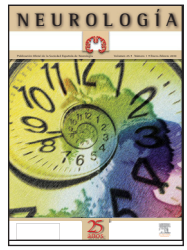
Neurología. 2010;**25(2)**:116-131

NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW

Chemotherapy-induced peripheral neuropathy: an unresolved issue

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Received on 12th December 2009; accepted on 28th December 2009

KEYWORDS
Chemotherapy-induced peripheral neuropathy;
Chemotherapy;
Neuropathy;
Toxic neuropathy;
Antineoplastic agent

Abstract
Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is the most prevalent neurological complication of cancer treatment, affecting a third of all patients who undergo chemotherapy. CIPN impairs functional capacity, compromises the quality of life and results in dose reduction or cessation of chemotherapy, representing a dose-limiting side effect of many antineoplastic drugs. In addition to classic, novel agents, bortezomib and oxaliplatin have been shown to have a significant risk of CIPN.
Methods: By reviewing literature, this article analyses relevant issues and recent advances regarding the pathogenesis, incidence, risk factors, diagnosis, characteristics and management of CIPN.
Results: Research into the pathophysiology and identification of risk factors for individual patients is growing. A future avenue of investigation includes the identification of patients at lower or higher risk based on their genotype. Best tools for CIPN assessment are not defined. Many agents have been claimed to be neuroprotectors without showing significant results in large randomised clinical trials.
Conclusions: Early recognition and subsequent dose reduction/discontinuation of the offending agent is the only way to minimise the development of this potentially debilitating complication. Due to the lack of effective prophylactic or symptomatic treatments up to now, neurological monitoring should be recommended in patient candidates to be treated with neurotoxic antineoplastic agents, mainly when they present baseline neuropathy. Development of reliable methods for CIPN assessment is essential.

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PALABRAS CLAVE
Neuropatía inducida por quimioterapia;
Quimioterapia;
Neuropatía;
Neuropatía tóxica;
Agente antineoplásico

Neuropatía inducida por quimioterapia: un problema no resuelto

Resumen
Introducción: La neuropatía periférica inducida por quimioterapia (NIQ) es la complicación neurológica más frecuente del tratamiento del cáncer, y afecta aproximadamente a una tercera parte de los pacientes. La NIQ deteriora la funcionalidad, compromete la calidad de vida y, frecuentemente, conlleva la reducción y/o suspensión del tratamiento, lo que representa un efecto adverso limitante de dosis de muchos antineoplásicos. Además de los clásicos, agentes nuevos como bortezomib y oxaliplatino presentan un marcado riesgo de neuropatía.
Métodos: Tras revisión de la literatura, se analizan los trabajos relevantes y los recientes avances sobre patogenia, incidencia, factores de riesgo, diagnóstico, características y manejo de la NIQ.
Resultados: El conocimiento sobre la fisiopatología de la NIQ es creciente. La investigación incluye la identificación de los genes relacionados con un mayor o menor riesgo de NIQ. La mejor herramienta que permita diagnosticar y graduar la severidad de la NIQ no está definida. Numerosos agentes se están investigando como potenciales neuroprotectores o tratamientos sintomáticos, con resultados negativos en la mayoría de ellos.
Conclusiones: El reconocimiento precoz y posterior reducción de dosis o suspensión del agente neurotóxico es actualmente la única forma de minimizar el desarrollo de esta complicación. Ante la ausencia de tratamientos preventivos o sintomáticos eficaces en la NIQ, sería recomendable la monitorización neurológica de los pacientes candidatos a recibir quimioterapia con agentes neurotóxicos, sobre todo si presentan una neuropatía de base o subclínica. Es necesario definir e implementar la mejor medida para evaluar la NIQ.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological complication in cancer treatment[1] and probably the most common toxic neuropathy in our environment. From the first reported case of sensory neuropathy secondary to cisplatin over 30 years ago[2], the problem of neurotoxicity in relation to these treatments has not disappeared from the oncology scene. It is also one of the most common side effects of the agents used in the first and/or second line of the treatment for various solid and haematological malignancies. Currently, schemes containing cisplatin and paclitaxel constitute the basis of treatment of tumours as prevalent as those of the lung and breast. In addition, the majority of haematological malignancies are treated with schemes including vincristine, another known neurotoxin. Among the factors that have helped to increase CIPN prevalence are the increase in the number of patients who are candidates for chemotherapy (CT) and greater survival due to the increased effectiveness of new drugs and therapeutic regimes. Likewise, administering colony stimulating factors during treatment with cytostatics, which seeks to minimise haematological toxicity, enables the administration of larger CT doses, thus raising the risk of developing neurotoxicity.

One important aspect to bear in mind is that the appearance of CIPN is a factor limiting cancer treatment. Its appearance causes delays in the administration of a new cycle, dose reductions per cycle or even discontinuation of therapy; this conditions the curative potential of the treatment and patient prognosis. At present, early recognition and initial management of CIPN are the best and only techniques available to prevent its progression towards a severe and disabling neuropathy. However, research in both clinical and experimental aspects of pathophysiology, prevention and treatment has intensified in recent years. The various reviews which have appeared in recent literature[3-9] are a reflection of the neuro-oncological community's growing interest. The study that follows, which updates the one published in this journal almost a decade ago[10], summarises those clinical features and the innovations relating to the management of these patients that we believe may be of interest to neurologists in general and to neuro-oncologists in particular.

Neuropathy induced by chemotherapy. An increasingly common problem?

CIPN rates available in the literature are highly variable; incidences have been reported ranging from 10 to 100%, depending on the study[11]. Among the factors influencing this variability are: *a*) type of cytostatic agent; *b*) treatment scheme administered (total dose, dose per cycle, number of cycles, time of infusion)[12-15]; *c*) combinations of different cytostatics[16]; *d*) type of tumour; *e*) patient characteristics

or concomitant treatment with other neurotoxic drugs; and *f*) diagnostic technique or criteria and assessment of the CIPN[17-19].

Some authors suggest that neuropathy associated with cytostatic therapy may be underestimated, both by the doctors themselves and by the patients, who may occasionally minimise their symptoms for fear of a potential suspension or reduction of the oncologic treatment and, therefore, of its benefit[20-22]. Another confounding factor, not insignificant when investigating the true CIPN incidence, is the fact that the rates described in many clinical trials do not always accurately reflect those actually observed in daily practice. Fundamentally, this is due to the selective inclusion criteria for most studies. For example, it is not uncommon to find studies that exclude diabetic patients or those suffering from prior neuropathy[18,23-26], which undoubtedly constitutes a bias when extrapolating safety results on neurotoxicity[27].

It is generally estimated that 30-40%[8-30] of all patients treated with chemotherapeutic agents develop peripheral neurotoxicity. However, incidences of up to 60%have been reported with cisplatin[31,32], paclitaxel[33-36], docetaxel[37,38], vincristine[39], oxaliplatin and bortezomib[40-43], the last two having been introduced in first-line treatment schemes recently. Oxaliplatin, a third-generation compound derived from platinum that is widely used in colon cancer treatment, causes acute and transient neurotoxicity in almost all patients treated; chronic or established neuropathy is observed in 29-67%[44-47]. With bortezomib, a compound that works by inhibiting proteasome and is indicated for the treatment of multiple myeloma, incidences of up to 64% have recently been reported in previously untreated patients[48], although most studies agree that it usually occurs in a third of the patients[49]. With thalidomide, an immunomodulatory drug popularly known for its teratogenic properties and that has been approved for the treatment of multiple myeloma[50,51], variable incidences have been reported depending on the duration of the treatment and the total cumulative dose; up to 80% of patients with myeloma who received treatment for more than six months[52-54]. Less well known in our country is the neurotoxicity secondary to ixabepilone, which reaches rates of 63%[55]. This drug was approved by the Food and Drug Administration (FDA) in 2007 for the treatment of advanced breast cancer; recently, it was not approved for clinical use by the European Medicines Agency (EMEA)[56], partly because of its neurotoxic risk[57]. Finally, arsenic trioxide-associated neuropathy, currently rare in developed countries, is likely to increase its incidence in the future because this drug is currently indicated for acute promyelocytic leukaemia treatment and is in the study phase for the treatment of various neoplasms[58].

While the neurotoxic profile of the previous chemotherapeutic agents is clearly established, for other drugs such as lenalidomide, a structural analogue of thalidomide, it is more controversial[59]. Richardson et al.[49] reported that up to 23% of patients treated for multiple myeloma developed treatment-associated neuropathy, being severe in 3% However, other authors have reported symptomatic improvement with lenalidomide in myeloma patients who had developed neuropathy from bortezomib[60]. It is true that spontaneous improvement cannot be excluded in these cases, nor can the possibility that the incidences observed are those naturally associated with the haematological base disease. Table 1 lists the chemotherapy agents with neurotoxic effects on the peripheral nervous system. Table 2 summarises the main epidemiological, pathophysiological, clinical, neurophysiological and prognostic aspects associated with the peripheral neurotoxicity related to the most commonly used cytostatic agents.

Physiopathology

The vulnerability of the peripheral nervous system to these agents and the prevalence of sensory impairment are

Table 1 Antineoplastic agents that cause chemotherapy-associated peripheral neuropathy

Platinum-derived compounds
Cisplatin (CDDP)
Carboplatin (CBDA)
Oxaliplatin (OXL)
Vinca alkaloids
Vincristine
Vindesine
Vinblastine
Vinorelbine
Taxanes
Paclitaxel
Docetaxel
Epothilones
Ixabepilone
Immunomodulatory drugs
Thalidomide
Bortezomib
Lenalidomide[a]
Alkylating agent
Procarbazine
Ifosfamide[a]
Inhibitor of topoisomerase
Etoposide (VP-16)
Metalloids
Arsenic
Antimetabolites
5-Fluorouracil (5-FU)[a]
Capecitabine[a]
Gemcitabine[a]
Fludarabine[a]
Cytarabine[a]
Farnesyltransferase inhibitors
Tipifarnib[a]
Antiprotozoal and anthelmintic
Suramin[b,c]

[a] Infrequent, anecdotal cases reported, unknown aetiopathogenesis.
[b] Not currently used in oncology.
[c] Demyelinating neuropathy.

Table 2 Characteristics of the peripheral neurotoxicity caused by the most frequently used antineoplastic agents

Agent	Tumour	Mechanism of action	Accumulated neurotoxic dose	Incidence	Clinical manifestations	NCS-EMG	Evolution
Cisplatin	Lung, breast, testicular, bladder, ovary, oesophagogastric	Irreversible binding to DNA, neuronal apoptosis	>300 mg/ m^2	30-40%	Pure sensory neuronopathy, may be asymmetric. Early (after 2nd or 3rd cycle)	Pure sensory axonal neuropathy (neuronopathy)	Irreversible in most patients
Carboplatin	Lung, breast, ovaries	Irreversible binding to DNA, neuronal apoptosis	>400 mg/ m^2	10-20%	Similar but less intense than with cisplatin	Pure sensory axonal neuropathy (neuronopathy)	Irreversible in most patients
Oxaliplatin	Colorectal, gastric	Irreversible binding to DNA, neuronal apoptosis	>750 mg/ m^2	Up to 50-60% <10% severe	Chronic: similar to cisplatin. Coasting effect described up to six months after treatment. Achilles arreflexia	Pure sensory axonal neuropathy (neuronopathy)	40% full recovery. Remaining at 4 years: 3,4% grade 2 and <1% grade 3
		Dysfunction of voltage-dependent sodium channels	Without cumulative doses	65-98%	Acute: distal paresthesias in hands, perioral and pharyngolaryngeal exacerbated by cold. Muscle contractions similar to neuromyotonia. Temporary: 48 h-15 days	Repetitive and neuromyotonic shocks	Always reversible
Paclitaxel	Lung, breast, ovaries	Dysfunction of cellular and axonal transport mediated by microtubules	> 200 mg/ m^2 > 500 mg/ m^2	70% 95%	Sensory neuropathy that can be early. Simultaneous paresthesia in hands and feet. Occasionally, perioral and tongue paresthesias. Distal and/or proximal weakness. Frequent arthromyalgia	Sensorimotor axonal neuropathy	Reversible in most patients
				Severe: 10-20%	Early Achillean hyporeflexia-arreflexia. Dysautonomia (>250 mg/ m^2) paralyzed ileum, orthostatic hypotension		

(Continued)

Table 2 Characteristics of the peripheral neurotoxicity caused by the most frequently used antineoplastic agents *(Continued)*

Agent	Tumour	Mechanism of action	Accumulated neurotoxic dose	Incidence	Clinical manifestations	NCS-EMG	Evolution
Docetaxel	Lung, breast, ovaries	Dysfunction of cellular and axonal transport mediated by microtubules	150-1100 mg/ m^2	Up to 50% Severe up to 25%	Similar to paclitaxel, may be more severe. Coasting effect described	Sensorimotor axonal neuropathy	Reversible in most patients
Vincristine	Haematological neoplasms, ovarian, testicular, lung, colorectal	Dysfunction of cellular and axonal transport mediated by microtubules	>1.4 mg/ m^2 Limiting dose: 30-50 mg	30-40%	Sensory and motor neuropathy, distal and symmetrical. Extensor muscle weakness of upper and lower extremities. Early (beginning at 2 weeks). Early hyporeflexia-arreflexia. Dysautonomia, 30% Coasting. Frequent pain	Sensorimotor axonal neuropathy. Demyelinating cases have been reported that mimic Guillain-Barré syndrome	Reversible, recovery may take up to 2 years
Vinorelbine	Lung, breast, ovarian, testicular	Dysfunction of cellular and axonal transport mediated by microtubules	25-30 mg/ m^2	6-29% 3%severe	Sensory > motor neuropathy, distal and symmetric. Dysautonomia (paralyzed ileum)	Sensorimotor axonal neuropathy	Reversible
Ixabepilone	Breast	Dysfunction of cellular and axonal transport mediated by microtubules	>40 mg/ m^2	21-67% Severe 3-20%	Sensory > motor neuropathy distal and symmetrical. Severe from the 4th cycle	Sensorimotor axonal neuropathy	Reversible
Bortezomib	Multiple myeloma, mantle cell lymphoma	Unknown	Controversial	30-64%	Sensory >> motor neuropathy	Sensorimotor axonal neuropathy	64%reversible up to pre-treatment status in less than 3 months
			30 mg/ m^2 Cases described after 1 cycle		Early (usually severe conditions in the first 4 cycles). Frequent arthromyalgia. Pain due to small fibre affectation in some patients		
Thalidomide	Haematological neoplasms	Unknown	Controversial >20 g	14-70% 7%severe	Sensory > motor neuropathy, distal and symmetric. Proximal weakness described. Reflexes are usually preserved	Sensorimotor axonal neuropathy	Irreversible
Arsenic trioxide	Haematological neoplasms	Blocking of Krebs cycle, lipid peroxidation	Unknown	17%	Subacute and progressive sensorimotor neuropathy. Mee's nail lines. Hyperkeratosis	Sensorimotor axonal neuropathy	Partially reversible

related to the absence of a blood-brain barrier in the posterior spinal ganglion and the greater permeability of the *vasa nervorum* with respect to haematoencephalic circulation[9,61]. However, the pathophysiological mechanisms directly involved in CIPN pathogenesis are only partially known, are probably multiple and do not always have a relation with the antitumour mechanism.

Through experimental *in vitro* and animal studies, platins (cisplatin, oxaliplatin) have been shown in several studies to induce apoptosis of sensory neurons of the posterior spinal ganglion after binding to DNA strands, with the consequent alteration of its tertiary structure. This structure is related, among other processes, with cyclin D1 activation and the intracellular signalling pathway of the mitogen-activated protein kinases (MAPK), promitotic proteins that induce the entry of the neuron into the cell cycle and the compensatory activation of apoptosis to prevent division in a cell already differentiated[62,63]. Vincristine and taxanes (paclitaxel and docetaxel), whose main mechanism of anti-tumour action is the alteration in microtubule depolymerisation, interfere with axonal transport and other basic cellular functions mediated by them, causing a dysfunction of the neuron that leads to consequent axonal degeneration[64]. In the specific case of paclitaxel, a phenomenon that is also described is the activation of calpains, cytosolic enzymes with proteolytic activity that produce cellular damage mediated by calcium[65]. Preclinical studies in animal models with calpain inhibitory agents have shown that they prevent axonal damage secondary to vincristine and paclitaxel[65,66].

Moreover, deficit of neurotrophic factors has also been implicated in CIPN[30,67]. Several authors have objectified a decrease in circulating levels of nerve growth factor (NGF), both in animals and in series of patients[68-70] who developed CIPN.

In another line, two experimental studies of neuropathy caused by cisplatin and paclitaxel-thalidomide have recently shown that peripheral nerve toxicity could have a partially vascular origin: these cytostatics would induce apoptosis of the endothelial cells of the *vasa nervorum,* with consequent nerve fibre ischemia. In addition, through gene therapy designed to induce vascular endothelial growth factor (VEGF) expression, the normalisation of nervous perfusion and recovery from neuropathy are achieved[71]. According to these data, it is possible that the increasingly widespread use of antiangiogenics adjuvant to treatment with CT may increase CIPN incidence. Thus, a phase III study that compared the conventional scheme of oxaliplatin with and without bevacizumab showed an increase in the incidence of severe CIPN in the group treated with antiangiogenic agents (16.3 versus 9.2%)[72]. Although the authors justified the rise by the increased number of cycles received by the bevacizumab group, the potential synergistic neurotoxic effect of antiangiogenesis cannot be ruled out.

Oxidative stress caused by the majority of antineoplastic drugs has traditionally been associated with the activation of neuronal apoptosis mechanisms. For example, membrane lipid peroxidation has also been proposed as a crucial phenomenon in the pathogenesis of neuropathy from cisplatin and arsenic[73]. The mechanism of acute neurotoxicity from oxaliplatin is different. The oxalate released by the latter produces a chelation of extracellular calcium that inhibits the entry of sodium into sensory neurons through a transient and non-structural dysfunction of the voltage-dependent sodium channels, by interfering in their depolarization[74]; this fact has been documented through studies that show sharp changes in axonal excitability[75]. Finally, knowledge about the underlying phenomena of neurotoxicity secondary to bortezomib is still very preliminary[76-79]. Recently, the Casafont group has demonstrated that bortezomib interferes with the processes of transcription, nuclear processing, transport and cytoplasmic translation of messenger RNA in the neurons of the posterior spinal ganglion[79].

Clinical aspects

The diagnosis of CIPN is easy for the physician, given the pervasive history of treatment with any of these agents. However, we must bear in mind that cancer patients may suffer from a peripheral nervous system disease due to other mechanisms in relation to their cancer (compressive, infiltrative, immune-paraneoplastic) or independent of it (metabolic or by toxicity of other drugs). While it is clear that any data deviating from the typical presentation leads to ruling these possibilities out, some authors recommend completing the screening of potential aetiologies of peripheral neuropathy even when the diagnosis of CT-associated neuropathy is clear[80].

CIPN occurs during treatment with the cytostatic drug or just after the last cycle[81]. The patient usually refers positive and/or negative symptoms from a given cycle, usually towards the end of the treatment. However, very early presentations, even after the first dose, have been reported with agents such as vincristine, cisplatin and bortezomib[26,32,82]. The so-called coasting effect, characteristic of cisplatin-mediated neuropathies[32,83], is also very rare. This was initially described with vincristine[84], but has also been observed in patients treated with docetaxel[85]. It consists of a progressively worsening neuropathy for weeks or months after the suspension of the causal agent. Finally, transient exacerbation of symptoms in patients with sensory neuropathy from oxaliplatin is not uncommon when they undergo surgery just after the completion of CT. This effect has been related to the release of clusters of inter-erythrocyte oxaliplatin in the plasma with the haemolysis associated with surgery[86].

The establishment of CIPN is usually subacute, with a progressive course if the causative agent is not reduced and/or suspended. However, oxaliplatin also produces acute and transient polyneuropathy. Patients present dysesthesia and thermal allodynia with cold hands, feet and oropharynx, which begin during the infusion and usually subside in about 48 hours. They are usually self-limited before the next cycle (15 days)[5].

Among the positive sensory symptoms reported by patients, we generally find paresthesia, spontaneous or mechanical, dysesthesia, allodynia and hyperalgesia. Hyperesthesia in the limits of sensory deficit is a common finding during neurological examination. Negative sensory symptoms are commonly described in relation to the

disability that they cause, such as inability to button up or to write[87]. Spontaneous pseudoathetoid movements of toes and fingers can be observed in patients with severe proprioceptive conditions, generally associated with platinum-based therapy; sensory ataxia, although common, rarely becomes disabling. Other symptoms which are less commonly recognised as a neurotoxic effect of these treatments are Lhermitte's phenomenon, typical of patients treated with platins[88], and pruritus, described with paclitaxel[9]. Burning pain in the palms of the hands and soles of the feet, which appears in some patients treated with oxaliplatin, bortezomib and vincristine, is not a constant symptom in all patients[11,89]. Myalgias, especially in the calves and forearms, often appear with bortezomib and paclitaxel[6,9], although they should not be included in the clinical spectrum of neuropathy.

The earliest clinical signs in most patients who develop CIPN are a decrease in the sensation of vibration and the loss of the Achilles jerk[7]. While hyporeflexia is often in proportion to axonal loss, it is interesting that with vincristine it is usually very early even when neuropathy is not established[9,83,90]. Conversely, reflexes may be preserved in neuropathy secondary to thalidomide[9,91,92]. Arthrokinetic sensitivity impact is often a late sign and only in the most severe degrees[19]. The distribution of symptoms and signs is related to the nature of the damage. In neuropathy secondary to platins, the affectation of extremities usually manifests simultaneously and an asymmetrical distribution following a neuronopathic pattern is not unusual[93]. However, with most agents it usually appears as a distal polyneuropathy starting in the lower extremities and with predominant affectation of the extensor muscles when there is motor fibre affectation.

Symptoms secondary to autonomic neuropathy are not uncommon in patients treated with vincristine (30%), paclitaxel (29% asymptomatic bradycardia) and bortezomib (12% orthostatic hypotension)[64,83,94,95]. Paralytic ileum, orthostatic hypotension and bladder and erectile dysfunction are common manifestations that may occur singly or habitually in the context of an already-established CIPN. Systematic studies focused on the assessment of autonomic fibres in CT-treated patients are scarce, and the evidence from preclinical studies in this regard is contradictory. This is the case of cisplatin, where autonomic affectation is reported anecdotally in patients and is well defined in animal models[93,96].

Risk factors

The main risk factors involved in the development of CIPN are the dosage and duration of treatment. In addition, demographic, comorbidity and even genetic factors have been proposed that predispose towards an increased risk of the neurotoxic effects of these agents. Subjects with neuropathy, although subclinical, therefore seem more vulnerable to the neurotoxic effect of most chemotherapeutic agents[97] and usually develop more severe neuropathies[80,98]. An increased risk of high-grade neuropathy has been reported with bortezomib in individuals with prior neuropathy[49]. Although these authors did not observe an increase in overall incidence, the studies of Cavaletti and our own experience show an increased risk of bortezomib neuropathy in patients with basal neuropathy[26]. In the case of hereditary neuropathies, the worsening or, more frequently, the unmasking of a Charcot-Marie Tooth (CMT) syndrome is a classic feature in subjects exposed to vincristine, with over 30 cases reported in the literature[99,100]. These are typically patients with the demyelinating autosomal dominant form (CMT 1A). Far less numerous are the cases of CMT revealed by treatment with cisplatin[101] and paclitaxel-carboplatin[102]. Neuropathy associated to CT treatment in these patients tends to be "catastrophic" and disabling; it manifests itself very early, at low doses and has a rapidly progressive course. Anecdotally, the literature also contains the report of a patient having hereditary neuropathy with lability to pressure unmasked after treatment with vincristine[103]. While CT treatment is not formally contraindicated in patients with basal neuropathy[8], some centres (including ours) commonly carry out a prior assessment of patients with a personal or family history of neuropathy, as well as conducting a neurological monitoring during chemotherapy treatment[104]. Furthermore, in patients with solid neoplasms and basal neuropathy, platins and taxanes with a lower neurotoxic potential (carboplatin and docetaxel) may be recommended as a first option[102]. Partially related to the risk of basal neuropathy, the role of diabetes mellitus as a neurotoxic risk factor in these patients is controversial[27]. Moreover, there are conflicting results with respect to age and risk of CIPN. While the work of Argyrou et al.[105] showed similar incidence and severity in patients younger than 65 years and over 65 years in a prospective study of 35 patients treated with paclitaxel and cisplatin, age has recently been shown to be a risk factor associated with bortezomib-induced neurotoxicity[106,107]. Finally, it has been postulated that alterations in liver and kidney function, related to the elimination of the toxic agent, could be potential risk factors although their true implication has not been unquestionably established[8].

Little is currently known about which genes or genetic variants (polymorphisms) may predispose subjects exposed to these drugs to an increased risk of peripheral neurotoxicity[108,109]. Pharmacogenetic studies based on the analysis of polymorphisms in genes encoding enzymes involved in metabolic pathways (CYP450), oxidative stress response (glutathione S-transferases [GST]), DNA repair or transport proteins (glycoprotein P), are attempting to establish a relationship between the interindividual differences in toxicity response to treatment and patient genetic load. To date, some polymorphisms have been described in the GST gene in patients with advanced colorectal cancer treated with oxaliplatin[110,111], with ovarian cancer treated with cisplatin[112] and with breast neoplasm treated with docetaxel[113] that predict the risk of developing CIPN; another group has found associations between various polymorphisms in the *ABCB1* gene (that encodes glycoprotein 1) and paclitaxel-[114] and docetaxel-induced[115] neurotoxicity. Although the information available is still very preliminary, it is likely that these studies will contribute in the future not only to predict the response to cancer treatment, but also to establish the individual risk of neuropathy associated with CT treatment. This would avoid unnecessarily toxic

therapeutic schemes and enable treatments to be individually tailored to optimise the appropriate dose in each case and thereby improve the safety of the administration of these agents.

Evaluation

The diagnosis of CIPN is clinical; anamnesis and clinical examination are the most reliable methods for its early detection[53,80,116]. The role of conventional neurophysiological studies with electroneurography (ENG) with or without electromyography (EMG) is more controversial; while some authors consider them complementary[80] or inconsistent[115], others defend, as a minimum, the performance of a sural nerve sensory potential to establish CIPN diagnosis and appropriate monitoring[118]. While it is true that these techniques do not always translate the severity of the neuropathy[17], it is evident that they have an undoubted value in determining the nature (demyelinating or axonal) and extension of the damage[116], which allows an objective quantification very useful for patient monitoring[118]. In addition, some authors feel the decrease in sural nerve potential could be even more sensitive than a neurological examination in detecting subclinical neuropathies, and even give it a prognostic value in the development of CIPN[25], although this has not been confirmed by other authors[70,91]. In our opinion, the lack of correlation between the decrease in sensory potential and symptom intensity, the involvement of fibres of different calibre in different proportions and, above all, the time lag between the onset of symptoms and changes in neurography are some of the limitations of conventional neurography, especially when attempting an early diagnosis. So far, neurophysiological monitoring has failed to show a clear benefit over clinical monitoring in CIPN detection[53]. More specific techniques such as quantitative sensory testing (QST) or the study of autonomic efferent fibres (Sympathetic Skin Response) have not proven more sensitive than clinical data for both early detection and assessment of response to CIPN treatment[29,119]. Axonal excitability techniques recently used for the study of oxaliplatin-induced neuropathy seem more promising. Park et al.[75] have shown a positive correlation between changes in axonal excitability at the time of oxaliplatin infusion and the risk of developing chronic neuropathy, thus giving these techniques a predictive value. Finally, skin biopsy for studying patients with CIPN, very useful in small and autonomic fibre neuropathies, is likely to increase soon, as evidenced by the recently published works that incorporate this technique in the study of CIPN[48,120]. There is currently an ongoing clinical trial that includes skin biopsy in patients with multiple myeloma treated with bortezomib (NCT00956033) to assess the usefulness of this technique.

The grading of CIPN severity is an unsolved problem. Oncological scales, developed to facilitate the oncologist's task when collecting all the side effects of a given treatment, are those commonly used in daily practice to diagnose CIPN and grade its severity (table 3). However, these are clearly insufficient to establish the intensity of peripheral neurotoxicity, especially once it is established[9,17,116]. Among their limitations are the overestimation of symptoms, the near absence of objective or quantifiable data, the absence of pain as a clinical datum and a marked interobserver variability, given that they require the interpretation of symptoms to grade them[17]. In an attempt to improve the assessment of this type of neuropathies, Cavaletti et al. demonstrated the correlation between the most commonly used oncology scales and the Total Neuropathy Score (TNS®) scale[121,122]. The TNS scale includes symptoms, clinical signs and neurophysiological parameters (table 4), thus allowing a more accurate, objective assessment of CIPN. In several countries, including ours, the CI-PERINOMS study (Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardisation Study) is currently underway. This study seeks to find the best method for neurological CIPN assessment, evaluating validity and reproducibility when examining interobserver and intraobserver reliability of various scales (including TNS) for the assessment of the severity of established CIPN[123]. Although one of the limitations of TNS is that it does not include neuropathic pain, its quantifiable character clearly provides an improvement in classifying and grading CIPN, which makes it a very useful tool for the management of this type of neuropathy, in our opinion.

On the other hand, CIPN affects the quality of life and may have a strong negative impact on the functional, social and emotional areas of the lives of these patients[20,124]. Along this line, following the American model of the FACT-G (Functional Assessment of Cancer Therapy) scale[125], the European Organisation for Research and Treatment of Cancer (EORTC) created the QLQ-CIPN questionnaire in 2005[20], aimed at assessing the quality of life in patients with CIPN[126]. Currently, EORTC has prepared the Spanish version, which has recently been validated at our centre. In addition to its required use in clinical trials with neurotoxic and/or neuroprotective agents, we believe (as other authors do) that it can provide additional information during the visit to the clinic, thus becoming useful in the monitoring of these patients.

Evolution

The evolution of CIPN, although favourable after discontinuation of treatment in most cases, is not always reversible. Some authors also argue that in some cases, rather than an improvement in neuropathy, there is a situation of "adaptation" to the symptoms[20]. An Italian study evaluating long-term toxicity in patients with ovarian cancer after combined treatment with carboplatin and paclitaxel showed that 15% of the patients presented neurotoxicity 6 months after completing the treatment[127]. In the case of oxaliplatin, while acute neuropathy is always reversible since it disappears before the next cycle, the symptoms of established neurotoxicity are partially reversible in 80% of patients and are only resolved completely within a period of between 6 and 8 months in 40% of them[5]; it is considered irreversible after 9 months following the end of the treatment[128]. Peripheral neuropathy secondary to vincristine is usually favourable in the long-term in most cases[90]. More daunting is cisplatin-induced neurotoxicity, which is usually irreversible in more than half of patients

once it is established[129]. In contrast, Richardson et al.[130] have reported improvement up to the pre-treatment condition in 64% of patients who developed bortezomib-induced CIPN grade 2. The study showed a higher rate of reversible neuropathies in patients in whom the bortezomib dose was adjusted each cycle based on the clinical findings. The authors emphasise that using this algorithm in the management had no impact on the effectiveness of the cancer treatment.

Treatment

Treatment of patients with CIPN should be based on two pillars: prevention (adjustment of dose and neuroprotection) and symptomatic relief. In recent years, there have been preclinical and clinical trials with numerous agents, with the objective of preventing the development of peripheral neurotoxicity[28,131]. These neuroprotective agents include trophic factors, antioxidants, anti-epileptic drugs and chelating agents. Among the chelating agents, infusions of calcium gluconate and magnesium sulphate, before and after infusion of oxaliplatin, initially seemed to be the solution against chronic and acute neurotoxicity[132]. However, these results could not be confirmed in a prospective study that had to be interrupted prematurely due to the suspicion of less antitumour activity in patients receiving calcium and magnesium[133]. This emphasises one of the critical points in neuroprotection: that antitumour effectiveness decreases as a side effect.

Among the trophic agents, we highlight NGF, whose neuroprotective potential in CIPN would be based on the observation of a decrease in circulating concentrations in the serum of patients treated with CT[68,69] and the experimental demonstration that exogenous administration of NGF may prevent CIPN[134]. In addition, there is clinical experience with positive results in patients with diabetic neuropathy[135]. However, local and systemic side effects of the exogenous administration of NGF to date make it a poor therapeutic option in oncology patients[83]. In line with these data, given the ability of glutamine and glutamate to increase local NGF synthesis[136] and their good results in experimental models, several small clinical trials, not controlled with placebo, have been developed to confirm it[23,137,138]. However, they failed to observe more than significant improvement in subjective parameters and some minor signs, but not in the neurophysiological parameters. Very recently, a double-blind, randomised, placebo-controlled study failed to reproduce this beneficial effect[36];so, despite the demonstrated lack of interference with antitumour effectiveness, the administration of oral glutamine/ glutamate to prevent CIPN cannot be considered at present[139]. Administering acetyl-L-carnitine (ALCAR) has also been proposed in an attempt to induce NGF synthesis. This compound has shown a neuroprotective effect in animal models[140,141] and has proven not to interact in the desired cytotoxicity of paclitaxel and carboplatin on neoplastic cells[142]. So far, we have only two studies of 25 and 27 patients with established neuropathy secondary to cisplatin and paclitaxel, non-controlled, with positive clinical and neurophysiological results[143,144]. Despite these insufficient preliminary results, some authors suggest administering ALCAR to prevent and/ or treat CIPN[145].

On the other hand, the role of antioxidants in the prevention of CIPN remains a major research field. Among agents with free radical antioxidant or inhibitor properties we find amifostine, whose protective capacity in cisplatin-induced neurotoxicity in *in vitro* studies[146] and in a series of patients[147] could not be reproduced in a phase II study[148]. These data, together with its poor tolerability primarily from severe hypotension, have contributed to its near abandonment in the investigation of neuroprotective strategies. However, glutathione (an endogenous antioxidant) and its precursor N-acetylcysteine are being evaluated intensively as potential neuroprotectors in CIPN. Some studies have demonstrated its clinical efficacy, most of them designed as double-blind, randomised and placebo-controlled[18,149,150]. Among the proposed mechanisms are, in addition to its ability to block free radicals, the ability to promote NGF effects[30], inhibit cellular apoptosis[151] and

Table 3 Escala NCI-CTC v3. National Cancer Institute-Common Toxicity Criteria versión 3

Adverse Event	Grade				
	1	2	3	4	5
Neuropathy: sensory	Asymptomatic; Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADL (Activity Daily Living)	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
Neuropathy: motor	Asymptomatic, weakness on exam/ testing only	Symptomatic weakness interfering with function, but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated.	Life-threating; disabling (e.g. paralysis)	Death

Table 4 Escala TNS (Total Neuropathy Score)

	Total Neuropathy Score				
Parameter	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger and toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbow or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/ assistance	Paralysis
Autonomic symptoms, nº	0	1	2	3	4 or 5
Pin sensitivity	Normal	Reduced in fingers and toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensitivity	Normal	Reduced in fingers and toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild (MRC:4)	Moderate weakness (MRC 3)	Severe weakness (MRC 2)	Parálisis (MRC 0-1)
Deep tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST vibration %ULN)	Normal to 125%ULN	126%150%ULN	151%200%ULN	201%300%ULN	> 300%ULN
Sensory Nerve SNAP; %LLN	Normal/ reduced to < 5%LLN	76%95%of LLN	51%75%of LLN	26%50%of LLN	0%25%of LLN
Peroneal nerve CMAP; %LLN	Normal/ reduced to < 5%LLN	76%95%of LLN	51%75%of LLN	26%50%of LLN	0-25%of LLN

Adapted from Cavaletti et al.[122] and reproduced with permission from the authors (Dr. D. Cornblath and Dr. V. Chaudhry[121]). QST: Quantitative sensory test; ULN: Upper limit of normal; LLN: Lower limit of normal; SNAP: Sensory nerve action potential; CMAP: Amplitude of the compound muscle potential; MRC: Medical Research Council.

decrease platin accumulation in the nuclei of neurons and the posterior spinal ganglion[118]. Despite these favourable results and the fact that glutathione has not been shown to decrease the anti-tumour efficacy of the cytostatics with which it is administered, its high intracellular concentrations have been associated with phenomena of resistance to these drugs[30]. Further safety studies are thus needed before its use can become widespread[152]. Also interesting are the studies evaluating vitamin E administration during CT treatment with neuroprotective intent. After observing the decrease in vitamin E concentrations in patients treated with cisplatin[153] and the obligatory preclinical studies developed by Pace et al, the same group was a pioneer in demonstrating its effectiveness as a neuroprotective agent in a series of 47 patients treated with cisplatin[154]. They found incidences of CIPN of 31%in the group that received vitamin E (300-400 mg/ 12 h/ orally) versus 86%in the one that did not receive vitamin supplementation. Subsequently, three further studies have shown similar results[155-157]. Recruitment for a randomised, double-blind, placebo-controlled trial that should confirm its potential neuroprotective benefit (NCT00363129) has recently been completed[158]. Finally, with regard to neuroprotection, agents such as carbamazepine[159,160] and oxcarbamazepine[161] offer conflicting and very preliminary results. The absence of a neuroprotective effect of the ACTH analogue (ORG 2766) in CIPN has been more validated, after failing to reproduce the favourable results[162] in subsequent studies of similar design (randomised, double-blind, placebo-controlled) in larger patient series[163,164].

In summary, the recently published meta-analysis on neuropathy and neuroprotection induced by agents derived from platins[152], whose results conclude that so far no drug or nutritional supplement has demonstrated an ability to prevent or limit cisplatin-induced neuropathy, could be extended to all agents tested to date. The available scientific evidence is still limited and more studies are needed to confirm the potential neuroprotective effect and to show that they do not interfere with antitumour activity, before they can be implemented in daily clinical practice[28,80].

Symptomatic treatment of patients suffering from CIPN, focused on the relief of positive symptoms, is equally disappointing. Given its similarity to diabetic neuropathy, there is a "continuity" when treating these patients with the same drugs. However, due to the variability of pathogenic mechanisms involved in CIPN, these should not necessarily

be effective for this type of patients[28,80]; this, unfortunately, is proven by the scarce scientific evidence at our disposal. Double-blind, randomised, placebo-controlled studies carried out with nortriptyline[165], amitriptyline[166], gabapentin[167] and lamotrigine[168] have not proven them effective for the symptomatic CIPN treatment. In the case of amitriptyline, the authors observed a positive effect in the improvement of patients' quality of life, despite the lack of efficacy in relieving neuropathic pain[163]. The small size of the samples (usually due to difficulties in recruiting) is one of the arguments used by most studies to justify their negative results. Positive results pointing to a potential therapeutic benefit with venlafaxin[169], topiramate[169] and pregabalin[170] are still very preliminary. Currently, some research focuses on drugs such as duloxetine, with a phase III study in progress, and on topical treatments that include amitriptyline, ketamine and menthol (NCT00471445)[28,171].

For some authors, the first step in the symptomatic CIPN treatment should be NSAIDs, with the addition of opioids if necessary[29,80], despite the lack of studies supporting their use, in addition to proposing physical rehabilitation and occupational therapy for the most severely affected patients. Finally, we must not forget that the evolution of CIPN is generally favourable and that the symptoms improve spontaneously in most cases; therefore, periodic patient evaluations and stopping these treatments when they are no longer needed are recommended.

Conclusions

From our point of view, the lack of correlation between the onset of neuropathy and the response to treatment with CT makes the neurotoxicity commonly associated with these drugs unacceptable as a "toll" inherent in cancer treatment. This is even truer for patients treated with palliative intent, where the goal is to relieve symptoms and improve quality of life for a limited period. Currently, prevention and early recognition of CIPN are crucial to avoid severe and disabling neuropathies. It is necessary to define and implement the best measure to assess CIPN. In the absence of preventive or effective symptomatic CIPN treatments, and while awaiting the identification of markers or risk factors that allow detecting patients at risk and facilitate individualised cancer treatment, as well as future neuroprotective agents, we would recommend neurological monitoring of patients eligible for receiving CT with neurotoxic agents, especially if they present basal or subclinical neuropathy.

Acknowledgements

The authors wish to thank Ms. Ana Baños for her excellent assistance in administrative tasks.

Financing

This study has been carried out in part thanks to a grant from the Fondo de Investigaciones Sanitarias (PI070493), Madrid, Spain.

Conflict of interests

The authors declare no conflict of interests.

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