Chemotherapy-induced Peripheral Neuropathy

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Recent advances in the development and administration of chemotherapy for malignant diseases have led to prolonged survival of patients and the promise of a return to normal lives. The cost of progress comes with a price, however, and the nervous system is frequently the target of therapy-induced toxicity. Unlike more immediate toxicities that affect the gastrointestinal tract and bone marrow, chemotherapy-induced neurotoxicity is frequently delayed in onset and may progress over time. In the peripheral nervous system, the major brunt of the toxic attack is directed against the peripheral nerve, targeting the neuronal cell body, the axonal transport system, the myelin sheath, and glial support structures, resulting in chemotherapy-induced peripheral neuropathy.

Introduction

The era of cancer chemotherapy began in the 1940s, and since then, cancer drug development has become a multibillion-dollar industry. Chemotherapy has been efficacious against a wide array of human cancers, providing prolonged survival and, in some instances, a cure, but such success comes at a price. By its very nature, conventional chemotherapy is controlled cytotoxicity, with the goal of destroying rampant cancer cells before chemotherapy causes irreparable harm to the patient. The central and peripheral nervous systems frequently bear the brunt of this "innocent bystander" toxicity. This brief review addresses the peripheral nervous system toxicity resulting from chemotherapy of solid and hematologic neoplasms.

Signs and Symptoms of Chemotherapy-induced Peripheral Neuropathy

Although the clinical spectrum of symptoms and adverse outcomes may appear stereotypical, mechanisms, patient susceptibilities, and responses to chemotherapy vary considerably. Clinical similarities discussed in the following text are manifestations of the limited responses by the peripheral nervous system to the assortment of toxic insults provided by various chemotherapy agents.

Several patterns of chemotherapy-induced peripheral neuropathy (CIPN) are commonly recognized. The first is early sensory symptoms, such as paresthesias and numbness, occurring usually between the first and third cycles of therapy. Motor weakness usually develops in a delayed fashion, and this is explained by the fact that sensory neurons and axons that transmit pain perception are unmyelinated and lightly myelinated fibers and are more susceptible than motor fibers to damage from exogenous toxins.

It is not uncommon for symptoms, and in particular sensory symptoms, to persist or even develop weeks to months after discontinuation of the chemotherapy. This phenomenon, known as "coasting," was first recognized with the vinca alkaloid vincristine. Sensory loss typical of axonal neuropathies, including diabetes or alcoholic neuropathy, manifests as a "stocking-glove" sensory loss to pin, touch, or both. It is an example of a length-dependent dying-back neuropathy and is felt to be due to the distal degeneration of sensory axons [1,2]. Injury to a neuron or its axon will impact the most distal portions of the neuron first, where axons are farthest from the cell body and most vulnerable to disruption of the nutritional cytoplasmic supply chain [1,3]. Patients will first notice paresthesias, pain, or both, in the toes and feet that with time and continued insult will advance proximally. By the time the fingertips are affected, a tear-drop pattern of sensory loss and dysesthesias has appeared on the abdominal wall, and sensory distortion will have migrated proximally up the leg, approaching or passing the knee. Myalgias are another presentation of neuropathic pain, and patients complain of muscle cramps and aching that are frequently exacerbated by activity. Autonomic signs and symptoms can be prominent because the fibers carrying these signals are likely

poorly myelinated and thus vulnerable. Dysautonomia may present as dry mouth, constipation, disorders of bladder emptying, and orthostatic intolerance [4,5]. Additionally, patients with pre-existing neuropathies of any kind (eg, diabetic, paraneoplastic, alcoholic, or hereditary) show an increased propensity to develop neuropathy when treated with neurotoxic agents used in cancer treatment [6–8].

Pathology and Pathogenesis of CIPN

Chemotherapy's toxic effects target the structures and functions of the peripheral nervous system, including the axon, myelin sheath, neuronal cell body, and supporting glial structures. Most toxic neuropathies affect axons, resulting in an axonopathy and causing distal, symmetric, sensory-predominant neuropathy that exhibits a "dying-back" pattern. The distal branches are the most vulnerable to axonal transport flow disruption, and like the farthest branches on a diseased tree, are the first to die; hence, the stocking-glove pattern of sensory loss. In its most severe form, it will lead to wallerian (or secondary) degeneration of the surrounding nerve sheath (ie, demyelination) distal to the injury, very similar to the more familiar, severe form of diabetic polyneuropathy. Neuronal cell body damage results in neuronopathies and manifests as global nerve cell failure.

When the myelin sheath of the Schwann cell is the target, the result is demyelination that initially spares the axon and results in disordered impulse conduction. In a mild or self-limited form, it may lead to segmental damage only. When the damage is severe, secondary axonal degeneration may occur, and the process can take on the appearance of a severe form of immune-mediated, acute inflammatory demyelinating polyneuropathy (ie, Guillain-Barré syndrome). Such a process has been reported with the chemotherapeutic agent suramin [9••].

The mechanisms of axonal and nerve cell damage are incompletely known, but laboratory models have allowed some insight. At the cellular level, similar to their effects on cancerous cells, chemotherapies that interfere with DNA replication and metabolic function of the neurons lead to apoptosis and irreparable mitochondrial injury. To inhibit tumor cell division, the plant alkaloids (the taxanes, vinca alkaloids, and podophyllotoxins) all function as microtubular poisons of mitosis, which explains the disruption of axonal transport. In the peripheral nervous system, vincristine and other vinca alkaloids disrupt microtubular transport down axons. In contrast, the taxane derivatives (paclitaxel and docetaxel) promote assembly of large, disordered arrays of microtubules in dorsal root ganglion (DRG) neurons, axons, and Schwann cells. The platinum agents bind DNA in the DRG and trigger apoptosis of neurons. Access to the DRG is gained through a peripheral nerve–blood barrier that is less restrictive than the central nervous system's blood–brain barrier. The experimental agent suramin is a reverse transcriptase inhibitor with a very long half-life; exposure to concentrations above 350 μg/mL can lead to an acute demyelinating neuropathy or a dose-dependent axonal neuropathy. Thalidomide, the recently reintroduced agent with activity against multiple myeloma, has antiangiogenic properties, but the mechanism for its axonal neuropathic effect remains unexplained.

Evaluation of Peripheral Neuropathy

Concern regarding permanent chemotherapy-induced neuropathic damage has spawned interest in the development and validation of reliable grading systems and predictive tools [10,11]. These grading systems utilize bedside clinical tools, noninvasive testing devices (including formal neurophysiologic testing), and even biopsies of the skin and nerve, all with the goal of detecting neurologic impairment in time for either dose limitations, discontinuation of the protocol, or institution of reparative therapy. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) [3] and other grading scales were developed to allow oncologists to grade neurological toxicity (Table 1), but guidelines for use are needed to accurately predict which symptoms are more likely to be associated with permanent deficit [12–14]. Unfortunately, the subjective nature of patients' complaints makes these measures less accurate. A comparison of the World Health Organization and Eastern Cooperative Oncology Group (ECOG) scales, developed for assessing global functioning of a cancer patient, with the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC) found discrepancies in over one third of the patients assessed. Many groups are attempting to remedy this glaring deficiency [14,15].

Recently, the Total Neuropathy Score (TNS) was validated against the NCI-CTC and ECOG oncologic grading scales for peripheral neurotoxicity in a multicenter study (Table 1). An unselected population of 428 cancer patients was evaluated at 11 different centers using a composite. This study's findings supported the TNS as a reliable tool for accurately grading and reporting CIPN, with the additional support of a formal comparison against better known and more commonly used toxicity scales. The TNS represents a valid alternative if neurophysiologic examination is not feasible [16•]. Quantitative sensory testing (QST) is currently used to carefully measure sensory thresholds to touch, pain, and temperature. It requires specialized equipment and a trained technician and is currently limited to major centers, but it is easily tolerated by patients. It has been introduced to enhance what clinicians bring to the bedside and has demonstrated utility in patients with CIPN, at least for the purposes of research [12]. In one study of paclitaxel-induced peripheral neuropathy, QST demonstrated altered soft-touch threshold (A-β or heavily myelinated nerve fiber function) in the area of ongoing pain and sensory disturbances, combined with altered sharp appreciation (A-δ or lightly myelinated fiber function). Heat thresholds were not altered, even in areas of ongoing

Table 1. Grading scales used in assessing chemotherapy-induced peripheral neuropathy

Scale	Score				
	0	1	2	3	4
Total Neuropathy Score*					
Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knee or elbow or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomic symptoms, *n*	0	1	2	3	4 or 5
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness (MRC 4)	Moderate weakness (MRC 3)	Severe weakness (MRC 2)	Paralysis (MRC 0–1)
DTR	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST vibration), *% ULN*	Normal to 125	126–150	151–200	201–300	> 300
Sural nerve SAP, *% LLN*	Normal/ reduced to < 5	76–95	51–75	26–50	0–25
Peroneal nerve CMAP, *% LLN*	Normal/ reduced to < 5	76–95	51–75	26–50	0–25
Eastern Cooperative Oncology Group	None	Decreased DTR, mild paresthesias, mild constipation	Absent DTR, severe paresthesias, severe constipation, mild weakness	Disabling sensory loss, severe neuropathic pain, severe weakness, bladder dysfunction, constipation	Respiratory dysfunction secondary to weakness, constipation requiring surgery, paralysis (chair/bedbound)
NCI-CTC 2.0, revised June 1, 1999 (neurosensory)	None	Loss of DTR or paresthesias but not interfering with function	Objective sensory loss or paresthesias interfering with function but not interfering with activities of daily living	Sensory loss or paresthesias interfering with activities of daily living	Permanent sensory loss that interferes with function

**Data from* Cavaletti et al. [16•].
CMAP—amplitude of the compound muscle action potential (normal > 2 mV); DTR—deep tendon reflexes; LLN—lower limit of normal; MRC—Medical Research Council; NCI-CTC—National Cancer Institute–Common Toxicity Criteria; QST—quantitative sensory test (normal < 2 μm); SAP—amplitude of the sensory action potential (normal > 6 μV); ULN—upper limit of normal.

pain, indicating preserved unmyelinated nerve fiber function (C-fiber function). The conclusion was that paclitaxel neuropathy preferentially affected myelinated nerve fibers and spared C-fibers [17]. This approach has been extended to other chemotherapeutic agents, including vincristine, CDDP (cis-diamminedichloroplatinum), and bortezomib. Vincristine and CDDP demonstrated unaffected heat thresholds and C-fiber function. Bortezomib demonstrated elevated heat pain thresholds and C-fiber dysfunction [4].

In an older study, QST did not fare any better than clinical evaluation with careful neurologic testing of patients with paclitaxel-induced peripheral neuropathy [18]. This study prospectively investigated patients treated with paclitaxel in doses less than 275 mg/m^2 per cycle, a dose considered the threshold for severe and dose-limiting neuropathy. Some patients received paclitaxel in combination with other potentially neurotoxic drugs. The authors found that QST changes (heat and vibration threshold) occurred at the time patients developed symptoms and a bedside sign of neuropathy, and that QST was no more sensitive than clinical examination. In addition, QST, as performed by the authors, did not detect subclinical neuropathy diagnosed on the basis of impaired neurophysiologic studies [18].

Laboratory- or office-based clinical neurophysiologic studies remain the most accessible and best studied of all available tests to confirm a clinical diagnosis of CIPN [14,19]. Nerve conduction studies and electromyography allow a specially trained physician to evaluate the electrical conductance properties of nerves and the motor responses of muscles to spontaneous and iatrogenically provided nerve impulses. The techniques have existed for nearly a half century in investigating various neuropathic and myopathic conditions. Compound motor action potentials (CMAPs) and sensory nerve action potentials (SNAPs) are considered the indicator studies for the diagnosis of axonal dysfunction, whereas impairment of nerve conduction velocities is an indicator of myelin disorders. The EMG electrode study, on the basis of type and amount of spontaneous recordable muscle activity during muscle activation, is able to 1) distinguish neuropathic from myopathic dysfunction, 2) detect different types of muscle disorders, and 3) differentiate neuromuscular transmission disorders (eg, myasthenia gravis, Eaton-Lambert syndrome) [14].

In the future, punch skin biopsy may assume a role in the assessment and management of CIPN due to its facility, the ease of performing serial biopsies, and the information provided. This procedure is particularly well suited to the evaluation of sensory neuropathies, such as painful and autonomic neuropathies, where small unmyelinated and lightly myelinated fibers are expected to be the target of the pathologic process [20,21]. Until this procedure is well studied in patients with CIPN, sural nerve biopsy will remain the procedure of choice to correlate SNAP amplitude findings with large fiber morphology [14,20,21].

Chemotherapeutic Agents Associated with CIPN

Some degree of iatrogenic neuropathy is tolerable in malignancies. However, the effect of paresthesias, pain, and weakness on quality of life should not be underestimated. Most agents discussed in the following text are neurotoxic in a dose-dependent manner, either with a single high dose or with cumulative lower doses over a long duration of treatment. This raises the clinically challenging issue of whether to reduce the dose at the risk of potentially reducing treatment efficacy, especially when therapeutic and toxic mechanisms are the same. Another complicating factor is that some malignancies can produce neuropathy directly or indirectly through paraneoplastic processes. Table 2 lists the agents discussed in this section. Vincristine and the vinca alkaloids are plant-derived drugs used extensively in the treatment of lymphoproliferative diseases. Vincristine causes an axonal neuropathy due to disruption of microtubular transport along the axon, and this is reflected in diminution of the amplitude of CMAPs and SNAPs. Delayed neurophysiologic testing may show slowing of the nerve conduction studies, the result of secondary demyelination of the axon. Other vinca alkaloids, such as vinblastine, vindesine, and vinorelbine, are less neurotoxic. The first symptoms are paresthesias, which occur early after the initiation of treatment, and early loss of ankle jerks. Autonomic neuropathy, presenting as constipation or ileus, can occur in up to one third of all patients; in a smaller percentage, severe neuropathies are associated with motor weakness. Weakness preferentially affects the extensors of the upper and lower extremities. Although the neuropathy is frequently reversible, recovery may take up to 2 years and coasting may occur. Pain generally is not a prominent feature at any stage of the neuropathy [5,7,14,22,23].

The taxane derivatives paclitaxel and docetaxel are responsible for a predominantly sensory, axonal neuropathy [24]. This class of drug targets the microtubular system of cancer cells and axons of the peripheral nervous system and inhibits microtubular depolymerization. It is estimated that 70% of patients who receive paclitaxel develop dose-related neurotoxicity [14], and the neuropathy is particularly sensitive to the dose per cycle. Patients will develop paresthesias soon after initiation of treatment and it will partially remit before the next cycle 3 weeks later. If treatment is continued without dose adjustment or other intercession, symptoms and signs may accumulate and weakness may develop. Risk factors for the development of neuropathy include not only cumulative dosing (nearly 95% of patients exposed to 500–800 mg/m^2 will develop a persistent neuropathy), but also pre-existing neuropathy and co-administration of other neurotoxic chemicals [14].

The neuropathology is that of a symmetric, predominantly sensory neuropathy, with greater axonal than demyelinative damage [25]. Extensive pharmacokinetic studies of paclitaxel, using time versus concentration

(area under the curve) profiling, have confirmed the fact that the more prolonged the systemic exposure, the greater the hematologic and neurologic toxicity [26]. Docetaxel, a related taxane, exhibits the same toxicity profile as paclitaxel, but spontaneous recovery following discontinuation is common [27].

The taxanes are commonly combined with carboplatin because both drug families exhibit efficacy against similar tumors (eg, lung cancer, ovarian cancer, and head and neck cancer) [28]. Although the combined therapy has been beneficial, their respective toxicities at the level of the neuron target different sites of cell function and amplify each drug's neurotoxicity [29]. It has not been established whether the enhanced toxicity is additive or synergistic [25].

The platinum complexes cisplatin, carboplatin, and oxaliplatin are a group of highly active antitumor agents that affect the DRG neurons where they cross-link and damage DNA, leading to premature neuronal cell death. The result is a neuronopathy affecting the entirety of the sensory neuron but frequently presenting with symptoms in the most distal axonal branches [2]. The neurotoxicity also exhibits coasting; the full impact is not realized until after the completion of chemotherapy or near its end [14,22,23]. The clinical features, similar to other neurotoxicities, are sensory in most cases, with numbness and paresthesias in the feet and hands that spread proximally with dose accumulation. Some patients may have pain, but foremost is the loss of vibratory sensation followed by loss of stretch reflexes. The sequence eventually may lead to severe sensory ataxia, whereas motor weakness occurs less often. Superficially, the presentation can look like the sensory neuronopathy associated with paraneoplastic syndromes, which is not surprising because this CIPN is a neuronopathy as well. Electrophysiologically, there is attenuation or loss of SNAP amplitude with relative preservation of nerve conduction velocities, indicative of axonal damage [22].

Carboplatin is less neurotoxic then cisplatin, but at high doses its toxic features resemble those of cisplatin. Oxaliplatin is unusual in its neurotoxicity. Similar to cisplatin, it exhibits dose-limiting neurotoxicity at a dosage higher than 200 mg/m^2. The chronic cumulative neuronopathy also resembles that of cisplatin electrophysiologically. A more interesting phenomenon is the acute syndromes that may develop, such as cold-induced paresthesias or dysesthesias, laryngospasm, and muscle contractions resembling neuromyotonia. Current evidence suggests that these may be the result of a voltage-gated channelopathy induced by the oxaliplatin [30,31].

Suramin is an experimental chemotherapeutic agent used to treat non-Hodgkin's lymphoma and adrenal, ovarian, and renal cell carcinoma. Its neurotoxic effects can present as a dose-dependent axonal sensorimotor neuropathy or a subacute demyelinating polyneuropathy resembling Guillain-Barré syndrome. The latter presentation can be catastrophic, with 25% of cases requiring ventilation. Proximal weakness greater than distal weakness can occur over 2 to 2.5 months, and the syndrome may progress despite protocol discontinuation (coasting). Toxicity appears to be related to cumulative doses greater than 157 mg/kg over an 8-week period [32].

Miscellaneous agents

Initially developed as an agent for insomnia and later removed from the market due to its harmful fetal effects in pregnant women, thalidomide has experienced resurgence over the past few years as a treatment option for patients with relapsed or refractory myeloma. It is also being studied in newly diagnosed myeloma patients. Doses of less than 50 mg/d and up to 800 mg/d have been used in patients with myeloma. Thalidomide is capable of producing a primarily sensory neuropathy, especially in the distal limbs, which is generally mild but may progress with continued therapy. Rates of incidence and severity are difficult to quantify for thalidomide-induced neurotoxicity [33].

Bortezomib is a new proteosome inhibitor agent approved for the treatment of multiple myeloma. Its neurotoxicity differs in that it affects small fibers, such as thermally sensitive C-fibers, resulting in burning causalgic pain [5,27]. The induction of a neuropathy appears to be idiosyncratic and occurs in 3% to 30% of treated patients. Symptoms include distal paresthesias and sensory loss, and the EMG is consistent with axonal damage [22,33].

Treatment Strategies

Treatment is focused on ways to eliminate or reduce drug-induced CIPN and on palliative management once CIPN is established. Once CIPN is established, options to eradicate the neurologic deficits are limited and supportive care is indicated. Table 3 has guidelines for treating patients with CIPN or those at risk of acquiring it.

Prevention of CIPN

There is a growing body of literature on measures used to prevent the development of CIPN. This literature deals with protective agents that would prevent neurotoxic side effects and obviate any need for dose reduction or discontinuation of chemotherapy. Enabling full-dose chemotherapy potentially would lead to improved tumor control and translate into improvement in quality of life and even cure. The criteria for an effective neuroprotective agent have been itemized as follows: 1) the agent must be well tolerated and without debilitating adverse effects, 2) the agent should not impede antitumor efficacy, and 3) the agent should effectively prevent the development of CIPN [23].

Certain potential neuroprotective agents showed promise in the laboratory but were found not to be effective in the clinic. These include the adrenocorticotropic hormone analogue Org 2766 [34,35], the free radical scavenger amifostine [34], and the leukemia-inhibitory factor (LIF)

Table 2. Compound-related signs and symptoms of chemotherapy-induced peripheral neuropathy

Compound	Neurotoxic dose	Sensory symptoms	Motor symptoms	Autonomic symptoms	NCS finding	EMG finding	Morphologic changes
Vincristine	> 4 mg cumulative dose	Always early manifestation of numbness and tingling of hands and feet, loss of achilles tendon reflex, and pain	Rare muscle cramps, severe weakness in distal muscles	Frequent paralytic ileus, postural hypotension	Less frequent slowing of sensory NCV with reduced amplitude	Rare signs of denervation in distal muscle	Demyelination with axonopathy, demyelination, axonal loss of the dying-back type, and DRG damage
Taxane	> 175–200 mg/m^2 cumulative doses	Frequent distal symmetrical paresthesia, loss of joint position sense, painful dysesthesias, lhermitte's sign, and pain	Less frequent progressive distal and/or proximal paresis; myalgias, rare case of myopathy	Rare paralytic, orthostatic hypotension, arrhythmia	Frequent reduced amplitude of sensory and motor CAP, almost normal NCV	Less frequent signs of denervation in distal muscles	Combined neuron- and axonopathy, severe nerve fiber loss, axonal atrophy and secondary demyelination, little axonal regeneration
Cisplatin	> 300 mg/m^2 cumulative doses	Frequent paresthesias, tingling of hands and feet, loss of tendon reflexes, impaired vibration and joint position sense, ataxia and lhermitte's sign	Absent muscle weakness in extremely rare cases	Rare orthostatic dysregulation	Frequent slowing of sensory NCV with reduced amplitude, pronged or absent H-reflex	None	Axono- and neuronopathy damage of large myelinated la fibers, damage to the cell bodies in the DRG
Carboplatin	> 400 mg/m^2 cumulative doses	Less frequently paresthesia, tingling of hand and feet, loss of tendon reflexes, impaired vibration and joint position sense, ataxia, and lhermitte's sign	Absent	Unknown	Less frequent only after high doses and combination with other drugs, slowing of sensory NCV with reduced amplitude, prolonged or absent H-reflex	None	Axono- and neuronopathy damage of large myelinated la fibers, damage to the cell bodies in the DRG
Oxaliplatin	> 300 mg/m^2 cumulative doses	Always almost instantaneously cold, triggered and/or aggravated by paresthesia, dysesthesia and pain are later typical signs seen under cisplatin	Less frequent muscle cramps, myotonia, etanic spasm; rarely muscle weakness	Unknown	Frequent low threshold of sensory and motor nerves, rarely repetitive firing, slowing of sensory NCV with reduced amplitude	Less frequent myotonic discharges, signs of denervation, complex repetitive discharges	Unknown
Suramin	> 350 mg/mL maximum plasma level	Frequent mild dysesthesia and paresthesia, tingling of hands and feet, loss of tendon reflexes, impaired vibration and joint position sense	Less frequent severe paresis with a Guillain-Barre syndrome–like picture	Unknown	Less frequent NCV slowing and conduction block	Rare signs of denervation	Demyelination with axonopathy, segmental demyelination in sural nerve biopsies

CAP—complex action potential; CMAP—compound motor action potentials; DRG—dorsal root ganglion; EMG—electromyogram; NCS—nerve conduction study; NCV—nerve conduction velocity; SNAP—sensory nerve action potential; SNCV—sensory nerve conduction velocity.
(*Adapted from* Quasthoff and Hartung [8].)

Table 2. Compound-related signs and symptoms of chemotherapy-induced peripheral neuropathy ***(Continued)***

Compound	Neurotoxic dose	Sensory symptoms	Motor symptoms	Autonomic symptoms	NCS finding	EMG finding	Morphologic changes
Thalidomide	>150 mg/d	Paresthesia in hands and feet, muscle cramp, impaired vibration and pain	Mild weakness and reduced ankle jerk	Unknown	Reduction in SNAP and CMAP	None	Axonal neuropathy
Bortezomib	> 0.20 mg/kg/d	Unknown	Unknown	Unknown	Significant decrease in SNCV	Unknown	Mild axonopathy, few neurons damaged in DRG

CAP—complex action potential; CMAP—compound motor action potentials; DRG—dorsal root ganglion; EMG—electromyogram; NCS—nerve conduction study; NCV—nerve conduction velocity; SNAP—sensory nerve action potential; SNCV—sensory nerve conduction velocity.
(*Adapted from* Quasthoff and Hartung [8].)

Table 3. Guidelines for treating patients with CIPN or those at risk of acquiring it

1. Be aware of patients at risk for CIPN, including patients with hereditary sensorimotor neuropathies or pre-existing neuropathic disorders such as diabetes, alcoholism, amyloidosis, or nutritional deficiencies. When possible, correct any treatable condition if the patient must be exposed to neurotoxic chemicals.
2. Avoid concurrent medicinal neurotoxic agents when possible, including G-CSF, isoniazid, nitrofurantoin, and other neurotoxins.
3. When chemotherapy-induced neurotoxicity appears, attempt to limit or eliminate the offending agent. However, this may not be realistic because many chemotherapeutic agents damage the nerves in a delayed fashion, well after the exposure.
4. Do not forget to address patients' disabling symptoms, even if they have been separated from the neurotoxic agent or are starting to recover.

CIPN—chemotherapy-induced peripheral neuropathy; G-CSF—granulocyte colony-stimulating factor.

[23,35–37]. The recently published study of LIF has been criticized for design flaws but, in light of the negative results, it is unlikely LIF will ever be studied again [23,35].

Despite these failures, a considerable number of agents continue to show promise as neuroprotective agents, and well-designed studies are being mounted to investigate their potential. One such study targets the unique neurotoxicity of oxaliplatin, the cold-induced dysesthesias and muscle contractions. It is thought that oxalate, a metabolite of oxaliplatin, causes the acute chelation of ionized calcium and magnesium, precipitating a neuronal voltage-gated Na^+ channelopathy. Investigators used calcium and magnesium infusions to obviate this toxic phenomenon and eliminated the sensorimotor symptoms to a significant degree without affecting the antitumor potency of oxaliplatin [38].

Capitalizing on the fact that CDDP neurotoxicity resembles vitamin E deficiency and that low vitamin E levels have been found in patients with CDDP neurotoxicity, several researchers have studied vitamin E therapy in small groups of patients using an open-label design. Dosing and the chemotherapy regimen were not identical between the two groups; nevertheless, both populations who were given vitamin E fared significantly better than control patients [39,40].

Acetyl-L-carnitine (ALC), an ester of L-carnitine, is presumed to play a role in neural protection by acetylating intracellular tubulin, ensuring the availability of acetyl-CoA in the mitochondria and enhancing the availability of neuronal nerve growth factor. In a nonrandomized, nonplacebo-controlled study, ALC given at 1 g three times daily was administered to 25 patients with grade 3 or higher neuropathy from concurrent paclitaxel or CDDP therapy or patients with grade 2 or higher neuropathy persisting for at least 3 months after discontinuing chemotherapy. Sensory neuropathy grade improved in 60% of patients, motor neuropathy grade improved in 80%, and SNAP amplitude improved in 88%. Randomized controlled studies of this treatment are warranted [41,42].

Glutamine, at a dose of 10 g three times daily for 4 days, was studied as a neuroprotective agent in patients receiving high-dose paclitaxel in a nonrandomized trial of 46 patients. It initially was given to prevent myalgias but was found to attenuate CIPN. The glutamine group suffered less weakness, less vibratory loss, and less toe numbness than the nonglutamine group. There was a trend for less impairment of the CMAP and SNAP on electrophysiologic studies that did not reach significance [43].

In a well-designed study, glutathione was studied to assess protection against oxaliplatin-induced neurotoxicity. The cumulative dose used in this population of colorectal cancer patients was 1200 mg/m^2, and patients were assessed after four, eight, and 12 cycles of chemotherapy. Glutathione was provided in doses of 1500 mg/m^2 before each dose of oxaliplatin, and the patients were followed with the NCI-CTC criteria and neurophysiology (sural nerve conductions and SNAP amplitudes). After the twelfth cycle, significantly more patients in the placebo arm suffered grade 2 to grade 4 toxicity compared with the glutathione arm; neurophysiologic tests showed deterioration only in the placebo arm. Glutathione had no effect on the response rate of oxaliplatin. The putative mechanism was thought to be the prevention of accumulation of platinum adducts in the DRG. The investigators concluded that glutathione is a promising agent for the prevention of oxaliplatin-induced neuropathy. It may show similar promise in reducing the neurotoxicity of other platinum-based chemotherapy [44].

In a recently published study of rats with experimental CDDP-induced peripheral neuropathy, erythropoietin, along with its carbamylated derivative, was found to be neuroprotective. CIPN was measured both neurophysiologically, using SNAP amplitudes, and histologically, using a biopsy of intraepidermal nerve fiber density; both large-fiber function and small-fiber morphology were, therefore, effectively studied. Neuroprotection was not associated with any difference in CDDP concentrations in the DRG, and the mechanism was believed to be due to upregulation of erythropoietin receptors in injured nerve tissue [45]. Human phase III studies have yet to be reported.

Pain management and other palliative measures

The patient afflicted with CIPN is likely to suffer from sensory loss, which is a "negative" symptom, and pain and paresthesias, which are "positive" sensory symptoms. Motor loss is less common but very disabling. It cannot be stressed how important physical therapy and occupational therapy are for this group of patients. Therapists are trained to evaluate patients with similar disabilities from other disease processes and are the greatest resource for ordering the appropriate activity program and orthotics. Many are well trained to assist in managing the pain

that so commonly accompanies neuropathy. In some instances, a patient may be considered a suitable candidate for admission to a rehabilitation unit, where physical therapy and occupational therapy play an invaluable role.

The role of counseling and psychological support also cannot be underestimated in these patients. It is not difficult to see how patients may feel victimized, having escaped death only to be burdened with disabling pain, weakness, and sensory loss. As difficult as pain is to measure, it is even more difficult to gauge emotional suffering. Spiritual and psychological counseling may be necessary.

Treatment of neuropathic pain

Unfortunately, no medications exist for relieving the sensory and motor loss associated with advanced, established CIPN; therapy is merely supportive. However, there is now a robust body of literature on the analgesic approach to the disturbing pain associated with neuropathy. An in-depth discussion is beyond the scope of this article, and the reader is urged to read one of the reviews on the subject [46,47••]. One only needs to review one recent study to recognize the current level of interest in the pharmacologic management of neuropathic pain, including that associated with CIPN [48]. The authors describe successful use of low-dose venlafaxine or topiramate in relieving oxaliplatin-induced neuropathic pain. Prospective studies using rigorous scientific technique are sure to follow.

Conclusions

The appearance of a growing body of literature on the clinical and basic science of CIPN attests to a growing recognition of the problem. Though CIPN is often predominantly sensory, its effects can be quite disabling, and the delay in its development after a cure seems to have been achieved serves only as a cruel reminder to the patient. New research in measuring CIPN has helped stimulate an interest in finding neuroprotective agents, but much more work needs to be done.

Disclosures

No potential conflict of interest relevant to this article was reported.

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- • Of importance
- •• Of major importance

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