tubulin and inhibit microtubule dynamics, leading to interference with the mitotic spindle,\textsuperscript{12} while bortezomib may also affect tubulin polymerization.\textsuperscript{17} In addition, interference with energy mechanisms of the axon may contribute to CIPN. Paclitaxel administration produced prominent abnormalities in axonal mitochondria,\textsuperscript{18} whereas bortezomib also was reported to affect endoplasmic reticulum and mitochondrial integrity, particularly in Schwann cells.\textsuperscript{19} In addition to energy deficiency, chemotherapies may damage the peripheral vasculature. As a case in point, thalidomide reduces peripheral nerve blood supply via antiangiogenic effects, leading to axonal degeneration.\textsuperscript{20}

Additional targets of neurotoxicity include direct axonal toxicity at the distal terminals, which may induce neurotoxicity and Wallerian degeneration following treatment with paclitaxel,\textsuperscript{21} vincristine,\textsuperscript{22} and thalidomide.\textsuperscript{23} Oxaliplatin may directly alter axonal voltage-gated sodium (Na\textsuperscript{+}) ion channel function, inducing an acute neurotoxicity manifested by peripheral nerve hyperexcitability.\textsuperscript{24-26} In some patients, bortezomib may induce primary myelin sheath degeneration.\textsuperscript{19} However, despite potential diverse mechanisms underlying the development of CIPN, common degenerative pathways may be triggered when the normal processes and energy delivery mechanisms of the peripheral nervous system become disrupted.

**Differential Diagnoses for CIPN**

The symptoms of CIPN may not be specific and may share considerable overlap with other forms of peripheral nerve disease. Appropriate baseline assessment of patients prior to the administration of potentially neurotoxic chemotherapy will assist in identifying those patients with preexisting sensory neuropathies, such as diabetic neuropathy. Consideration of the onset and progression of neuropathic symptoms and relationships with the timing of chemotherapy administration will also assist in identifying patients with CIPN.

Rarely, cancer may also be associated with the development of paraneoplastic neuropathy, in which onconeural antibodies target peripheral nervous system epitopes, producing neurological syndromes that may be similar to CIPN in some cases. Paraneoplastic neuropathies may present prior to diagnosis of the underlying malignancy or, conversely, may occur in patients already undergoing treatment and as such may be difficult to dissociate from CIPN in rare cases.\textsuperscript{27} Patients with paraneoplastic neuropathies often demonstrate marked proprioceptive loss in proximal areas and rapid progression of disability, which are not characteristic features of CIPN and should prompt clinical reevaluation. Subacute sensory neuropathy is the most common paraneoplastic disorder,\textsuperscript{28} and typically presents with sensory ataxia and pain but may demonstrate prominent autonomic symptoms.\textsuperscript{29} Subacute sensory neuropathy may be associated with anti-Hu antibodies in patients with small cell lung cancer, although the syndrome has also been reported in individuals with breast cancer and
Hodgkin disease. Anti-CV2 antibodies may also cause sensorimotor peripheral neuropathy in patients with small cell lung cancer or thymoma, in addition to central nervous system involvement.

Hematological malignancies can be associated with paraneoplastic neuropathies. This is particularly common in patients with multiple myeloma prior to treatment, with baseline neuropathy reported to be present in 20% of patients, although more than 50% of patients may have objective evidence of large- or small-fiber nerve dysfunction. The premalignant precursor of multiple myeloma, monoclonal gammopathy of Waldenström macroglobulinemia, characterized by IgM paraproteinemia, is often associated with predominantly axonal neuropathy. While there are no randomized controlled trials of treatment options for patients with paraneoplastic neuropathies, treatment of the underlying malignancy and immunotherapy are the typical treatment paradigms.

Clinical Assessment

Currently there is no standardized approach to the assessment of chemotherapy-induced neurotoxicity. Consensus is that such a measure must include both objective evidence of neurological deficits and assessment of symptoms from a patient perspective, as clinician-based reporting of adverse events during chemotherapy typically underestimates the significance of symptoms compared with patient reports. The development of a “gold standard” measurement of CIPN would improve the design of future clinical trials and thereby facilitate the development of future neuroprotective therapies. Ideally, such a gold standard should incorporate clinical examination, objective neurophysiological parameters, and patient-reported outcomes. Assessment at baseline and throughout treatment appear to be critical to identify preexisting neuropathy and conditions that may predispose to neuropathy, in addition to recognizing the earliest signs of peripheral nerve damage. Long-term follow-up is also essential to identify the true impact of CIPN, and we recommend that patients be investigated after the completion of treatment to identify persistent neurotoxicity (preferably at a minimum of 3 months posttreatment, when symptoms have stabilized). Such visits can easily be aligned with recommended general follow-up.

Clinical Grading Scales

The most common CIPN assessments are clinician-administered grading scales, including the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Neuropathy Sensory subscale (Table 2). However, there is only a moderate level of interobserver agreement, with 46% to 71% reliability reported between assessors and considerable interscale variation. While rigorous observer training leads to higher reliability, the NCI scale is also limited by ceiling and floor effects, with limited responsiveness to change due to the small number of available severity grades.

The Total Neuropathy Score (TNS; developed by Johns Hopkins University) is a composite score with a larger value range (0-40) that combines symptom scores with objective scoring of sensory loss and neurophysiological parameters. The TNS has been validated in a multicenter setting as a sensitive measure of CIPN and reliably correlates with other measures of sensory dysfunction. The wider range of values enables more precise and responsive grading of symptomatic progression, and addresses the lack of distinction between moderate and severe neurotoxicity (NCI grades 2 and 3). For example, 70% of patients with cancer who were scored as unchanged using the NCI scale demonstrated progressive worsening of sensory neuropathy when assessed using the TNS scale. The TNS clinical version (TNSc) uses only clinical measures with no need for specialist equipment, and the TNS reduced version (TNSr) omits formalized vibration threshold testing and assessment of motor and autonomic symptoms. These TNS versions have also been validated in patients with CIPN, with good interrater reliability noted. Griffith et al undertook a systematic review of CIPN assessment methods using a study quality assessment tool, and rated the TNS and its variants with a quality score of moderate, corresponding to 5.4 of 7. A number of initiatives are currently underway to formally identify the best approach to CIPN assessment, including the multinational CI-PeriNomS (Chemotherapy Induced-Peripheral Neuropathy Outcome Measures Study) study, which has reported initial validity and reliability findings for a number of CIPN assessment scales.
Importantly, the study identified good validity and reliability values for several assessment methods including the NCI-CTCAE, TNSc, and patient-reported outcomes measures. However, the TNSc was considered preferable to the NCI-CTCAE in terms of responsiveness. Responsiveness is a key issue in CIPN assessment and it is important to select methods that are appropriately sensitive to change. Further data on the relative responsiveness of these measures will be forthcoming. In the interim, the TNS scale appears to be superior to the NCI scale and may be optimal to adopt for future studies, particularly those of neuroprotective agents. In routine clinical practice, use of the TNSc may be more appropriate as it does not require specialized equipment or training.

Patient-Reported Outcomes

Patient-reported outcomes are becoming increasingly important to provide a comprehensive assessment of CIPN significance and severity. Perhaps not surprisingly, patients report significantly greater neuropathy than is reported by clinicians. In a study of 85 patients treated with chemotherapy, 19% reported neuropathic symptoms, 56% of whom experienced moderate to severe symptoms. In contrast, clinicians rated only 12% of the same cohort as symptomatic, and of these 90% of patients were classified as having mild neuropathic symptoms. In a study of 696 patients treated with oxaliplatin, there was 65% agreement between patient-reported outcomes and clinician-based toxicity criteria with regard to neuropathy, but patients identified the onset of neuropathy 2 months earlier than clinicians. Patient-reported outcomes provide an accurate assessment of neuropathy. Accordingly, several patient questionnaires are now available, including the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 questionnaire, the Functional Assessment of Cancer/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire, and the Patient Neurotoxicity Questionnaire (PNQ). In addition, future versions of the NCI scale will include patient assessment components.

The FACT/GOG-Ntx is a questionnaire comprising 12 neuropathy-related questions and has been validated with excellent internal consistency. The questionnaire strongly correlates with measures of daily functioning, quality of life and objective neuropathy, identifying that 81% of patients treated with bortezomib had neuropathy, while formal neurological assessment similarly

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**TABLE 2. Assessment of CIPN Via Neuropathy Grading Scales**

| GRADE | 0 | 1 | 2 | 3 | 4 |
|-------|---|---|---|---|---|
| **NCI Common Terminology Criteria for Adverse Events**<sup>49</sup> | | | | | |
| Neuropathy Sensory Subscale | None | Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function | Sensory alteration or paresthesia (including tingling), interfering with ADL | Sensory alteration or paresthesia interfering with ADL | Disabling |
| **Total Neuropathy Score**<sup>52-54</sup> (developed by Johns Hopkins University) | | | | | |
| Sensory symptoms | None | Symptoms limited to fingers or toes | Symptoms extend to ankle or wrist | Symptoms extend to knee or elbow | Symptoms above knees or elbows, or functionally disabling |
| Motor symptoms | None | Slight difficulty | Moderate difficulty | Require help/assistance | Paralysis |
| Autonomic symptoms | Normal | Reduced in fingers/toes | Reduced to wrist/ankle | Reduced to elbow/knee | Reduced to above elbow/knee |
| Sensory symptoms | Normal | Reduced in fingers/toes | Reduced to wrist/ankle | Reduced to elbow/knee | Reduced to above elbow/knee |
| Strength | Normal | Mild weakness | Moderate weakness | Severe weakness | Paralysis |
| Deep tendon reflexes | Normal | Ankle reflex reduced | Ankle reflex absent | Ankle reflex absent, others reduced | All reflexes absent |
| Sural amplitude | Normal/reduced to <5% of LLN | 76%-95% LLN | 51%-75% LLN | 26%-50% LLN | 0%-25% LLN |
| Peroneal amplitude | Normal/reduced to <5% of LLN | 76%-95% LLN | 51%-75% LLN | 26%-50% LLN | 0%-25% LLN |
| Vibration sensation | Normal to 125% of ULN | 126%-150% ULN | 151%-200% ULN | 201%-300% ULN | >300% ULN |

CIPN indicates chemotherapy-induced peripheral neuropathy; NCI, National Cancer Institute; ADL, activities of daily life; LLN, lower limit of normal; ULN, upper limit of normal.
identified 83% of patients. The questionnaire also provides greater sensitivity, with each increase in NCI grade corresponding to a 4- to 6-point worsening on the FACT/GOG-Ntx scale. Questionnaire results have also been correlated to quantitative measures of nerve damage including vibration threshold detection. The FACT/GOG-Ntx also correlated with measures of daily functioning and quality of life, suggesting that it also assesses functional impact. Systematic review of studies including the FACT/GOG-Ntx scale indicated a quality score of moderate (4.5 of 7). Studies also have reported moderate to high internal consistency reliability (Cronbach’s 0.82-0.94). The EORTC QLQ-CIPN20 is a similar questionnaire, with reportedly good reliability and greater sensitivity than NCI grading, with 62% of patients with CIPN reporting “quite a bit” to “very much” tingling, while only 13% of patients in the same cohort were graded with severe grade 3 neuropathy. A recent study has confirmed the validity and responsiveness of the EORTC QLQ-CIPN20, with good internal validity (Cronbach’s 0.88) and a large effect size with respect to responsiveness to change (Cohen’s 0.82). The PNQ includes assessment of the functional impact of neuropathy symptoms, and has also been found to be a valid and sensitive measure in patients with CIPN, detecting a wider distribution of severity compared with NCI scores. A novel outcome measure, the CIPN Rasch-built Overall Disability Score (CIPN-R-ODS), has been specifically developed to assess patient disability and functional outcomes. The CIPN-R-ODS is an interval-based measure that addresses difficulties with ordinal scales to provide assessment of functional disability. Given the increasing importance of patient-reported outcomes in assessment and management, it is recommended that one of these validated scales be used in all studies addressing CIPN. The benefits of including direct patient evaluations include a more comprehensive and accurate assessment of CIPN, improved understanding of the impact of CIPN symptoms on the patient, and a better correlation of toxicity findings with functional outcomes.

**Specific Chemotherapy and Symptom Scales**

A number of chemotherapy-specific scales have been developed to address symptomatic differences between chemotherapeutic agents. The Oxaliplatin-Specific Neurotoxicity Scale attempts to dissociate between acute and chronic forms of neurotoxicity produced by oxaliplatin, with 3 severity grades encompassing neuropathic symptoms resolving within 7 days (grade 1), persisting for longer than 7 days (grade 2), and leading to functional impairment (grade 3). Such scales have been demonstrated to lead to the earlier detection of neurotoxicity and a better assessment of persistent neuropathic symptoms. Similarly, a specific scale has been developed for cisplatin-induced neuropathy. The Scale for Cisplatin-Induced Neurotoxicity comprises 3 subscales assessing neurotoxicity, ototoxicity, and Raynaud phenomena. In addition, the importance of more specific assessments is also being recognized to address the symptomatic burden and functional consequences of CIPN. Chronic pain represents a significant issue in cancer survivors following chemotherapy. More than 50% of patients with CIPN report pain, with severe pain reported by up to 25%. Patients often report significantly higher pain levels than are scored by clinicians. A specific Neuropathic Pain Scale for chemotherapy-induced neuropathy has been developed to address patient-reported neuropathic pain, although further validation is required.

**Objective Assessment**

The gold standard for the objective neurophysiological assessment of CIPN involves the use of nerve conduction studies (NCS), which measure the amplitude and conduction velocity of compound sensory action potentials (CSAPs) and compound motor action potentials (CMAPs). NCS provide valuable information about the extent of axonal loss in patients with CIPN. Reduction of CSAP amplitude is a common finding in patients with CIPN, confirming the development of axonal sensory neuropathy. NCS may also provide an assessment of conduction velocity, temporal dispersion, conduction block, and more proximal F-wave latencies, which are important to rule out other causes of CIPN-like symptoms (particularly inflammatory neuropathies). While NCS are the standard for neuropathy assessment and the only method routinely available to objectively monitor CMAP and CSAP amplitudes, NCS parameters may not change until late in the course of chemotherapy. In addition, NCS require specialized equipment and personnel and may cause discomfort to the patient, particularly in the context of generalized medical problems and the side effects of chemotherapy. A complementary technique to NCS, nerve excitability studies, has been adapted for clinical use, and has demonstrated utility in identifying the onset of oxaliplatin neuropathy prior to the development of changes in NCS and before neuropathic symptoms were clinically significant. On the whole, traditional NCS techniques remain the gold standard approach to assess clinical neuropathy and should be used in clinical trials of neuroprotective agents to provide objective evidence of nerve damage or neuroprotection. Quantitative sensory testing (QST) involves determination of the detection threshold for sensory stimuli to quantify changes in sensory perception, involving a range of testing procedures including vibration threshold detection, thermal
detection, and sharpness detection. The development of standardized QST protocols may increase the accuracy and relevance of the technique for patients with CIPN. Vibration perception threshold measured in the feet is a sensitive QST method for the assessment of CIPN.5,83,89 The development of cold hyperalgesia (increased pain in response to a cold stimulus) may be of assistance in predicting the development of severe neuropathy in patients treated with oxaliplatin.90 In addition, the use of calibrated tuning forks91 and monofilaments92 have been shown to be valid quantitative measures of sensory loss in patients with peripheral neuropathy. Such measures can be undertaken quickly with very little training, and provide an objective assessment of nerve function.

### Pharmacogenetic Assessment

Recently, the use of pharmacogenetic techniques to identify genetic polymorphisms has enabled further identification of potential differences in susceptibility to neurotoxicity between individual patients. However, there remains a lack of consensus on the association between genetic variants and the risk of neurotoxicity. Further studies with standardized objective measures of neuropathy and larger patient numbers will be required to fully assess the involvement of genetic polymorphisms in the risk of neurotoxicity.93

Polymorphisms in glutathione S-transferase detoxification enzymes (GSTPI-105) have been variably associated with an increased risk of severe neuropathy in patients treated with oxaliplatin.94-99 Similarly, in patients treated with cisplatin, there have been some associations with polymorphisms in GSTPI and the related GSTM1 genes.97,100 Polymorphisms in genes associated with drug efflux and metabolism (ABCB1, cytochrome P450 2C8 [CYP2C8]) have been linked to neurotoxicity in patients treated with paclitaxel,101 although multiple studies have also been unable to identify relevant associations.102,103 A related gene encoding the CYP3A family of cytochrome P450 enzymes may be a pharmacogenetic predictor of neurotoxicity severity in patients treated with vincristine, with CYP3A4 variants demonstrating less efficient clearance and more severe neuropathy compared with CYP3A5.104,105 A range of polymorphisms have also been identified with genome-wide association analysis in association with oxaliplatin,106 paclitaxel, bortezomib, thalidomide, and vincristine.107,108

### Chemotherapies Associated With CIPN

#### Taxanes

Taxanes, such as paclitaxel and the semisynthetic analog docetaxel, may produce sensory neuropathy,89,109,110 with symptoms of paresthesia and numbness in the extremities.110 Deficits in fine motor skills and walking ability may occur in severe cases.89,109,110 In addition, myalgias and arthralgias often develop within 1 to 4 days following paclitaxel infusion as part of a paclitaxel-associated acute pain syndrome.111 The severity of acute pain has been associated with the later development of sensory neuropathy, suggesting a common mechanism.111

Taxane-induced neuropathy is dose-dependent, with symptoms typically occurring at cumulative doses of greater than 300 mg/m² (Table 3).83,89,112 Increasing single and cumulative paclitaxel dose levels are also associated with a greater risk of neurotoxicity.83,89,112,113 A shorter infusion duration has also been demonstrated to increase the incidence of neurotoxicity (eg, 3 hours compared with 24 hours).114,115 Although there is no difference between similar infusion durations, (eg, 1 hour and 3 hours).116 There has been much debate over the relative neurotoxicity of weekly versus 3-weekly taxane administration schedules. Weekly administration of taxanes was typically associated with a lower rate of severe neurotoxicity compared with 3-weekly schedules.117-123 Recent evidence from a large trial of 2716 patients also suggested that weekly paclitaxel was associated with lower rates of severe neurotoxicity compared with a 2-weekly administration schedule (grade 3: 10% for weekly vs 17% for 2-weekly).124 However, this finding was not universal125 and several studies have identified higher rates of peripheral neuropathy with the weekly administration of paclitaxel-based regimens.126-128 Paclitaxel dose level was important, with a weekly dose of 175 mg/m² producing severe neurotoxicity in over 75% of patients,118 and the effects of increasing dose may potentially overcome the benefit of a weekly schedule.125,127 In addition, new formulations of paclitaxel to improve solubility and delivery, including nanoparticle albumin-bound (Nab) paclitaxel and liposomal-encapsulated paclitaxel, may also assist in enabling lower doses and reduced toxicity.129

Paclitaxel-induced neuropathy was reported to be at least partially reversible, potentially due to axonal recovery after treatment.5,130 However, chronic paclitaxel administration may eventually lead to axonal degeneration, producing symptoms that are longer-lasting, possibly reflecting the consequences of long-term axonal transport dysfunction. Overall, mild to moderate symptoms may persist long-term,131,132 with 39% of patients presenting with objective neurological abnormalities at 3 years of follow-up.132 In addition, both paclitaxel and docetaxel are often administered in conjunction with platinum-based chemotherapies such as cisplatin or carboplatin, which may produce significant additional neurotoxicity in patients with BRCA-related breast cancer, triple-negative cancers, and ovarian cancer.33,131 While the combination with carboplatin is less neurotoxic than cisplatin, almost 25% of patients demonstrated ongoing symptoms following the completion of treatment with carboplatin-taxane regimens.131
While 50% of patients treated with paclitaxel recovered within 9 months, symptoms of peripheral neuropathy persisted in 41% of patients at 3 years, suggesting that neurotoxicity can persist long-term. Patient-reported symptoms and sensory testing identified approximately 67% to 80% of patients with persistent numbness one year following adjuvant treatment for early-stage breast cancer. In addition, paclitaxel has also been demonstrated to cause persistent deficits in balance more than 2 years after treatment.

**Oxaliplatin**

Oxaliplatin, a third-generation platinum analog that is active against both early-stage and advanced colorectal cancer, produces significant neurotoxicity, a potential dose-limiting side effect of treatment. Oxaliplatin produces 2 spectrums of neurotoxicity: acute, which occurs following infusion, and with chronic administration. Significant acute neurotoxicity occurs in most patients (85%–95%), developing during or immediately following infusion, and typically resolving within a week. The most common symptoms are distal limb and mouth paresthesias exacerbated by cold exposure, jaw pain on biting, and mouth numbness. Motor signs and symptoms may also occur, including muscular spasm-like contractions, fasciculations, and cramps. At a higher cumulative dose, oxaliplatin induces a typical CIPN sensory neuropathy in 20% to 50% of patients, characterized by distal paresthesia and numbness, and leading to functional disability.

Chronic oxaliplatin-induced sensory neuropathy appears to be dose-dependent, with severe neuropathy typically occurring in 10% to 20% of patients at a cumulative dose of 750 mg/m² to 850 mg/m² (Table 3). The incidence of neuropathy increased sharply with cumulative dose, with severe neuropathy estimated to occur in 10% of patients after 9 treatment cycles and in 50% after 14 treatment cycles. Neupathy also increased in incidence and severity with greater single doses. A prolonged infusion duration (6 hours) produced significantly less severe neurotoxicity than the standard 2-hour infusion (6.2% vs 18.7%). “Stop-and-go” treatment strategies, with oxaliplatin given for a shorter period (usually 3 months) and then reintroduced after an oxaliplatin-free interval, produced lower rates of severe neurotoxicity (grade 3: 11% vs 26%). Decreased dose density may also reduce neurotoxicity, with patients receiving 3-weekly regimens (XELOX 3-weekly dose of 130 mg/m² of oxaliplatin with oral capecitabine) developing lower rates of severe neurotoxicity than those receiving 2-weekly schedules (FOLFOX6 leucovorin, fluorouracil, and 100 mg/m² of oxaliplatin) (grade 3: 11% vs 26%). However, 3-weekly schedules may not reduce neurotoxicity when compared with 2-weekly schedules with a lower single dose (FOLFOX4 leucovorin, fluorouracil and 85 mg/m² of oxaliplatin). The total cumulative oxaliplatin dose was found to be a major factor, as patients treated with 2-weekly oxaliplatin at a dose of 85 mg/m² demonstrated a significantly increased incidence of severe neuropathy.

### Table 3. Chemotherapy Dose and Duration as a Risk Factor for CIPN

| Factor                  | Consensus                                      | Chemotherapy       | References                      |
|-------------------------|------------------------------------------------|--------------------|--------------------------------|
| Single dose level       | Increased single doses are associated with greater neurotoxicity | • Taxanes          | 83,89,112,113                  |
|                         |                                                 | • Oxaliplatin      | 140                            |
|                         |                                                 | • Cisplatin        | 81,155,157,158,160,162,164     |
|                         |                                                 | • Vincristine      | 168                            |
|                         |                                                 | • Thalidomide      | 186,187                        |
|                        |                                                 | • Bortezomib       | 69                             |
| Cumulative dose level   | Increased cumulative doses are associated with greater neurotoxicity | • Taxanes          | 83,89,112,113                  |
|                         |                                                 | • Oxaliplatin      | 84,135,138,140                 |
|                         |                                                 | • Cisplatin        | 81,155,157,160                 |
|                         |                                                 | • Vincristine      | 168-170                        |
| Lack of consensus       | Regarding the relationship between cumulative dose and neurotoxicity | • Thalidomide      | 33,188                         |
| Dose threshold          | relationship, increasing risk until a plateau at 40 to 45 mg/m² | • Bortezomib       | 34,69,200,201                  |
| Infusion duration       | Longer infusion duration may reduce neurotoxicity | • Taxanes          | 114-116,141                    |
|                         |                                                 | • Oxaliplatin      |                                 |
| Treatment duration      | Longer duration of treatment increases the risk of neurotoxicity | • Thalidomide      | 33,190                         |
| “Stop-and-go” regimen   | may be associated with lower neurotoxicity     | • Oxaliplatin      | 142,143                        |

CIPN indicates chemotherapy-induced peripheral neuropathy.
neurotoxicity compared with patients treated with XELOX regimens, a finding that was attributed to the 6% greater oxaliplatin dose (grade 3: 10% vs 13%).

Initial assessments characterized oxaliplatin-induced neuropathy as largely reversible, with a median recovery time of 13 weeks. Studies using clinician-based grading scales identified 0.5% to 0.7% of patients with severe neurotoxicity at 18 to 48 months after treatment. Overall, 15% of patients were reported to have neurotoxic symptoms at 2 years posttreatment using the NCI scale. However, the addition of patient-reported outcome measures demonstrated increased prevalence, with 60% of patients reporting lasting neuropathic symptoms interfering with function compared with 10% of patients graded with severe neuropathy by clinicians. Six months after oxaliplatin treatment, 32% of patients reported persistent numbness and tingling (ranging from “somewhat” to “quite a bit more severe”) using the FACT/GOG-Ntx scale, while only 5.2% of the same cohort were classified as having moderate or severe neuropathy (NCI grades 2 or 3). At 7 years after oxaliplatin treatment, there remained significant numbness in the hands and feet reported by patients, with 29% reporting at least “somewhat severe” neuropathic foot symptoms at follow-up. In addition, patients treated with oxaliplatin had an odds ratio of 2.78 for persistent foot numbness or tingling compared with other patients. Furthermore, clinically significant neuropathic symptoms persisted in patients 2 to 11 years after oxaliplatin treatment, as reported via the patient-reported outcome scale EORTC QLQ-CIPN20.

In addition, more than 75% of patients are reported to demonstrate lasting neurophysiological abnormalities with persistent reductions in sensory amplitudes. At 18 months since oxaliplatin treatment, there was no recovery observed in vibration perception thresholds in the feet and 75% of patients demonstrated balance impairment. Taken in total, these findings suggested that rather than recovery, patients undergo adaptation to chronic symptoms, but have lasting deficits in sensory nerves that persist in the long term.

Cisplatin

Symptoms of cisplatin-induced neuropathy are similar to those of other CIPNs: tingling and numbness, progressing to loss of proprioception and deep tendon reflexes. CSAP amplitudes were decreased, consistent with degeneration of large sensory neurons in the DRG. The cumulative cisplatin dose was strongly associated with the risk of neurotoxicity, with neuropathy developing at cumulative doses greater than 350 mg/m² (Table 3). After 1 cycle of bleomycin, etoposide, and cisplatin (20 mg/m² of cisplatin on days 1–5), 5.2% of patients displayed mild neurotoxicity, although following 3 cycles, neurotoxicity was reported to develop in 20% to 30% of patients. An additional treatment cycle of cisplatin significantly increased the percentage of patients with neurotoxicity with 30% of patients experiencing off-treatment worsening of symptoms,158 although following 3 cycles, neurotoxicity was reported to develop in 20% to 30% of patients. An additional treatment cycle of cisplatin significantly increased the percentage of patients with neurotoxicity at both the time of treatment (24% vs 37%) and at follow-up 2 years later (28% vs 36%). Rates of neurotoxicity also increased with higher single doses of cisplatin. Furthermore, more than 50% of patients continued to progress symptomatically after the cessation of treatment, often with the development of new symptoms, including muscle cramps.

Persistent sensory neuropathy may occur in more than 20% of patients following cisplatin-based treatment, although the percentage of patients affected varies widely depending on the duration of follow-up, assessment technique used, dose, duration of treatment, and other risk factors. The risk of persisting neuropathy was strongly dose-dependent. In addition, reactive platinum remains in peripheral blood mononuclear cells for many years after cisplatin treatment, and analysis of serum platinum levels up to 20 years after cisplatin treatment has revealed significant associations with the severity of neurotoxicity. There are often discrepancies between objective neurophysiological- and subjective symptom-based assessments. With objective testing, up to 80% of patients may demonstrate cisplatin-induced nerve damage, suggesting that cisplatin-induced neuropathy is irreversible but that patients adapt with functional changes that underlie symptomatic recovery over time.

Vincristine

The vinca alkaloid vincristine induces a glove-and-stocking distribution sensory neuropathy in 35% to 45% of patients. Vincristine-induced neuropathy typically develops first in the hands and then feet, leading to functional disability with fine motor tasks and walking. “Coasting” was also prominent in vincristine-induced neuropathy, with 30% of patients experiencing off-treatment worsening of symptoms. In addition to sensory symptoms, motor and autonomic neuropathies were also prominent. Patients treated with vincristine experienced muscle cramps and distal muscle weakness. Autonomic symptoms included reduced heart rate variability, postural hypotension, and bladder and bowel disturbance. Less commonly, ocular palsies and vocal cord paralysis developed. Vincristine treatment was also associated with the development of acute motor neuropathy, similar to Guillain–Barré syndrome variant acute motor axonal neuropathy. While this may be considered rare, it is important to distinguish from acute inflammatory demyelinating
neuropathy, which can also develop in patients with leukemia and lymphoma related to immune system dysfunction.\textsuperscript{176-178} These clinical presentations can be indistinguishable without electrodiagnostic studies and have different treatment implications, as the suspicion of an immune-mediated neuropathy would warrant treatment with immunotherapy.\textsuperscript{178,179}

Vincristine administration may also induce severe acute neurotoxicity in patients with hereditary sensorimotor neuropathy (Charcot-Marie-Tooth disease).\textsuperscript{180} If vincristine alkaloid treatment produces severe and acute neurotoxicity in a patient without a history of inherited neuropathy, appropriate testing should be undertaken to rule out undiagnosed Charcot-Marie-Tooth disease. Antifungal treatment with azole-based agents may also exacerbate vincristine-induced neuropathy via inhibition of the hepatic enzyme cytochrome P450 complex isoenzyme 3A that is responsible for vincristine metabolism.\textsuperscript{104,181} Accordingly, it is recommended that azole-based agents be avoided during vincristine administration\textsuperscript{181} as azole treatment may dramatically increase the incidence of severe neurotoxicity.

The development of vincristine-induced neuropathy was strongly dose-dependent (Table 3), with neuropathy developing at dose of 2 to \textit{6 mg/m²}.\textsuperscript{168-170} Vincristine-induced neurotoxicity was also related to single doses, with patients receiving a 4-mg dose demonstrating worse neurotoxicity than those receiving 2 mg.\textsuperscript{168} Total dose levels have been capped at 2 mg regardless of body surface area, as increased neuropathy occurs in patients treated in excess of these doses.\textsuperscript{170} However, the development of liposome-encapsulated vincristine may enable higher doses to be administered, without increasing the neurotoxicity side effect profile, even in extensively pretreated patients.\textsuperscript{182}

Vincristine-induced neuropathy has been reported to be largely reversible, although some patients report lasting dysfunction, with sensory symptoms persisting longer than motor symptoms.\textsuperscript{169} Typically mild sensorimotor symptoms resolved within 2 months.\textsuperscript{170} However, long-term follow-up of patients with non-Hodgkin lymphoma who were treated with vincristine revealed that 32\% had mild sensory symptoms that persisted at 34 months after vincristine treatment\textsuperscript{169} and 14\% had disabling sensory neuropathy at 9 years after treatment.\textsuperscript{183} In comparison, \textit{30\%} of children with acute lymphoblastic leukemia had neuropathic symptoms 7 years following chemotherapy, with objective evidence of persistent neuropathy identified in 100\% of these patients.\textsuperscript{184} Importantly, patients with sensory neuropathy following treatment for B-cell lymphoma reported a lower quality of life than those without neuropathy,\textsuperscript{185} indicating that persistent neuropathy has an important impact on patients’ lives.

**Thalidomide**

Neuropathy remains one of the common adverse events of thalidomide treatment,\textsuperscript{32} representing the most common reason for thalidomide dose reduction and cessation in patients with multiple myeloma.\textsuperscript{32,33,186} The overall incidence of neuropathy ranges up to 83\% of patients\textsuperscript{32,33,187} presenting as a sensory neuropathy with prominent symptoms of paresthesia in the hands and feet, numbness, and mild motor involvement including muscle cramps and weakness.\textsuperscript{33,188,189} Thalidomide-induced neuropathy involves both small- and large-fiber sensory dysfunction and is most prominent in the distal lower limbs.\textsuperscript{32}

Even with extremely low doses, the duration of exposure to thalidomide is strongly associated with the development of neurotoxicity.\textsuperscript{190} The median duration of thalidomide treatment in patients with neuropathy is 3 times greater than that of patients who do not develop neuropathy.\textsuperscript{32} Long-term maintenance therapy with thalidomide for greater than 1 year leads to peripheral neuropathy in 75\% of patients, with severe neuropathy reported in approximately 35\%.\textsuperscript{191,192} Dose levels are also associated with the development of neuropathy. Lower single daily doses (100 mg/day vs 400 mg/day) produced significantly less neuropathy (56\% vs 68\% for all grades\textsuperscript{186} and 12\% vs 22\% for grades greater than 1\textsuperscript{187}) and reduced the need for dose reductions due to neurotoxicity, with 42\% of patients in the high-dose cohort experiencing a dose reduction compared with 8\% of the low-dose cohort.\textsuperscript{186}

The thalidomide analog lenalidomide displays a different profile of clinical activity and produces a different toxicity profile. In a direct comparison trial, while thalidomide produced severe neuropathy in 10.6\% of patients, lenalidomide produced severe neuropathy in only 0.9\%, although with greater hematological toxicity.\textsuperscript{193} The long-term outcomes of thalidomide in patients with multiple myeloma remain relatively unknown. Trials have identified that neuropathic symptoms typically improved within 3 to 4 months after the cessation of thalidomide treatment in 90\% of patients.\textsuperscript{194} However, studies in patients with other disorders who were treated with thalidomide for more than 2 years have suggested limited and slow reversibility of neuropathy.\textsuperscript{189}

**Bortezomib**

Bortezomib is the first of a new class of proteasome inhibitors to enter clinical use, and is highly active in multiple myeloma.\textsuperscript{69} However, bortezomib induces a painful sensory neuropathy in 50\% of patients, with moderate or severe neurotoxicity developing in up to 30\%.\textsuperscript{34,69} Bortezomib-induced peripheral neuropathy is predominantly sensory, with paresthesia and numbness occurring in distal
areas, particularly lower limbs.\textsuperscript{32} In contrast to other CIPNs, bortezomib-induced neuropathy involves prominent small fiber involvement, characterized by sharp, burning pain in the toes and soles of the feet.\textsuperscript{195} Autonomic involvement may develop, including orthostatic hypotension, suppressed heart rate variability, and delayed gastric emptying,\textsuperscript{195} but motor involvement is uncommon.\textsuperscript{32,196} Typically, 10% of patients must discontinue bortezomib treatment due to neuropathic symptoms.\textsuperscript{34} In rare cases, bortezomib may also produce a demyelinating sensorimotor neuropathy (similar to an immune-mediated neuropathy) in a small number of patients, which responds to immunotherapy.\textsuperscript{197}

The incidence and severity of bortezomib-induced neuropathy were dependent on the single-dose level, with 37% of patients treated with 1.3 mg/m\textsuperscript{2} developing neuropathy compared with 21% of patients treated with 1.0 mg/m\textsuperscript{2} (Table 3).\textsuperscript{199} Importantly, dose modification seemed to have an important impact on reversibility, with a higher percentage of patients experiencing recovery after undergoing dose reduction protocols (68% vs 47%).\textsuperscript{198}

Dose intensity was a significant risk factor, with patients treated with twice-weekly bortezomib developing significantly greater neurotoxicity than those treated once weekly (grade 3: 28% vs 8%).\textsuperscript{199} However, bortezomib-induced neuropathy demonstrated a “dose threshold” relationship, with the onset of neuropathy occurring at a cumulative dose of 16 to 26 mg/m\textsuperscript{2} and increasing in incidence until 40 to 45 mg/m\textsuperscript{2} but with no dramatic increase beyond this plateau.\textsuperscript{69,200} In trials with lower dose intensity, this plateau effect still occurred at a cumulative dose of approximately 45 mg/m\textsuperscript{2}, although following a longer duration of treatment.\textsuperscript{201} Similarly, patients who underwent prolonged bortezomib treatment did not experience increased levels of neuropathy beyond the plateau dose.\textsuperscript{69}

While studies using subjective grading scales demonstrated resolution of bortezomib-induced neuropathy with a median of 2 to 3 months after treatment in 60% to 85% of patients,\textsuperscript{69,193,198} more than 25% of patients may be left with persistent neuropathy.\textsuperscript{202} In addition, a study that used objective assessment of nerve function suggested that neuropathy persisted in the long term without

\begin{table}
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\begin{tabular}{|l|l|l|}
\hline
\textbf{PREVENTION} & \textbf{CATEGORY} & \textbf{AGENTS} \\
\hline
Acetyl-L-carnitine & Antioxidant & Cisplatin; carboplatin/ paclitaxel \\
\hline
Alpha lipoic acid & Antioxidant & Paclitaxel \\
\hline
L-carnitine L-tartrate & Antioxidant & Paclitaxel \\
\hline
Glutamine & Antioxidant & Bortezomib \\
\hline
Glutathione & Antioxidant & Carboplatin/paclitaxel \\
\hline
Vitamins B6, B12 & Antioxidant & Cisplatin; taxanes; vinca alkaloids \\
\hline
Fish oil & Dietary intervention; antioxidant & Taxanes \\
\hline
Pregabalin & Anticonvulsant & Oxaliplatin; paclitaxel \\
\hline
Venlafaxine & Antidepressant & Oxaliplatin \\
\hline
Riluzole & Neuroprotectant & Oxaliplatin \\
\hline
Calcium/magnesium infusion & Neuroprotectant & Oxaliplatin \\
\hline
GM1 monosialoganglioside & Neuroprotectant/ ganglioside & Cisplatin \\
\hline
Minocycline & Antibiotic & Oxaliplatin \\
\hline
Polyamine-depleted diet & Dietary intervention & Oxaliplatin \\
\hline
Cryotherapy & Intervention (temperature) & Paclitaxel \\
\hline
\end{tabular}
\caption{Current Clinical Trials in the Prevention and Treatment of CIPN\textsuperscript{a}}
\end{table}

\begin{table}
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\begin{tabular}{|l|l|l|}
\hline
\textbf{TREATMENT} & \textbf{CATEGORY} & \textbf{AGENTS} \\
\hline
Dietary amino acid supplements & Dietary intervention; antioxidant & CIPN \\
\hline
Acupuncture & Intervention & Thalidomide; bortezomib; paclitaxel; oxaliplatin \\
\hline
Electronic stimulation M5-A scrambler & Intervention (stimulation) & CIPN \\
\hline
Ethosuximide & Anticonvulsant & CIPN \\
\hline
Photon stimulation & Intervention (infrared light) & CIPN \\
\hline
Topical gel & Analgesic & CIPN \\
\hline
Tetrodotoxin & Voltage-gated sodium channel blocker & CIPN \\
\hline
Oxycodone/ naloxone & Opioid analgesic & CPIN \\
\hline
Cannabinoids & Analgesic & Cisplatin; vincristine; paclitaxel \\
\hline
Angiotensin II type 2 receptor antagonist & Analgesic & CIPN \\
\hline
\end{tabular}
\caption{Current Clinical Trials in the Prevention and Treatment of CIPN\textsuperscript{a}}
\end{table}
improvement in small-fiber or large-fiber nerve dysfunction at one year of follow-up, indicating that clinical recovery may not reflect resolution of neurological deficits.

Neuroprotective Approaches and Treatment Strategies

At present, dose modification and interruption remain the most successful approaches for the prevention of CIPN. Fortunately, higher-dose therapy schedules are not often required to achieve the best outcomes, and so there is scope for dose modification. Structured dose-modification protocols may demonstrate a significant benefit in ameliorating neurotoxicity. Implementation of a dose reduction protocol in patients treated with bortezomib reportedly led to improved “reversibility” of neuropathic symptoms in patients who underwent dose reduction. However, further studies are required to address the efficacy of specific dose reduction protocols for other neurotoxic chemotherapies. While there is evidence more broadly that the cumulative dose is associated with the development of neuropathy, the specific improvements with dose reduction protocols are not well described. Shorter treatment courses, longer infusion durations, and providing breaks in treatment (such as in “stop-and-go” regimens) have also assisted in reducing neurotoxicity rates. The identification of individual patients at high risk of developing severe neurotoxicity prior to administration will be crucial to reducing the incidence of neurotoxicity. Specifically, patients with a preexisting neuropathy or a condition that predisposes to peripheral neuropathy, such as diabetes mellitus, are typically at higher risk.

There are currently no therapies with a confirmed neuroprotective benefit available for clinical use in patients with CIPN. While a number of potential approaches are being investigated in clinical trials (Table 4) and many neuroprotective compounds have already been studied, there has been limited success to support the introduction of neuroprotective therapies in clinical trials for CIPN, and any successes to date have often failed to be replicated in larger-scale randomized controlled trials. Accordingly, a
key element in the search for neuroprotective agents remains the design of clinical trials with physiologically relevant, robust, and sensitive endpoints, including patient-reported outcomes.

Several antioxidant compounds designed to protect neuronal cell bodies against DNA damage and toxic accumulation have been assessed. Of these, glutathione and glutamine are still under development, with some preliminary positive findings. A related thiol, N-acetylcysteine, ameliorated oxaliplatin–induced neurotoxicity in a pilot study. In addition, vitamin E supplementation has also been demonstrated to reduce the incidence of neuropathy in patients treated with cisplatin and paclitaxel, but this finding was not confirmed in a phase 3 trial. A number of other antioxidants and vitamins are currently undergoing assessment in clinical trials (Table 4). However, none of these compounds have a proven clinical role at present and evidence of benefit will clearly be required to justify larger prospective clinical trials.

With regard to oxaliplatin–induced neurotoxicity, calcium (Ca\(^{2+}\)) and magnesium (Mg\(^{2+}\)) infusions administered before and after treatment with oxaliplatin have been reported to provide some benefit in reducing neurotoxicity and improving the reversibility of neuropathic symptoms, possibly related to oxalate–mediated chelation of Ca\(^{2+}\) and Mg\(^{2+}\) ions. Similarly, retrospective meta-analyses suggested that Ca\(^{2+}\) and Mg\(^{2+}\) infusions may be of benefit without reducing chemotherapy efficacy. However, recent evidence from a randomized placebo-controlled trial of 353 patients treated with oxaliplatin indicated that infusions of Ca\(^{2+}\) and Mg\(^{2+}\) did not demonstrate efficacy in preventing or reducing neurotoxicity. In addition, there remains some controversy over the potential effects of Ca\(^{2+}\) and Mg\(^{2+}\) infusions on reducing the therapeutic efficacy of oxaliplatin.

Antiepileptic and antidepressant medications may have potential for symptom control in patients with CIPN based on their use in the more general treatment regimens for neuropathic pain. While a number of therapies have been studied to date, no treatments have specifically been recommended for CIPN. There is preliminary evidence to support the introduction of valproate, venlafaxine, and oxcarbazepine. A phase 3 trial in patients treated with oxaliplatin indicated that venlafaxine reduced acute symptoms and may also have prevented severe chronic neurotoxicity. In addition, a randomized controlled trial in patients with painful CIPN indicated that duloxetine was effective in reducing patient-reported pain ratings. However, several antiepileptic or antidepressant agents have failed to demonstrate significant activity in clinical trials, including amitriptyline, gabapentin, and lamotrigine. Again, randomized clinical trials will be required to determine the benefits of antiepileptic and antidepressant medications in patients with CIPN.

A number of experimental symptomatic treatments are currently being studied in patients with CIPN (Table 4), including neurostimulation techniques, topical analgesic creams, acupuncture, and dietary modifications. However, the role of these interventions in treating patients with CIPN remains unclear.

Given the lack of proven and effective treatments for CIPN, a larger focus has been placed on clinical management and patient education strategies to mitigate against secondary injury arising as a result of neuropathy. Therapy to improve balance and gait difficulties may be recommended for suitable patients and occupational therapy may be warranted to assist patients in adapting their activities and their environment. Of relevance, the assessment of physical performance in cancer survivors has revealed a significant association between chronic neuropathy, functional difficulties, and falls, suggesting that CIPN may produce lasting dysfunction in up to 58% of patients. CIPN is an important factor in increasing the risk of falls, with 20% of patients experiencing falls during chemotherapy. Patients who experienced falls reported significantly greater symptoms of neuropathy, with greater functional impairment linked to the degree of neuropathy.

Conclusions

CIPN remains a clinically significant and potentially serious side effect of cancer treatment, with increasing relevance to the millions of cancer survivors worldwide. The number of cancer survivors with disability due to CIPN is underreported, as the use of patient-reported outcomes and objective assessment tools typically reveal greater neurotoxicity than clinician assessment. Improved understanding concerning the pathophysiology underlying the development of CIPN and the diverse mechanisms across different chemotherapies seems crucial to the development of future neuroprotective strategies. Appropriate, standardized, and objective assessment tools combined with validated instruments that also document patient-reported symptoms will be necessary to identify the long-term impact of CIPN in cancer survivors. The dividend of improved cancer outcomes with advances in treatment may be compromised if we fail to develop approaches to minimize the chronic consequences of toxicities such as CIPN.
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