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REVIEW ARTICLE/BRIEF REVIEW

Brief review: Chemotherapy-induced painful peripheral neuropathy (CIPPN): current status and future directions

Bref énoncé: La neuropathie périphérique douloureuse induite par la chimiothérapie (CIPPN): situation actuelle et perspectives

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Abstract

Purpose *Chemotherapy-induced painful peripheral neuropathy (CIPPN) affects up to 90% of cancer patients treated with chemotherapy agents. Despite the fact that it is relatively common, the underlying pathophysiology is still unclear and its treatment remains generic. Mechanisms of CIPPN are multifactorial, dependent on the specific chemotherapeutic agent used, and include multiple patient-related factors, including genetic factors that may predispose patients to either develop or not develop CIPPN. The purpose of this article is to review mechanisms, clinical signs and symptoms, diagnosis, treatment options, and prognosis for patients who develop CIPPN. We also offer research considerations for this complex and unpredictable phenomenon.*

Principal findings *Chemotherapeutic agents can damage the peripheral nervous system, including the nerve terminals, axons, cell body, and myelin sheath of sensory nerves. Herein, we describe some of the anatomical and functional changes that are thought to take place at various levels of the nervous system. On a clinical level, patients with CIPPN report multiple symptoms. It is essential to obtain an accurate history from the patient and to perform a thorough physical examination in order to obtain the patient's subjective perspective. Additionally, objective measurements may be needed in order to articulate clearly the effects of this complex syndrome and to ensure an accurate diagnosis, treatment, and prognosis.*

Conclusions *The management of CIPPN remains a clinical challenge for pain practitioners. As more research is being carried out to elucidate its pathophysiology and therapy, the innovative use of several non-traditional categories of drugs seems promising in the management of this complex phenomenon. Studies addressing predictability and possible genetic predisposition are necessary not only for preventive measures but also for targeted treatments.*

Résumé

Objectif *La neuropathie périphérique douloureuse induite par la chimiothérapie (CIPPN) affecte jusqu'à 90 % des patients cancéreux traités par chimiothérapie. Bien qu'elle soit relativement fréquente, la physiopathologie sous-jacente à cette neuropathie est encore mal connue et son traitement reste générique. Les mécanismes de la CIPPN sont multifactoriels, dépendants des agents spécifiques utilisés pour la chimiothérapie, et incluent de nombreux facteurs liés au patient, notamment des facteurs génétiques pouvant prédisposer ou non au développement de la CIPPN. L'objectif de cet article est de revoir les mécanismes, les signes et symptômes cliniques, le diagnostic, les options thérapeutiques et le pronostic des patients qui développent une CIPPN. Nous proposerons également des axes de recherche sur ce phénomène complexe et imprévisible.*

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Constatations principales *Les agents chimiothérapeutiques peuvent endommager le système nerveux périphérique, notamment les terminaisons nerveuses, les axones, le corps cellulaire et la gaine de myéline des nerfs sensitifs. Ici, nous décrivons certaines modifications anatomiques et fonctionnelles qui semblent survenir à différents niveaux du système nerveux. Sur le plan clinique, les patients atteints de CIPPN signalent de nombreux symptômes. Il est essentiel d'obtenir un historique précis du patient et d'effectuer un examen physique approfondi afin d'avoir le point de vue subjectif du patient. De plus, des mesures objectives peuvent être nécessaires afin de comprendre clairement les effets de ce syndrome complexe et pour en assurer un diagnostic, traitement et pronostic précis.*

Conclusions *La gestion de la CIPPN reste un défi clinique pour les spécialistes de la douleur. Au fur et à mesure que de nouvelles études sont menées pour élucider sa physiopathologie et son traitement, l'utilisation novatrice de plusieurs familles de médicaments non traditionnels semble prometteuse dans la gestion de ce phénomène complexe. Des études portant sur la prévisibilité et la prédisposition génétique sont nécessaires, non seulement pour prendre des mesures préventives, mais aussi pour des traitements ciblés.*

Chemotherapy-induced painful peripheral neuropathy (CIPPN) in patients treated for cancer is difficult to diagnose, treat, and determine a prognosis due to multifactorial mechanisms, the specific chemotherapeutic agent used, and multiple patient-related factors. Estimates indicate CIPPN affects up to 90% of cancer patients treated with chemotherapy agents and from 20-50% of women treated for breast cancer.[1] The onset can be immediate or occur well after the end of treatment; however, not all cancer patients treated with chemotherapy develop CIPPN. Furthermore, not all chemotherapy-induced peripheral neuropathy is painful. The duration of CIPPN varies from weeks to months or years and is dependent on the type of chemotherapy used.[2-4] Symptoms associated with CIPPN vary in presentation, consistency, and duration, and with the agents used for treatment, further contributing to the complexity of this insidious and elusive pain syndrome.[5] The pathophysiology of CIPPN remains elusive at the macro and micro physical nerve structural levels and appears to have a genetic component that needs further exploration.[6-8] The purpose of this review is to identify current mechanisms, clinical signs and symptoms, diagnosis, treatment options, and prognosis for CIPPN induced by the taxanes, specifically paclitaxel. Furthermore, we explore future research opportunities at the genetic level in an effort to predict who will and will not develop CIPPN due to paclitaxel and to determine best practice treatment options.

Table 1 Classification of CIPPN-inducing chemotherapy agents

Classification	Agent	Trade name	Type of nerve damage
Platinum-based compounds	Cisplatin	Platinol®	Sensory
	Carboplatin	Paraplatin®	
	Oxaliplatin	Eloxatin®	
Vinca alkaloids	Vincristine, Vindesine, Vinblastine, Vinorelbine	Oncovin® Vincasar Pfs®	Sensory & motor
Taxanes	Paclitaxel	Taxol®	Sensory & motor
	Docetaxel	Taxotere®	
Proteasome inhibitors	Bortezomib	Velcade®	Sensory

CIPPN = chemotherapy-induced painful peripheral neuropathy

Clinical evidence suggests that treatment for cancer with neurotoxic agents may result in variable degrees of neuropathy.[6] Specific classes of chemotherapy agents have been implicated in the development of CIPPN, including platinum-based derivatives, vinca alkaloids, taxanes, and proteasome inhibitors (Table 1).

Mechanisms of CIPPN

Chemotherapeutic agents can damage the peripheral nervous system, including the nerve terminals, axons, cell body, and myelin sheath of sensory nerves. Herein, we describe some of the anatomical and functional changes that take place at various levels of the nervous system.

Skin nerve endings

Studies have shown that taxanes, vinca alkaloids and platinum-based agents all decrease the number of intraepidermal nerve fibres in the rat hind paw.[9,10] Interestingly, in one study, pretreatment with minocycline prevented the decrease in nerve fibres.[10] The loss of nerve terminals may produce hyperexcitability in the nerve fibres and induce spontaneous discharges.[11]

Primary sensory neurons and dorsal root ganglia (DRG)

Clinically, CIPPN patients have paresthesias and decreased vibration sensitivity.[14] Animal studies have shown that

vincristine induces abnormal function of A-beta, A-delta, and C-fibre sensory nerves in the vincristine-induced chronic pain patients[12] and in the motor and autonomic nerves.[13] Cisplatin, paclitaxel, and bortezomib significantly reduce the velocity of caudal nerve conduction and produce axonal degeneration in the sciatic nerve.[14]

Platinum drugs bind to DNA strands and induce apoptotic cell death. Particularly, they bind to the cell bodies in the DRG in the peripheral nerves and thus result in peripheral neuropathy. Further, oxaliplatin can damage DNA, leading to chronic neuropathy, and it can also alter the function of voltage-gated sodium channels in the peripheral nerves.[15,16] Interestingly, carboplatin produces significant neuropathy less frequently.[17]

While cisplatin accumulates in the DRG and peripheral nerves,[18,19] paclitaxel stabilizes microtubules, decreases epidermal nerve fibres, and activates macrophages and microglia in the DRG, peripheral nerves, and spinal cord.[20,21] Additionally, with large cumulative doses, paclitaxel can affect the motor nerves.

Paclitaxel, vincristine, cisplatin, and bortezomib form swollen and vacuolated mitochondria in axons within the mitochondria, which increases their permeability and leak, results in release of intracellular calcium, and consequently activates a caspase-mediated apoptotic pathway.[22-24]

Paclitaxel and vincristine also increase alpha-2-delta-1 subunits of calcium channels in the DRG and dorsal horn. Additionally, they increase cytosolic calcium from extracellular and intracellular stores of mitochondria.[25-27]

Paclitaxel, oxaliplatin, and vincristine increase Na+ current in the DRG and make neurons susceptible to paresthesias and fasciculations.[28-30] Oxaliplatin decreases the expression of mechano-gated and temperature-sensitive potassium channels (TREK1, TRAAK types) and increases the expression of pro-excitatory channels such as the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels.[31] Cisplatin, oxaliplatin, and paclitaxel upregulate transient receptor potential vanilloid 1 (TRPV1), transient receptor potential A1 (TRPA1), transient receptor potential M8 (TRPM8), and transient receptor potential vanilloid 4 (TRPV4) in the DRG neurons, which leads to hyperexcitability of nociceptors.[32-34] Oxaliplatin, paclitaxel, vincristine, and bortezomib also increase free radicals in DRG cells secondary to an increase in cytosolic calcium.[35-37] Further, paclitaxel, vincristine, and oxaliplatin activate calcium-dependent proteases, calpains and caspases in DRG cells and thus initiate neuronal apoptosis.[38,39] Paclitaxel and cisplatin increase neuropeptide Y, substance P, and calcitonin gene-related peptide (CGRP) in DRG neurons.[40,41] Vincristine increases 5-hydroxytryptamine 2A receptors of 5-hydroxytryptamine on the DRG neurons and dorsal horn of the spinal cord and sensitizes both peripheral nociceptive fibres and spinal dorsal horn neurons.[42,43]

In summary, anti-cancer agents activate ion channels, including sodium, calcium, potassium of DRG, and glutamate-activated N-methyl-D-aspartate (NMDA) receptors to alter cytosolic ionic milieu, particularly intracellular calcium that triggers secondary changes such as release of free radicals to induce neuropathic pain. Damage to mitochondria leads to an increase in permeability and release of intracellular calcium, activation of protein kinase C, phosphorylation of TRPV, activation of capases/calpains, and generation of nitric oxide and free radicals, resulting in cytotoxicity to axons and neuronal cell bodies.

Spinal cord and dorsal horn and the brain

Paclitaxel increases spontaneous activity and after-discharges of deep spinal lamina neurons to noxious mechanical thermal stimuli of the skin. In addition, paclitaxel increases after-discharge and abnormal windup to transcutaneous electrical stimuli and decreases the expression of glutamate transporter proteins in the dorsal horn.[44]

Vincristine may cause increased sciatic nerve excitability and induce a state of glutamate excitotoxicity through enhancing NMDA receptor expression and diminishing CGRP expression, thus resulting in axonal degeneration.[45] Finally, oxaliplatin increases protein kinase C activity and upregulates gamma/epsilon isoforms of protein kinase C in the thalamus and periaqueductal areas of the brain.[46,47]

Immune cells

Chemotherapeutic agents can penetrate the blood-nerve barrier and bind to the peripheral axons and the DRG. In addition, they affect macrophage, epidermal Langerhans cells, and glial cells. Paclitaxel and vincristine increase the number of protein gene product 9.5-positive Langerhans cells in the skin.[9] Further, taxanes induce upregulation of matrix metalloproteinases (MMPs) in Schwann cells, DRGs, and peripheral nerves. Especially, MMP-1 in the Schwann cells, neutrophils, and neurons degrades myelin and activates macrophage in the DRGs and peripheral nerves. In addition, MMPs induce inflammatory cytokines (e.g., interleukin [IL]-1, IL-6, IL-8), tumour necrosis factor-α, and nitric oxide from satellite cells, myelin, macrophages, and glial cells. In summary, they directly or indirectly act on primary neurons to induce

hypersensitivity of peripheral nerves, which is a hallmark of neuropathic pain syndrome.[48-50]

Clinical signs and symptoms

Chemotherapy-induced painful peripheral neuropathy is caused by several classes of neurotoxic chemotherapy agents, including vinca alkaloids, taxanes, platinum-based compounds, and proteasome inhibitors.[2-4] Neuropathic pain is considered part of the dysfunctional pain syndromes and neither protects nor supports healing and repair.[8] The clinical signs and symptoms, severity, and duration vary depending on the type of neurotoxic chemotherapeutic agent administered and the frequency and dosages. Neuropathic pain may appear after the first treatment or weeks/months later and is more common in patients with preexisting nerve damage from CIPPN or other diseases (e.g., diabetes).[5,51-54] Use of neurotoxic chemotherapeutic agents results in similar and different clinical signs and symptoms, including pain and numbness, motor impairment, and decreased pinprick and vibration perceptions.[6] Paclitaxel induces sensory impairment and pain, whereas vincristine is more often associated with peripheral sensorimotor effects, including motor dysfunction such as foot drop. Reconciliation of the types of neurotoxic chemotherapeutic agents received by the patient is an important factor in determining what signs and symptoms to expect. Effects of neurotoxic chemotherapeutic agents generally involve the distal extremities symmetrically, characterized by a "stocking and glove" phenomenon with paresthesia or dysesthesia, numbness, and tingling originating in the hands and feet.[2,5] Numbness and tingling in the hands and feet may be an early sign of impending development of CIPPN.

Symptoms are also dependent on the sensory fibres affected. For example, damage of small nerve fibres (SNF) is more likely to present as neuropathic pain and allodynia.[52,55] Both sides can be affected and symptoms may be more predominant on one side of the body. Alteration in sensory, motor, and autonomic functioning appears to be the primary pattern for CIPPN.[1,5,7,51] Sensory symptoms are dose-related and cumulative; they can be delayed in appearing and include both positive and negative signs. Abnormal sensation such as paresthesia and dysesthesia are common clinical symptoms. Other symptoms include loss of proprioception, ataxia, loss of balance, and decreased sensation of vibration. Motor symptoms range from minor motor dysfunction to paralysis and tend to begin primarily in the distal extremities. Examples include hypotonia, as a result of involvement of the lower peripheral motor neurons and muscles, and hyporeflexia, often caused by damage to unmyelinated nerve fibres and resulting in hypotension, cardiac conduction irregularities, impotence, bowel and bladder dysfunction, constipation, paralytic ileus, and urinary retention.[1,2,5,51,53,56,57]

There are multiple instruments used to evaluate chemotherapy-induced symptoms, side effects, and adverse events. The most common scales used are those from the World Health Organization (WHO), Eastern Cooperative Oncology Group (ECOG), National Cancer Institute of Canada - Common Toxicity Criteria, and the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[53,54] The WHO scale grades peripheral neuropathy from 0 (none) to 4 (paralysis), follows progression of sensory function and motor function, but does not address deep tendon reflexes. Vague and obscure terms are used to grade neurotoxicity, e.g., "mild weakness" and "marked motor loss", which lack specific criteria for grading. The ECOG includes more objective assessment of motor (deep tendon reflexes) and sensory (paresthesia) function and includes an autonomic component (constipation). Unfortunately, limits of the ECOG scale include its single-item approach when denoting the presence or absence of neuropathy and suffers from the same deficit as the WHO by using vague terms, e.g., "disabling sensory loss".[1,51,53]

Recent efforts suggest evidence that subgroups of patients can be clustered by the severity of their symptoms, especially those treated with taxanes, vinca alkaloids, and platinum classes of neurotoxic chemotherapeutic agents.[2,5,58,59] In a study of 40 breast cancer patients, five different symptom scales was used to identify symptom clusters, showing that a comprehensive assessment of symptoms may lead to more accurate identification of those patients receiving neurotoxic chemotherapeutic agents who may develop CIPPN.[5]

In summary, patients with CIPPN report multiple symptoms. Eliciting an accurate picture from the patient is most important in order to obtain their subjective perspective. Nevertheless, objective measurements are also needed in order to articulate clearly the effects of this complex phenomenon and to ensure an accurate diagnosis, resulting treatment, and prognosis. Thus, the importance of a comprehensive history and physical examination cannot be overemphasized and must include input from patients and their significant others. Assessment of the various symptoms that each patient experiences is vital in determining the type, level of severity, and diagnosis of CIPPN.

Diagnosis

The diagnosis of CIPPN is generally made based on case history and clinical presentation. Occasionally,

electrophysiological studies can be beneficial to confirm the diagnosis. The symptom history/assessment includes pain, loss of deep tendon reflexes, or the presence of symmetrical "stocking-glove" numbness or paresthesia after neurotoxic chemotherapy.[4,6,52,53,57] History and physical examination are essential for an accurate diagnosis of CIPPN. A specific knowledge of the pattern of neuropathy associated with specific neurotoxic chemotherapy agents is also essential.[53,54] Loss of dexterity in the hands is often perceived as being clumsy; in addition, smell and taste changes and hearing loss have been associated with certain neurotoxic chemotherapy agents.

The National Comprehensive Cancer Network recommends using a comprehensive pain assessment algorithm to assess neuropathic pain.[60] It is vital to quantify the intensity and characteristics of the pain experienced by the patient through the patient interview. Also, it is helpful for patients to keep a pain diary in which they record the intensity, location, and quality of pain as it occurs. Unidimensional pain scales, such as a numerical pain rating scale and the Wong-Baker FACES® Pain Rating Scale are used with adult and pediatric patients, respectively.[61-63] The Brief Pain Inventory (BPI) and McGill Pain Questionnaire are examples of multidimensional instruments to measure pain. The McGill Pain Questionnaire evaluates the "sensory, affective and evaluative" nature of pain in addition to pain intensity.[60,64] The BPI records pain location, intensity, and interference with daily activities. It can be completed quickly and is easily used in the outpatient setting.[65,66]

Use of quantitative sensory testing (QST) is an objective means to assess and quantitate impairments in motor skills, touch, warmth, and heat. In a recent study, 14 patients and 18 healthy controls developed neuropathy after paclitaxel and vincristine and received QST 18 months apart. Test results showed impairments in motor skills, touch deficits, and impaired warmth/heat deficits.[6]

Common neurophysiological tests used to confirm the diagnosis of CIPPN include nerve conduction velocity measurements of sensory nerve action potential, motor nerve conduction velocity, compound muscle action potential, and needle electromyography. Nerve biopsies are rarely indicated for CIPPN.[54]

The role of skin biopsy is evolving, and guidelines have been established for quantification of linear density of intraepidermal nerve fibres as a reliable method to assess the diagnosis of small fibre neuropathies—if agreed upon counting rules are used.[54,67] Results of a recent study to investigate changes in the density of Meissner's corpuscles and epidermal nerve fibres (ENFs) thought to contribute to multiple forms of neuropathy among 14 CIPPN patients and 18 healthy controls have identified deficiencies in both Meissner's corpuscles and ENFs.[6]

Table 2 Neuropathic pain treatment guidelines

	Canadian	European	International
First-line drugs	TCA	TCA	TCA
	Anticonvulsants	Anticonvulsants	Anticonvulsants
	Carbamazepine	Topical lidocaine	SNRI
			Topical lidocaine
Second-line drugs	SNRI	SNRI	Opioids
	Topical lidocaine	Opioids	
Third-line drugs	Opioids	Opioids	Carbamazepine
			Topical capsaicin mexiletine

Canadian = Canadian Pain Society; European = European Federation of Neurological Societies; International = International Association for the Study of Pain Neuropathic Pain Special Interest Group; TCA = tricyclic antidepressants; SNRI = selective serotonin norepinephrine reuptake inhibitor

The National Cancer Institute's Common Terminology Criteria for Adverse Events scoring of grade 1 or higher sensory neuropathy and at least 4 on a numerical pain rating scale of 0-10 serve as an average representation of chemotherapy-induced pain and are commonly used as baseline criteria for identifying patients with CIPPN.[3,6,52]

In summary, the diagnosis of CIPPN is complex and requires a thorough history and physical examination. While electrophysiological studies could be somewhat beneficial, laboratory studies (blood and serologic testing) and magnetic resonance imaging are seldom used.[2,3,52,53,56,57,68] Other factors to consider in assisting with the diagnosis of CIPPN include analysis of motor, sensory, and autonomic functions, and attention to gait and quality of life is also recommended.

Management of CIPPN

Pharmacological treatment

The management of neuropathic pain is a challenge for clinicians. Commonly used drugs, including anticonvulsants, antidepressants, and opioids, have only modest analgesic effects at best. Those drugs are administered as a mono or combination therapy. Table 2 summarizes current published guidelines for the treatment of neuropathic pain, including CIPPN.

Anticonvulsants

Any of the old generation or new generation anticonvulsants can be used for treating CIPPN; however, gabapentin and pregabalin are most frequently used. The starting dose of gabapentin is 100-300 mg at bedtime,

which is gradually increased every three to seven days to twice daily and then to three times daily. The maximal dose is 3,600 mg daily in three to four divided doses. The starting dose of pregabalin is 25-75 mg at bedtime, which is gradually increased every three to five days to twice daily and then to three times daily. The maximal dose is 600 mg daily in three divided doses. Their common side effects are dizziness and sedation.[69-71] The chemical structure of gabapentin is similar to gamma-aminobutyric acid, which is an inhibitory neurotransmitter in the central nervous system. Nevertheless, the main mechanism of action is binding to voltage-gated calcium channels, blocking the alpha-2-delta subunit of calcium channels, and thus producing hyperpolarization.[70]

Antidepressants

Tricyclic antidepressants (TCAs), such as amitriptyline (tertiary amine) and nortriptyline (secondary amine) are widely used as adjuvant analgesics to treat CIPPN. Less commonly, the selective serotonin norepinephrine reuptake inhibitors (SNRIs) are used. The starting dose of amitriptyline and nortriptyline is 10-25 mg daily at bedtime, and the maximal dose is 100-150 mg·day^{-1}. The dose is gradually increased by 10-25 mg about every seven days.[69] The side effects of TCAs are sedation, dry mouth, blurred vision, constipation, urinary retention, orthostatic hypotension, and hypertension. Tricyclic antidepressants non-selectively block the reuptake of serotonin and norepinephrine in the central nervous system (CNS).

Selective serotonin norepinephrine reuptake inhibitors

The selective SNRI (duloxetine, venlafaxine) inhibits the reuptake of serotonin and norepinephrine in the CNS and has been reported to have an analgesic effect in neuropathic pain. Duloxetine has shown efficacy in clinical trials of chemotherapy-induced peripheral neuropathy. The recommended dose is 30-60 mg once a day. The most common side effect is nausea; others include somnolence, dizziness, constipation, and sexual dysfunction.[72] Citalopram, a selective serotonin reuptake inhibitor, is started at a dose of 20 mg·day^{-1} and is increased to a dose of 40 mg·day^{-1},[73] however, its efficacy is controversial.

Topical agents (capsaicin, lidocaine)

Lidocaine inhibits the transport of ions across nerve membranes and prevents initiation and conduction of impulses. Applying the 5% lidocaine patch to painful areas has analgesic effects in the mixed peripheral neuropathy. The most common adverse effect is a mild local reaction.[69]

Capsaicin may release substance P from primary afferent nociceptors via the TRPV1 receptor and then deplete substance P. It blocks the action potential from peripheral sites to the CNS. The most common side effect is erythema.[74]

Opioids

In general, the use of opioids alone or in combination with other drugs for managing any type of neuropathic pain (including CIPPN) has been controversial. Nevertheless, based on our clinical experience, some patients do benefit from using these agents despite their side effects. That said, the use of opioids should be closely monitored to minimize their overuse and/or abuse.

Others

Commonly used medications, such as nonsteroidal anti-inflammatory drugs (e.g., acetylsalicylic acid and indomethacin) do not have analgesic effects in neuropathic pain patients.[75]

Non-pharmacological treatment: acupuncture, physical therapy/occupational therapy, massage

The non-pharmacological treatments, such as acupuncture, physical therapy/occupational therapy, and massage therapy may reduce cancer-related neuropathic pain (including CIPPN) and are relatively safe with very few side effects.[76] Further, learning coping mechanisms and cognitive behavioural therapy could be very helpful in selected groups of patients.

Prevention

Early detection, monitoring, preemptive pain management, and possibly adequate post chemotherapy pain management are thought to prevent CIPPN.[1,5,77,78] All the same, it is not clear if early physical therapy can prevent CIPPN. Several neuroprotective drugs have been considered for the prevention of CIPPN and have shown promise in preliminary reports, but they are not for general use due to insufficient evidence supporting their efficacy. The list of these drugs includes amifostine, glutathione, glutamine, erythropoietin, and acetyl-L-carnitine, acetylcysteine, adrenocorticotropic hormone (ACTH), BNP7787, calcium and magnesium, diethyldithiocarbamate, Org 2766, oxcarbazepine, and vitamin E.[53,54,79-86]

Prognosis

The prognosis for patients experiencing CIPPN is multifactorial; it is dependent on the specific chemotherapeutic agent used and includes multiple patient-related factors. Severity increases with duration of treatment; it is dose-related and progression may cease when treatments are completed. Exceptions include the platinum-based compounds whereby the sensory loss may progress for several months after cessation of treatment, commonly described as "coasting".[6,52,53,80] Preexisting neuropathy from other disease processes, such as diabetes, must also be considered in the prognosis of CIPPN patients. On the other hand, there are patients with preexisting neuropathies who do not develop CIPPN. Therefore, more research is needed to elicit optimal prognoses for those who develop CIPPN.

Conclusions

Chemotherapy-induced painful peripheral neuropathy continues to be a challenge to clinicians and the patients whom we serve. A thorough medical history and physical examination are critical in making the correct diagnosis and in guiding appropriate therapy. In addition, a better understanding of the pathophysiology of CIPPN can be fostered through further clinical trials evaluating neuropathic medications and the underutilized neuroprotective agents that will bring us a step further in the management CIPPN. Studies focusing on the genetic predisposition to CIPPN are necessary, not only to establish preventive measures but also to develop targeted treatments.

Competing interests None declared.

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