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# Neuropathy Secondary to Chemotherapy: A Real Issue for Cancer Survivors

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## 1. Introduction

Cancer is still a major public health problem worldwide, being one of the leading causes of population mortality. In 2000, malignant tumors were responsible for 12 percent of the nearly 56 million deaths worldwide from all causes. In many countries, more than a quarter of deaths were attributable to cancer (Parkin et al., 2005). According to the World Cancer Report, which is the most comprehensive global examination of the disease to date, cancer rates are expected to further increase by 50% to 15 million new cases by 2020. Absolute deaths from cancer worldwide are projected to continue to rise to over 11 million by 2030 (Parkin et al., 2005). However, due to advances in multimodal treatment, screening and therefore early detection, as well as chemoprevention, the number of cancer survivors are also expected to increase in the near future (Parkin et al., 2005). This fact highlights the relevance of fostering and maintaining survivors' quality of life (QOL).

Most patients diagnosed with cancer will receive chemotherapy over the course of the disease with a neoadjuvant, adjuvant, or palliative. Several major classes of chemotherapeutic agents can be grouped by their underlying mechanism of action (Hausheer et al., 2006). All these drugs can also have different profiles of toxicity according to their mechanism, some very serious. One of the most common and distressing adverse event is peripheral neuropathy whose incidence is now growing. In fact many chemotherapeutic agents belonging to different groups associate a dose-limiting chemotherapy-induced peripheral neuropathy (CIPN). The different properties of these agents are contributing to the pathogenesis of this toxicity, leading to variation in incidence, severity, kind of damage, etc. depending on the agent considered (Hausheer et al., 2006).

CIPN involves sensory and motor nerve damage or dysfunction with a prolonged course, which causes permanent damage in some long-term cancer survivors with the subsequent impairment in their QOL (Hausheer et al., 2006). CIPN affects not only QOL, since toxicity may have an impact on the planned therapy, and such alterations could have negative consequences for the outcome, especially if the patient's malignancy is responding to treatment (Hausheer et al., 2006). Despite the increasing awareness of this potential toxicity and the improved knowledge of the pathogenic mechanisms, emerging evidence suggests that the incidence of CIPN is substantially under-reported in clinical trials, due mainly to

relevant limitations in the available grading scales that are commonly used for assessment (Cavaletti & Marmiroli, 2010).

Agent	Mechanism of anticancer action	Most frequent clinical uses
Cisplatin	Alkylating, crosslink to DNA	Lung cancer, Bladder cancer, Ovarian cancer, Testicular cancer, Gastric cancer, Head and neck cancer, Cervical cancer, Malignant mesothelioma
Carboplatin	Alkylating, crosslink to DNA	Ovarian cancer, Lung cancer
Oxaliplatin	Alkylating, crosslink to DNA	Colorectal cancer
Paclitaxel	Hyperpolymerisation of microtubules	Ovarian cancer, Breast cancer, Kaposi sarcoma, Lung cancer (non-small-cell), Head and neck cancer, Gastric cancer
Docetaxel	Hyperpolymerisation of microtubules	Breast cancer, Gastric cancer, Prostate cancer, Head and neck cancer, Lung cancer (non-small-cell)
Ixabepilone	Hyperpolymerisation of microtubules	Breast cancer
Vincristine	Depolymerisation of microtubules	Acute leukaemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, Rhabdomyosarcoma, Neuroblastoma, Wilms tumour
Vinorelbine	Depolymerisation of microtubules	Lung cancer (non-small-cell), Ovarian cancer, Breast cancer, Prostate cancer
Bortezomib	Proteasome inhibition	Multiple myeloma, Mantle cell lymphoma
Thalidomide	Antiangiogenic Immune-modulator	Multiple myeloma

Table 1. Mechanisms of anticancer action and most frequent clinical uses of neurotoxic agents (Cavaletti, G. & Marmiroli, 2006).

The challenges in diagnosing and assessing the extent of functional impairment in a reliable and reproducible manner is a paramount consideration for the clinician to make a clinical decision as well as in clinical trials involving the prospective evaluation of neurotoxic chemotherapy or interventions aimed at the prevention or mitigation of CIPN (Gándara et al., 1991). The drugs most commonly associated with CIPN are platinum analogues, antitubulins, the proteasome inhibitor bortezomib, and thalidomide, which are very commonly used in a wide range of solid and haematological malignancies (Windebank &

Grisold, 2008). In addition, most cases will receive a combination of several chemotherapeutic compounds aiming to enhance the effectiveness of such treatment but with the disadvantage of inducing CIPN more often than individual agents (Cavaletti & Marmiroli, 2010).

The clinical manifestations of CIPN are subjective and predominantly manifest as pure sensory symptoms, most frequently reported as progressive distal symmetrically distributed. The most important symptoms are numbness, tingling, "pins and needles", burning sensations, decreased or altered sensation, or increased sensitivity that may sometimes be painful in the feet and hands (Hilkens & Van den Bent, 1997; Lipton et al., 1989). The primary clinical goal in assessing these patients is to determine the presence of these complications after making a correct differential diagnosis and also to evaluate their severity because sometimes they can interfere with activities of daily living (ADL). These assessments are critical for making decisions related to the continuity, dose-intensity, or dose-density of the anticancer treatment (Cavaletti & Marmiroli, 2010). Although the most important spectrum of CIPN symptoms is sensory in nature, motor weakness may also be reported and when present is observed in patients with more persistent and severe sensory symptoms (American Society of Health-System Pharmacists, 2002). In fact, isolated motor weakness with the complete absence of sensory involvement has not been described, but if observed in a patient, consideration should be given to other conditions that may produce pure motor weakness, including steroid myopathy which is proximal, diabetic, or paraneoplastic motor neuropathy (Hausheer et al., 2006). The onset of CIPN is usually gradually progressive, although in some patients it can appear immediately after the administration of a neurotoxic drug or even during the infusion. This condition may thus pose difficulties for the clinician, especially to diagnose those patients with coexisting problems or disorders that involve the peripheral nervous system (Hausheer et al., 2006). No standard treatment currently exists for the prevention, mitigation, or management of CIPN (Hausheer et al., 2006).

This chapter will focus on all these aspects of CIPN including the clinical manifestation, diagnosis, management, mechanisms underlying its onset, assessment, and current status of neuroprotection. The different agents used in anticancer treatments that might be related to toxicity will also be reviewed.

	Sensory	Sensory and motor
Platinum agents	X	
Bortezomib	X	
Thalidomide	X	
Taxanes		X
Epothilones		X
Vinca alkaloids		X

Table 2. Classification of the most important agents reported in CIPN (Hilkens & Van den Bent, 1997; Lipton et al., 1989).

## 2. Pathogenic mechanisms and clinical features of CIPN

The underlying pathogenic mechanisms for the development of CIPN have not been fully elucidated. In fact, a variety of mechanisms have been proposed. Different chemotherapeutic agents cause highly similar patterns and spectra of clinical manifestations, which include the length-dependent, symmetrical stocking-glove distribution with predominantly sensory symptoms subjectively reported by the patient (Gregg et al., 1992; McKeage et al., 2001; Verdu et al., 1989). The next sections will review the pathogenic mechanisms clinical features associated with every group of drugs or isolated agents previously mentioned in this chapter.

## 3. Platinum analogues

The profiles of general toxicity and neurotoxicity differ among the three platinum drugs (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009). Although platinum-based chemotherapies (mainly cisplatin and carboplatin) are a mainstay for the treatment of most solid tumours, their clinical use is severely curtailed by dose-limiting nephro-, oto-, and neurotoxicities (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009). Neurotoxicity induced by platinum agents is characterised by a dose-dependent, cumulative, predominantly painful sensory neuropathy, presenting with symptoms in the distal extremities. These agents are most frequently associated with the development of axonopathy, but platinum-induced neuronopathy may also be observed, especially with higher doses of platinum (McWhinney et al., 2009). Due to the absence of therapies that either cure or prevent platinum-induced CIPN, especially with the advent of newer members of this class of anticancer agents, we need a better understanding of the underlying pathophysiology to develop more-effective therapies or even preventive measures.

Cisplatin, carboplatin, and oxaliplatin differ in solubility, chemical reactivity, oxygenated leaving groups, pharmacokinetics, and toxicology (McKeage, 1995). The leaving groups on each molecule are responsible for the differences in each drug's reactivity with nucleophiles, which is likely to contribute to their differences in toxic profiles (Hah et al., 2006; McWhinney et al., 2009). Despite of these differences, the primary mechanisms involved in their neurotoxicity are likely to be similar.

These agents can enter the DG and peripheral nerves, as opposed to the brain, mainly through passive diffusion, although current data indicate the presence of metal transporters that may also be involved in their entrance into the cell (Krarup-Hansen et al., 1999; Thompson et al., 1984). Current research indicates that after entering the DG cell, these agents will form an adduct with DNA (Cavaletti & Marmiroli et al., 2010). In fact, platinum agents undergo aquation to form a positively charged molecule that interacts with DNA to form crosslinks and finally DNA/platinum adducts (Cavaletti & Marmiroli et al., 2010). These DNA intrastrand adducts and interstrand crosslinks will alter the tertiary structure of DNA leading on the one hand to alterations in cell-cycle kinetics with postmitotic DG neurons trying to reenter the cell cycle and on the other hand to the promotion of apoptosis (Gill & Windebank, 1998).

The level of these compounds in DG neurons at a given cumulative dose has been significantly correlated with the degree of neurotoxicity (Cavaletti et al., 1992; Dzagnidze et al., 2007; Gregg et al., 1992; Meijer et al., 1999). The severity of neurotoxicity, however, involves other factors (Cavaletti et al., 1992; Dzagnidze et al., 2007; Gregg et al., 1992; Meijer

et al., 1999; Verdu et al., 1999). The level of hydrolysis of cisplatin and oxaliplatin differs from that of carboplatin, which is higher. This finding may contribute to the difference in the associated neurotoxic severity patterns (McWhinney et al., 2009). In this way, patients from clinical trials treated with these agents have shown that the severity of neurotoxicity is more commonly seen with cisplatin than with oxaliplatin and is much more severe than that observed with carboplatin (McWhinney et al., 2009).

In the case of cisplatin, the differences in the degree of neurotoxicity could also be associated with the different plasma levels of the intermediary products of the aquation to the process of DNA adduct formation (McWhinney et al., 2009). Although these drugs cause the main cellular damage by the formation of these DNA adducts, additional complexes of covalently crosslinked platinum-DNA-protein have been proposed as another mechanism more specifically studied with cisplatin (Chvalova et al., 2007). These complexes lead to disruption of nuclear metabolism and spatial organization of chromatin, and even inhibit DNA replication and repair (McWhinney et al., 2009). Another suggested underlying mechanism is the involvement of oxidative stress and mitochondrial dysfunction as a trigger of neuronal apoptosis. This process might be mediated by an increased activity of tumour protein p53 and mitochondrial release of cytochrome C (Cavaletti & Marmiroli, 2010).

Even though the exact mechanism of neuronal apoptosis is not fully understood, one proposal has suggested that the machinery of DNA repair is unable to repair the damaged DNA (Gill & Windebank, 1998). Polymorphisms in the DNA-repair genes, including genes for base-excision repair, nucleotide-excision repair, mismatch repair, and double-strand break repair pathways, cause the individuals to be less proficient in repairing carcinogen-induced damage (Cavaletti & Marmiroli, 2010). Moreover, platinum-DNA complexes (Zhu et al., 2005) interfere with the normal function of cellular proteins (i.e. binding or interactions with other proteins), and apoptosis has been observed in DG neurons following treatment with cisplatin, both *in vitro* and *in vivo*, and is correlated with increased platinum-DNA binding in these DG neurons (Cavaletti & Marmiroli, 2010). Finally, all these platinum compounds appear to affect the axons, myelin sheath, neuronal cell body, and the glial structures of the neurons. In support, levels of platinum are significantly higher in the DG than in the brain and spinal cord, which are protected by the blood-brain barrier (Hausheer et al., 2006).

Oxaliplatin and cisplatin differ in their severity of neurotoxicity to the DG, with cisplatin being more neurotoxic. In fact, cisplatin produces about three times more platinum-DNA adducts in the DG than do equimolar doses of oxaliplatin (McWhinney et al., 2009). Acute oxaliplatin neurotoxicity is thought to be caused by transient dysfunction of nodal, axonal, voltage-gated sodium channels, probably owing to an oxalate chelating effect on both calcium and magnesium ions that could interfere with the kinetics of sodium channels (McDonald et al., 2005; Ta et al., 2006). However, the small-conductance  $\text{Ca}^{++}$ -activated  $\text{K}^{+}$  channels, encoded by the SK1-3 genes, are also involved in membrane excitability, playing a role in after-hyperpolarisation at the motor-nerve terminal. Because the SK3 gene is characterised in Caucasians by a highly polymorphic CAG motif within exon 1, SK3 gene polymorphism may influence the development of acute nerve hyperexcitability in oxaliplatin-treated patients. The results of the study by Basso et al. (2011) have suggested that oxaliplatin neurotoxicity may be related to distribution of the polymorphic CAG motif of the SK3 gene, which might modulate nerve after-hyperpolarisation. The allele with 13-14 CAG repeats could mark patients susceptible to acute oxaliplatin neurotoxicity.

The platinum drugs all share the 'coasting' phenomenon, which is an increase in the severity of symptoms for weeks, or even months, following the withdrawal of treatment (Cavaletti & Marmiroli, 2010).

Consequently, CIPN induced by platinum agents is a significant factor affecting the efficacy of the platinum drugs, as patients may experience either more negative side effects than benefits from this drug class or be forced to forego further therapy with an active agent.

### 3.1 Cisplatin

Cisplatin is a widely used chemotherapeutic agent with antitumour activity for a wide range of cancers. Along with its potent anticancer activity, though, cisplatin has also significant toxicities. Cisplatin-induced CIPN is the most common dose-limiting toxic effect. The reported incidence as a single agent ranges from 49-100% depending on the dose, schedule, treatment duration, and the drugs used previously. This toxicity is dose-related and generally appears after cumulative doses in excess of 300 mg/m<sup>2</sup> (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009).

Cisplatin-induced CIPN is first characterised by painful paraesthesias and numbness in symmetrical stocking and glove distribution which typically occurs during the first few drug cycles and is thought to be produced by axonopathy. Sometimes this toxicity can be accompanied by progressively reduced or absent reflexes in the affected extremities. In several cases, loss of vibration sense, paraesthesia, and ataxia can be apparent after several cycles. Motor weakness and other central and autonomic symptoms such as Lhermitte's sign, myelopathy, bilateral jaw pain, and urinary dysfunctions may also appear (Park et al., 2009).

In most patients, neurotoxicity occurs late along the course of treatment, but some patients report an earlier onset of symptoms after the administration of a single dose of cisplatin, especially with doses as high as 100 mg/m<sup>2</sup> or more. The mechanism proposed for this late toxicity is neuronopathy (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009). In both cases, we must remember that all these symptoms can be progressive even after the end of treatment and in many cases are irreversible. Moreover, if cisplatin is used in combination with other drugs such as taxanes or vinca alkaloids, the appearance of neurotoxicity is more likely (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009).

### 3.2 Carboplatin

Neurotoxicity secondary to carboplatin is less frequent (4–6%) (American Society of Health-System Pharmacists, n.d.) than that observed with cisplatin or the third-generation platinum, oxaliplatin (15–60%), and is typically less severe (U.S. Food and Drug Administration, n.d.). Risk of CIPN induced by carboplatin increases in patients older than 65 years and in patients previously treated with cisplatin. Additionally, carboplatin does not cause the loss of hearing that is seen in the majority of patients treated with cisplatin (Chaney et al., 2005; Kartalou & Essigmann, 2001; Wang & Lippard, 2005). Carboplatin-induced CIPN is clinically indistinguishable from that induced by cisplatin, and although reported to be less severe, several studies suggest that the severity may be similar for both drugs.

### 3.3 Oxaliplatin

The more recently developed oxaliplatin has provided a more dramatic reduction of nephro- and ototoxicity than its counterparts (McWhinney et al., 2009). It is structurally different from both cisplatin and carboplatin. The neurotoxicity of oxaliplatin, though, has been described as the most common and dose-limiting toxicity this agent can associate. Oxaliplatin can cause two different types of neurotoxicity.

One type is an acute, transient, dose-related, and painful sensory peripheral neuropathy that is exacerbated by exposure to cold and is very frequent (Becouarn et al., 1998; Gilles-Amar et al., 1999; Grothey, 2003; Grothey & Schomoll, 2001). In fact, at least 90% of patients receiving oxaliplatin will develop symptoms during or soon after its administration, even from the first dose, but the symptoms typically solve within hours to days (Cassidy & Misset, 2002; Gamelin et al., 2002; Giacchetti et al., 2000; Maindrault-Goebel et al., 2001). This acute form consists of paraesthesia, dysaesthesia, and hypoaesthesia in hands, feet, perioral area, or throat and in many cases is precipitated by cold air, cold objects, or cold drinks. Pharyngolaryngeal dysaesthesia is reported by a small number of patients but is very disturbing. It is characterised by a subjective sensation of dyspnea and/or dysphagia accompanied by laryngospasm and stridor (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009). The acute neurotoxicity may appear with notable signs of hyperexcitability similar to an acute myotonia (Hart et al., 1997; Saadati & Saif, 2009). This syndrome is an infrequent condition characterised by the inability to release gripped objects, muscle stiffness, slowed muscle relaxation, increased sweating, and less commonly, paraesthesia. The exact mechanism of myotonia is unknown. It has been postulated that either persistent sodium-channel activity or decreased potassium conductance can be a mechanism for producing axonal hyperexcitability and repetitive discharges in human nerve cells (Hart et al., 1997; Saadati & Saif, 2009; Zielasek et al., 2000). Atypical acute neurotoxicities are sometimes described. One case combined acute motor and sensory hyperexcitability but affected only one hemibody contralateral to the arm of infusion (Uña, 2009). The patient had a history of previous brain ischemic transient attacks, which might have played a role in the atypical presentation of acute neurotoxicity. This asymmetry of symptoms may have been due to the subclinical neurological changes in neurons or axons after ischemia (Uña, 2009).

The second type of neurotoxicity, which is a more chronic, cumulative, sensory form, is persistent and has a gradual onset after multiple exposures to the drug. Although this type of neurotoxicity often decreases with drug discontinuation, it does not disappear (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009). In fact, after stopping the administration of oxaliplatin, the chronic neurotoxicities improve in most patients within 4–6 months and will completely disappear in approximately 40% of patients by 6–8 months. This chronic pattern of sensory neuropathy has been observed in about 50% of patients who received oxaliplatin with infusional 5-FU/LV in a clinical trial but generally appears in approximately 16–21% of patients (Krishnan et al., 2005). It is characterised by paraesthesias, dysaesthesias, and hypoaesthesias that can interfere with ADL (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006; McWhinney et al., 2009).



#### 4. Antitubulins: Taxanes

The two taxanes (paclitaxel and docetaxel) are widely employed in standard anti-neoplastic practice and have demonstrated anticancer activity against many types of malignancies. Although these agents are now well established, they can cause some side effects, including the suppression of bone marrow (mainly neutropenia), hypersensitive reactions, dermal reactions, edema, and neurotoxicity, especially a sensory type that is usually persistent and difficult to manage. This toxicity will usually result in dose modification and changes in the planned treatment with the potential impact to the patient's prognosis.

Taxanes produce a symmetric, axonal, predominantly sensory, distal neuropathy with less prominent motor involvement. The exact mechanism for CIPN induced by taxanes is still unknown. These drugs target the soma of sensory neurons causing direct damage to cells. On the other hand, a process of "dying back", starting from distal nerve endings followed by effects on Schwann cells, neuronal bodies, or axonal transport. Reduced cytoplasmic flow in the affected neurons is the most widely accepted mechanism of taxane neurotoxicity. High concentrations of taxanes in the DG, macrophage activation in both the DG and peripheral nerves, and microglial activation within the spinal cord are other mechanisms that can contribute to the genesis of taxane-induced neuropathy (Cavaletti et al., 1995, 1997, 2000; Persohn et al., 2005). The incidence of this peripheral neuropathy is related to several factors, such as single or cumulative dose per course. Risk factors include treatment schedule, prior or concomitant administration of platinum compounds or vinca alkaloids, age, and pre-existing peripheral neuropathy of other causes.

Therapy based on antitubulin drugs usually induces paraesthesias, numbness, and/or pain in a stocking-and-glove distribution. At a clinical examination, neuropathy would be detected as reduced vibration perception or sense of position, pain and temperature sensation, and impaired deep-tendon reflexes. If the treatment continues, muscular weakness can occur, mostly in foot, finger and ankle extensor muscles. Neuropathic pain, usually restricted to the glabrous skin of the fingertips and toes, can be observed in some patients, and myalgias are common following the administration of taxanes.

##### 4.1 Paclitaxel

Paclitaxel-induced CIPN is a schedule- and dose-dependent, cumulative toxicity, with dose being the most important risk factor for developing CIPN. The standard approved doses and schedule of paclitaxel are 135 and 175 mg/m<sup>2</sup> administered every three weeks over three hours of intravenous infusion. A weekly schedule, though, has gained acceptance and is an increasingly widespread practice. Paclitaxel-induced CIPN has been reported for all schedules or doses, although with weekly schedules, the overall reported CIPN ranged from 59-78%. The speed of the infusion has also been correlated with the severity of CIPN. However, a randomised open-label study of weekly one-hour versus three-hour infusions of paclitaxel (100 mg/m<sup>2</sup>) has shown that differences in the incidence of induced CIPN between the two schedules were not significant. Although this study was small, the findings suggested that the duration of the paclitaxel infusion by itself does not appear to have a significant effect on the incidence or severity of paclitaxel-induced neuropathy. Weekly schedules may allow less time to neurological recovery, which may underlie the higher

incidence of CIPN, probably due to the greater accumulation of paclitaxel in the peripheral nerves and the greater disruption of peripheral axonal transport (Shemesh & Spira, 2010).

This toxicity is manifested by a sensory neuropathy that can associate motor symptoms in some cases. Axonopathies and neuronopathies have also been reported (Lipton et al., 1989; Openshaw et al., 2004; Rowinsky et al., 1990; Salmá et al., 1994). Clinical features are the following: symmetrical, progressive, length-dependent stocking-glove distribution of paraesthesias; numbness; tingling; burning pain; dysaesthesias; or decreased vibration and proprioception. The loss of deep tendon reflexes might be manifested in latter phases. If the patient receives high doses of paclitaxel, the neuropathy can include motor and autonomic dysfunction and even coma and death secondary to an acute and serious encephalopathy. All these symptoms are not completely reversible. Some researchers suggest that Cremophor (polyoxyethylated castor oil), which is a vehicle used to formulate paclitaxel, is responsible for the CIPN (Henningsson et al., 2001; ten Tije et al., 2003). Several lines of evidence, though, do not support this conclusion (New et al., 1996). In fact, paclitaxel by itself is highly neurotoxic and accumulates in mammalian DG cells in culture leading to a disruption of microtubules. On the other hand, several taxanes are formulated without Cremophor and all have induced neuropathy with similar manifestations and severity (Hausheer et al., 2006). Besides all these data, Cremophor has not demonstrated any neurotoxicity in animals. The available evidence thus does support taxane by itself as the neurotoxic agent (Hausheer et al., 2006).

#### 4.2 Docetaxel

Docetaxel is a semisynthetic analogue of paclitaxel with a different profile of toxicity. Its use as an anticancer treatment has spread in recent years. This agent has activity against different tumours as a single agent or in combinations. Docetaxel-induced CIPN is clinically indistinguishable from paclitaxel-induced CIPN. The most neurotoxic dosages are related to schedules exceeding 36 mg/m<sup>2</sup> per week (Fazio et al., 1999; Tankanow, 1998). The manufacturer reports an incidence of CIPN ranging from 20-58%, and various studies have reported that with doses between 75-100 mg/m<sup>2</sup>, the incidence of CIPN varies between 6-59%, being up to 14% in grade 3 and 4 toxicities (Burnstein et al., 2000). Although some studies have suggested a mild neurotoxicity, some patients experience more severe damage and symptoms with cumulative doses over 400 mg/m<sup>2</sup> (Katsumata, 2003; Tankanow, 1998).

#### 4.3 Abraxane

Abraxane is a relatively recent agent approved for anticancer treatment. It is an albumin-stabilised, nanoparticle formulation of paclitaxel designed to overcome poor water solubility and the hypersensitive reactions associated with paclitaxel (Anonymous, 2004). It also has less severe myelo-suppression. When this new taxane appeared data supported a lower neurotoxicity than conventional paclitaxel with Cremophor. The above study showed that Abraxane at a dosage of 260 mg/m<sup>2</sup> by intravenous infusion every 3 weeks produced a significantly higher incidence of severe neurotoxicity than that observed with conventional paclitaxel infused for 3 hours at a dose of 175 mg/m<sup>2</sup>. The

data demonstrated that 10% of patients receiving Abraxane versus 2% with paclitaxel experienced severe CIPN.

### 5. Antitubulins: Epothilones

Epothilones such as ixabepilone are microtubule-targeting anticancer agents. These compounds induce polymerisation of tubulin dimers in microtubules *in vitro* and stabilise preformed microtubules against conditions favouring depolymerisation (Altmann et al., 200; Bollag et al., 1995; Kowalski et al., 1997).

They are very similar to taxanes in their mechanism of anticancer activity and have a common binding site on tubulin, so these two classes of anticancer agents might also share, at least in part, the same mechanism of CPN (Cavaletti & Marmiroli, 2010). Epothilone-induced CIPN is very similar to that induced by taxanes. A considerably faster recovery in patients receiving epothilones is the most important difference between the two types of CIPN (Cavaletti & Marmiroli, 2010).

### 6. Antitubulins: Vinca alkaloids

This group of anticancer compounds includes several agents such as vincristine, vinblastine, vinorelbine, vindesine, and most recently vinflunine (Cavaletti & Marmiroli, 2010). In contrast to taxanes and epothilones, these drugs alter the neuronal cytoskeleton. They prevent the polymerisation of tubulin from soluble dimers into microtubules, leading to a loss of axonal microtubules and alterations in their length, arrangement, and orientation. Finally, Wallerian-like axonal degeneration occurs, and axonal transport is also affected (Lobert et al., 1996; Sahenk et al., 1987; Tanner et al., 1998; Topp et al., 2000). The affinity for tubulin differs among all these agents (decreasing in the following order vincristine, vinblastine, vinorelbine, and vinflunine), with affinity being responsible for the distinct severities of neurotoxicity (Lobert et al., 1996).

Vincristine commonly produces isolated sensory CIPN but may be associated with severe motor neuropathy (Postma et al., 1993). This toxicity is very important and is considered a major dose-limiting side effect. An autonomic neuropathy and demyelination are sometimes manifested (Postma et al., 1993). The dose level and the cumulative dose are the most important factors associated with the development of severe vincristine-induced CIPN. The appearance of this toxicity tends to occur two to three weeks after injection (Hausheer, et al., 2006). The most frequent complaints are sensory symptoms such as symmetrical length-dependent paraesthesias, pain, numbness, or tingling in the hands and feet, but muscle cramps or loss of deep-tendon reflexes may also occur (Quasthoff, s. & Hartung, 2002; Tarlaci, 2008). Other symptoms are postural hypotension or urogenital dysfunction related to autonomic alteration, although the most frequent symptoms of this dysfunction are colicky abdominal pain and constipation (92, 93). Other dysautonomic manifestations are less common (Quasthoff, s. & Hartung, 2002). In fact, sensory symptoms and loss of ankle stretch reflexes (which is due to muscle spindle toxicity) are the earliest and almost universal signs of neuropathy. A study by Pal (1999) showed that the loss of ankle reflex appears at two weeks, and paraesthesia in four to five weeks. By the end of this study, though, the ankle reflex was absent in all patients, sensory signs and symptoms were

present in 75% (impaired vibration detection being the most frequent), and 62.5% presented with constipation.

Weakness in the form of a length-dependent, symmetrical, progressive distal axonopathy is the most common clinical presentation. When this alteration is mild, the patient loses the capacity to walk on the heels, but this neuropathy can become serious enough to render the patient immobile (Hausheer, et al., 2006). Some cases have been also described of vincristine-induced CIPN with neuropathic pain, which are very distressing and painful with very difficult treatments. The study by Park et al. (2010) investigated the antinociceptive effect of memantine and morphine on a vincristine-induced CIPN model in rats. The authors concluded that systemic morphine and memantine have an antinociceptive effect in animal models. These results suggest that both morphine and memantine may be an alternative approach for the treatment of vincristine-induced, peripheral, neuropathic pain. Other experimental studies have also shown beneficial effects of hydroalcoholic extract of *Acorus calamus* comparable to those obtained with pregabalin. The beneficial effects of the extract are attributed to its anti-oxidative, anti-inflammatory, and calcium-inhibitory properties (Muthuraman et al., 2011). Repeated dosages of imipramine have been considered effective after opioid-analgesic, resistant, mechanical allodynia induced by vincristine in rats (Saika et al., 2009).

The use of vincristine and other vinca alkaloids has also been associated with cranial-nerve palsy, a feature not associated with other neurotoxic antineoplastic drugs.

The toxicity induced by vinca alkaloids usually appears after cumulative doses of 6 to 8 mg, and a severe neurotoxicity occurs after a dose of 30 mg (Trobaugh-Lotrario et al., 2003). This fact must be kept in mind in order to stop the treatment before complications arise. During vincristine treatment, sensory symptoms can even precede the clinical evidence of peripheral nerve damage, but impairment of large sensory-fibres is relatively uncommon.

Recovery generally occurs within one to three months after the cessation of treatment, although symptoms can sometimes persist (Hausheer, et al., 2006). Other vinca-alkaloids have fewer incidences of neurotoxicity than does vincristine, with neutropaenia as the most relevant dose-limiting toxicity.

## 7. Bortezomib

Bortezomib is a proteasome inhibitor used as a treatment for multiple myeloma (Mohty et al., 2010). The reported mechanism of action involves the reversible inhibition of the 26S proteasome in mammalian cells. This inhibition prevents the targeted proteolysis that affects multiple, cellular, signalling cascades, leading to cytotoxicity (Hausheer, et al., 2006). This agent can also cause a peripheral neuropathy with a particular profile, which makes it easy to diagnose, although its pathophysiology is not well understood despite many results from experimental studies. The neuropathy may be a class effect of proteasome inhibitors.

In rats, bortezomib induces a significant and dose-dependent reduction in the conduction velocities of sensory nerve fibres, with recovery taking several weeks (Cavaletti et al., 2007). Examination of the sciatic nerve showed mild to moderate pathological changes, involving predominantly the Schwann cells and myelin, although axonal degeneration was also observed (Cavaletti et al., 2007). Bortezomib also induces changes in DG neurons such as

satellite-cell intracytoplasmatic vacuolisation due to damage to mitochondria and the endoplasmic reticulum, resembling the changes described in Schwann cells of the sciatic nerve (Silverman et al., 2006). In animal models, bortezomib interferes with transcription, nuclear processing and transport, and cytoplasmic translation of messenger RNA in DG neurons (Casafont et al., 2010). The final result is widespread damage of myelinated and unmyelinated axons (Bruna et al., 2010; Meregalli et al., 2009,104).

Some studies indicate that mitochondrial and endoplasmic reticulum-mediated dysregulation of calcium plays an important role in the origin of bortezomib-induced neuropathy (Landowski et al., 2005; Montagut et al., 2006). In fact, bortezomib is able to activate the mitochondrial-based apoptotic pathway according to several findings. The mitochondrial uniporter has been identified as a critical determinant of cytotoxicity, which can be mediated by dysregulation of  $Ca^{++}$  homeostasis (Landowski et al., 2005). Moreover, derangement of the neurotrophin network has also been described, since bortezomib inhibits the activation of NF $\kappa$ -B, thereby blocking the transcription of the trophic Nerve Growth Factor (Cavaletti & Nobile-Orazio, 2007; Montagut et al., 2006). In another study, the DG neuronal cell bodies were shown to be the primary target for CIPN induced by proteasome inhibitor-. After proteasome inhibition *in vivo*, chromatolysis followed by cytoplasmic accumulation of eosinophilic material and evidence of neurofilaments and juxtannuclear electron-dense cytoplasmic deposits were observed within the DG neurons (Argyriou et al., 2008; Cavaletti & Nobile-Orazio, 2007). These lesions were attributed to the levels of blood and cellular proteasome inhibition. In addition, Poruchynsky et al. (2008) demonstrated that proteasome inhibitors increase tubulin polymerisation and stabilisation in tissue-culture cells. This finding represents a possible mechanism contributing to neuropathy and cellular toxicity. Finally, neurotoxicity may be triggered by some autoimmune or inflammatory factors. In a large randomised study, administration of bortezomib was associated with the development of CIPN in approximately 37% of patients, with 14% experiencing grade 3 neuropathy (Anonymous, 2005). This toxicity is sensory, but motor symptoms have sometimes been associated. The most common symptoms are a burning sensation, hyperaesthesia or hypoaesthesia, paraesthesias, and neuropathic pain. Dose reductions are considered as good management to improve these symptoms leading to a resolution in most patients (Anonymous, 2005).

## 8. Thalidomide

Thalidomide is an oral immunomodulatory agent used in the treatment of patients with multiple myeloma. Thalidomide-induced CIPN is a common toxicity, sometimes very serious and permanent. The mechanisms of thalidomide-induced CIPN are not well known (Hausheer et al., 2006). Proposals include a reduction in the blood supply to nerves due to thalidomide's anti-angiogenic properties, direct cytotoxic effects on DG neurons, or dysregulation of neurotrophin activity through effects on NF $\kappa$ -B. In fact, alteration in the usual process of Wallerian degeneration due to a reduction in TNF- $\alpha$  and a secondary inhibition of NF $\kappa$ -B have already been described (Mileshkin & Prince, 2006). Studies based on biopsies of sural nerves were performed to elucidate the exact mechanism, showing that Wallerian degeneration and a selective loss of large-diameter fibres without demyelination were lesions underlying this toxicity (Mileshkin & Prince, 2006). A study by Kocer et al. (2009) has suggested that thalidomide-induced CIPN is a dose-dependent, peripheral

neuropathy, mainly localised to the peripheral nerves in a length-dependent manner. Another study has shown that variations in genes involved in a drug's neurotoxicity are likely to influence a patient's risk of developing this adverse effect. In fact, the most significant SNPs (single nucleotide polymorphisms) associated with thalidomide-induced CIPN were seen in the ADME (drug Absorption, Distribution, Metabolism, and Excretion), ABC, cytochrome, and solute-carrier families of genes (Johnson, 2008).

The incidence of thalidomide-induced CIPN is about 30%, often reported as a dose-limiting but not a cumulative problem (Hausheer et al., 2006). This toxicity usually appears after a prolonged period of time receiving this treatment, although some reports have shown that it can occur after a short treatment and sometimes once the treatment has been stopped. The most common symptoms include numbness, tingling, paraesthesias, and/or dysaesthesias with or without sensory loss. They occur in the hands and feet. The symptoms usually do not affect muscle strength, although mild weakness might appear, and deep-tendon reflexes may be reduced or absent. The Lhermitte phenomenon can occur but is very rare.

	Thalidomide	Bortezomib
Incidence	> 70%	< 40%
Grade 1-2	50%	30%
Grade 3-4	20%	<10%
Main type of neuropathy	Mainly sensory	Mainly sensory
Motor signs	Often	Rare
Painful neuropathy	Rare	Often
Risk factors	Prolonged treatment	Unknown
Consequences	Limits doses and duration of treatment	Managed with dose modifications
Reversibility	No	> 50%

Table 3. Characteristics of CIPN induced by bortezomib and thalidomide (Modified from Mohty et al, 2009).

Several studies have attempted to identify the risk factors and/or predictors of the onset, course, or long-term persistence of this neuropathy; the results, however, have been conflicting and, overall, inconclusive (Hausheer et al., 2006; Mohty et al., 2010). Possible risk factors or predictors for a more severe neuropathy include age, sex, comorbidities, changes in the levels of circulating growth factors or other biological markers, pre-existing peripheral neuropathy (about 15% of patients with multiple myeloma have some degree of disease-related peripheral nerve damage before chemotherapy), and previous treatment with potentially neurotoxic antineoplastic drugs (Argyriou et al., 2010; Hausheer et al., 2006; Mohty et al., 2010). None of these factors, though, has been systematically evaluated. Pharmacogenetic studies to evaluate individual susceptibility have failed due to the absence of identified genetic targets. In addition, only a small number of studies have been performed in patients treated with specific classes of neurotoxic antineoplastic agents, and these studies focused exclusively on platinum drugs or taxanes. Controlling and monitoring the patient is very important in order to detect this toxicity as early as possible and to stop treatment immediately to reduce the global damage.

## 9. Diagnosing CIPN

Several types of criteria are used to assess these patients, such as the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), World Health Organization (WHO) guides, Eastern Cooperative Oncology Group (ECOG) scales, Ajani criteria, and quantitative sensory tests (QST) such as vibration-perception threshold (VPT), nerve-conduction velocity tests (NCV), nerve biopsy, or electrophysiologic measurements such as electromyography (EMG), which have usually been applied in combination with neurologic evaluations. However, the assessment of CIPN currently has no gold standard. Many studies have reported that objective assessments of CIPN including neurologic evaluation, QST, electrophysiological testing, and nerve biopsy must be used in an attempt to diagnose and objectively quantify CIPN.

The limitations of these approaches include the lack of standardisation, poor correlation of objective findings with patient-reported symptoms and severity, the additional time and resources consumed during the performance of these tests, and the fact that some are invasive and painful to patients. Also, the expectation that an objective method could reliably diagnose or quantify the severity of a predominantly subjective medical condition may be unreasonable. The clinical assessment of subjective symptoms (assessment of patients) is most commonly and reliably assessed by patient-based questionnaires and scales that have also shown to be convenient for patients and their providers. The use of physician-based methods or objective diagnostic tools seem not to have any clinical advantage in assessing CIPN.

### 9.1 Neurophysiological evaluation

Nerve-conduction studies (NCS) could be effective in studying CIPN in clinical trials (Bird et al., 2006). In fact, they might be crucial in defining as soon as possible the subclinical changes and in assessing the extent of the damage. Moreover, some evidence indicated that an extremely careful neurophysiological evaluation of the peripheral nerves could discriminate between low and high risk of developing severe CIPN, but the validity of this approach has not been confirmed (Lanzani et al., 2008). These methods have more limitations, such as very poor patient compliance due to the high incidence of discomfort during these procedures, and patients not uncommonly withhold consent to NCV repetitions.

Another major limitation of NCS is the measurement of velocity and amplitude in the largest and fastest-conducting nerves fibres and so cannot provide information about small fibres. Furthermore, NCS and nerve biopsies are applied to regions proximal to CIPN distribution, which may at least partially explain the poor correlation and diagnostic usefulness of these two methods. A normal finding in a NCS cannot exclude the presence of neuropathy. Even if the nerve damage is very intense and extensive, the NCV results can be normal because they only reflect the status of surviving fibres. Besides this theoretical advantage of early recognition of subclinical CIPN, neurophysiological examination of the peripheral nerves is the most effective noninvasive method to assess the pathological features underlying nerve damage (that is, demyelination versus axonopathy). Early recognition of the pathogenic mechanism can be relevant in patients with an atypical course of peripheral neuropathy during chemotherapy or also in patients with other neurologic disorders, such as diabetes, that could coexist. In almost all cases of CIPN, the final event occurring in peripheral nerves is an axonopathy with loss of nerve fibres, indicated by

reductions in amplitudes of sensory and compound motor action potentials upon neurophysiological evaluation. In contrast, the hallmark of demyelinating neuropathies is a reduction in the velocity of nerve conduction.

EMG examination of skeletal muscles has rarely been used in the assessment and monitoring of CIPN, possibly because motor impairment is rarely a major feature of CIPN, and needle examination is more invasive than NCS. In addition, EMG scoring and replication are difficult. Somatosensory-evoked potentials have occasionally been used to monitor sensory deterioration in oncologic patients. These studies are mainly used to evaluate preganglionic disorders of nervous system and DG but also postganglionic disorders that could be otherwise evaluated by routine NCS (Hausheer et al., 2006).

Objective measures of assessing CIPN, such as NCS, EMG, nerve biopsy, and detailed neurologic evaluations have not reliably demonstrated their accuracy and are not routinely used to make clinical decisions for managing these patients.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neuralgia (a)	Mild pain	Moderate pain, L-ADL	Severe pain, sc-ADL		
Dysaesthesia (b)	Mild sensory alteration	Moderate sensory alteration; L-ADL	severe sensory alteration; limiting sc-ADL		
Paraesthesia (c)	Mild symptoms	Moderate symptoms; L-ADL	severe symptoms; limiting self-care ADL		
Peripheral motor neuropathy (d)	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; L-ADL	severe symptoms; assistive device indicated sc-ADL	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy (e)	Asymptomatic; loss of deep tendon reflexes or paraesthesias	Moderate symptoms; L-ADL	severe symptoms; sc-ADL	Life-threatening consequences; urgent intervention indicated	Death

(a) Intense, painful sensation along a nerve or group of nerves.

(b) Distortion of sensory perception, resulting in an abnormal and unpleasant feeling.

(c) Functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.

(d) Inflammation or degeneration of the peripheral motor nerves.

(e) Inflammation or degeneration of the peripheral sensory nerves.

Limiting-Activities of Daily Living (L-ADL): preparing meals, shopping, using the telephone, managing money, etc.

Self-care Activities of Daily Living (sc-ADL): bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Table 4. Chemotherapy-induced peripheral neurotoxicity-related terms as reported in National Cancer Institute—Common Toxicity Criteria version 4.03 (NCI-CTCAE v4.03).



## 9.2 Nerve biopsy and histopathological studies

Even though sural nerve biopsy and postmortem examinations of CIPN were very useful in the past, due to most cases being treated with more than one neurotoxic agent and specimens being obtained at different times during or after chemotherapy, the estimation of the impact of these confounding factors or the underlying cancer in these pathological changes was difficult to establish. Consequently, most of the available data on the pathological changes induced by anticancer drugs have been obtained in rodent experimental models (Cavaletti et al., 2008). Generally, except in atypical cases, nerve biopsy in CIPN in clinical practice is not indicated.

Skin biopsy has emerged as an alternative to obtain pathological information in patients with CIPN (Lauria, 2005). It is a minimally invasive procedure that can be repeated in the same patient throughout the course of treatment to measure the density of intra-epidermal fibres. This procedure can be performed very distally and could, therefore, be more sensitive than NCS, particularly in small-fibre neuropathies. Moreover, it allows the investigation of the presence of re-innervation and may provide prognostic information about the long-term course of CIPN, which would be very important. Despite all these potential advantages, skin biopsy is subjectively interpreted, so its value in CIPN evaluation remains to be confirmed.

## 9.3 The role of neuroimaging

The role of neuroimaging in evaluating CIPN is very limited and so is only considered as an adjunct to research in selected patients. Magnetic Resonance Imaging (MRI) might help to demonstrate the involvement of central-nervous pathways and to verify spinal-cord pathological changes induced by cisplatin (Sghirlanzoni et al., 2005) and thalidomide (Giannini et al., 2003) therapies.

## 9.4 Assessment of patients

The reported incidence and prevalence of CIPN vary greatly according to different series due to the different methods of assessment and the large number of anticancer agents and schedules used. In most clinical trials, the appearance and severity of CIPN is evaluated by using Common Toxicity Criteria (CTC) scales created by the National Cancer Institute (NCI) in the USA. The latest version of the CTC scale now used is NCI CTCAE 4.0 (4.0.3 version). This scale, however, has several limitations (Cavaletti & Marmiroli, 2010). The interobserver disagreement (Cavaletti & Marmiroli, 2010) seen with the previous versions and the tendency to underestimate the severity of the CIPN are likely to be compounded, because the scale evaluates the occurrence and severity of sensory and motor CIPN by considering almost exclusively the symptoms reported by the patient, graded with the unspecific terms 'mild', 'moderate' and 'severe', and the subjective evaluation of the impact of these symptoms on the patients' ADL (Postma et al., 1998). This scale also introduces separate definitions to express every symptom, such as dysaesthesia, paraesthesia, etc., instead of just using the generic "peripheral neuropathy". With these data, a formal neurological evaluation would not be necessary to assess the seriousness of a CIPN, although the lack of validation in large groups of oncological patients makes an accurate grading of CIPN difficult. Moreover, an accurate neurological examination is subject to the cooperation of patients and the skills and interpretations of clinicians (Krarup, 1999).

Another limitation of CTC scales is the narrow scoring range that does not allow accurate and fine graduation of the impairment and could result in a so-called ceiling effect. Also the quality of information they provide on the location, type, and severity of functional impairment is poor (Cavaletti et al., 2006). In fact, these scales are unable to establish the pathological changes underlying CIPN and cannot distinguish between different types of fibres affected or sites of neurotoxic target, resulting in evaluations of sensory impairments located in the same region as having the same score (Hausheer et al., 2006). Aiming to overcome all these limitations and to improve CIPN evaluation and monitoring, other clinical scales have been developed with a higher quality of neurological information. These scales are used for specific drugs or classes of agents but are time-consuming, require special training, and have never been formally validated in comparison with CTC scales (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006). Another major issue in patients with cancer is the appearance of neuropathic pain as a symptom of CIPN. In such cases, an accurate distinction between iatrogenic and cancer pain must be made. Different scales have been used to differentiate between these types of pain, but none has been specifically developed for patients with CIPN (Antonacopoulos et al., 2010; Argyriou et al., 2009).

Despite all these limitations, the use of CTC scales to evaluate CIPN has several advantages such as quick administration, easy generalisation to most antineoplastic agents, ease of learning by oncologists, and technical simplicity (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006). The 'patient-oriented' evaluation of symptoms and functional impairment has become an important priority in the assessment of these oncological patients (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006). This approach has become relevant because the number of long-term survivors and the amount of attention being paid to the quality of life of these patients are increasing. This subjective judgment is very important for all patients but mainly for those with intermediate grades of severity of CIPN, and can be used to properly and quickly manage the CIPN to avoid severe grades (Hausheer et al., 2006).

To meet the above objective, several questionnaires and scales based on the patients' perceptions of their QOL and on functional limitations in daily activities have been created to measure the severity of CIPN (Hausheer et al., 2006). The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) and the FACT-Taxane patient-based tools have been studied in patients with CIPN (Cella et al., 2002). These two questionnaires specifically evaluate CIPN and the symptoms related to other neurologic functions such as hearing, sight, etc. These scales, however, do not have a scoring system for establishing the CIPN grade needed for determining the modification of treatment doses or the discontinuation or delay of treatment to avoid severe impairment. The EORTC QIQ-CIPN20 (European Organisation for Research and Treatment of Cancer 20-item module for CIPN) questionnaire is another tool used with the same goal (European Organisation for Research and Treatment of Cancer, 2005). FACT/GOG-Ntx (Cella et al., 2002) and EORTC QIQ-CIPN20 (European Organisation for Research and Treatment of Cancer, 2005) have been described as the most effective tools, but they still need to be formally tested and compared with an objective CIPN evaluation in large oncological series. In recognition of the importance that these questionnaires have gained, the FDA released guidelines in December 2009 for the use of measurements of patient-reported outcomes in the development of medical product to support labelling claims (U.S. Food and Drug Administration, 2009).

### 9.5 Combining methods: Semi-quantitative assessment and composite scales in CIPN

These methods have been commonly used to evaluate neuropathies other than CIPN but have also been used to examine the CIPN, due to the expertise accumulated (Hausheer et al., 2006; Shy et al., 2003). Among the most sensitive neurological signs of CIPN are the impaired vibration sensation and epicritic (two-point discrimination) touch perception (Cavaletti et al., 2004; Hausheer et al., 2006). The semi-quantitative assessment using thresholds of vibrational and thermal perception has only occasionally been used as an endpoint for clinical trials and is rarely used in clinical practice (Forsyth et al., 1997). These methods, though, are not widely used. They are expensive, their results vary according to the device used, the availability of instrumentation is low, and no formal comparisons have been made with accepted clinical scales for most neurotoxic drugs. These methods are also highly influenced by the examiner's training and expertise and by the patients' cooperation, so their actual advantage over careful clinical examination is still being debated (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006).

Combination methods are being used to enhance the possibility of detecting and scoring CIPN and to characterise the type of sensory impairment (Hausheer et al., 2006). These methods include different combinations of clinical evaluation of symptoms and signs of CIPN, neurophysiological examinations, testing threshold of vibration perception, and sometimes the evaluation of QOL and ADL functions (Cavaletti & Marmiroli, 2010).

Composite scales are methods based on clinical aspects and instrumental techniques. In fact, these methods combine the use of neurophysiological and semi-quantitative evaluations (Cavaletti & Marmiroli, 2010). These scales were assumed to be more accurate for evaluating CIPN but have not been validated on a large scale. Regardless, they have gained acceptance with cancer patients (CI-PERINOMS Study Group, 2009). Composite scales allow a thorough investigation of several features of CIPN and its accurate scoring (Cavaletti & Marmiroli, 2010). These scales are thus potentially useful for clinical trials, but the need to perform instrumental examinations makes their use in daily practice difficult. For this reason, some have proposed that only the clinically based segments should be used. Moreover, when these reduced versions were compared to CTC scales, they showed superior effectiveness in CIPN grading. In addition, their use was feasible (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006). Despite this evidence, the Total Neuropathy Score (TNS), the most commonly used composite scale, and its slightly modified versions used to evaluate the neurotoxicity of various chemotherapy agents were not designed to detect and report the occurrence of neuropathic pain in the course of CIPN (Cavaletti et al., 2003).

## 10. Prevention of CIPN

The development of CIPN may deteriorate QOL of cancer patients by interfering with ADL such as dressing, eating, or walking, leading finally to a decrease in physical independence.

Though several agents, such as growth factors, antioxidants, anticonvulsants, and antidepressant agents, have been evaluated as potential chemopreventive compounds, no effective treatment exists for preventing or limiting the occurrence and severity of CIPN (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006).

The ideal CIPN chemopreventive agent should prevent or alleviate CIPN without interfering with chemotherapeutic antitumour activity and with no additional toxicity (Albers et al., 2007; Cavaletti & Marmiroli, 2006; Kannarkat et al., 2007; Toyooka & Fujimura, 2009; Wolf et al., 2008).

Most of the available data on neuroprotectants have been obtained using animal models. The most extensively studied drugs are platinum and anti tubulin agents.

The earliest attempts to prevent CIPN were based on the use of compounds such as amifostine, diethyldithiocarbamate, and BNP7787, which can protect different tissues from toxic agents. Results, however, were conflicting, and the effectiveness of these agents is inconclusive. Indeed, the use of these agents may actually reduce anticancer activity (Masuda et al., 2011; Moore et al., 2003).

### 10.1 Growth factors

Neuron development and survival are supported by several growth factors that interact with cognate receptors expressed by neurons and glial cells (Cavaletti & Marmiroli, 2010).

In the earliest preclinical studies, several members of the neurotrophin family, namely nerve growth factor (NGF), brain-derived neurotrophic factor, and neurotrophin 3, were investigated (Aloe et al., 2000; Gao et al., 1995; Tredici et al., 1999). Leukaemia inhibitory factor, which is a cytokine involved in the differentiation of stem cells and the regeneration of neurons, was tested in a randomised, double-blind, placebo-controlled clinical trial in paclitaxel-treated patients. The results were discouraging without any evidence of neuroprotection (Davis et al., 2005).

NGF has been postulated as an effective protectant against cisplatin CIPN. A randomised prospective study was conducted to evaluate the potential safety and efficacy of subcutaneously administered recombinant human (rh) NGF in 1019 patients with diabetic neuropathy (Apfel et al., 2000). Patients were randomised to receive this product or placebo three times weekly for three consecutive months. Changes from baseline neuropathy were examined and compared between the two treatment groups by quantitative sensory tests: Neuropathy Impairment Score, Neuropathy Symptoms and Change, monofilament test, and NCS. The results showed that rhNGF had no significant benefit compared to a placebo.

The ACTH analogue, Org 2766, is a neurotrophic factor studied for the prevention of CIPN. This agent and NGF promote survival of neurons exposed to neurotoxic chemotherapy (Hovestadt et al., 1992). Org 2766 has shown effectiveness in preventing cisplatin-induced CIPN in animal experiments and in cases of impaired velocity of sensory-nerve conduction. A study by van der Hoop et al. (1990) of patients with ovarian cancer confirmed these findings and showed that Org 2766 had no adverse impact on the efficacy of anticancer treatments. Other studies, though, have claimed that the length of the follow-up period in the above study was too short to detect CIPN development. A more prolonged follow-up of the patients included in the Van der Hoop study failed to demonstrate the expected advantage (Roberts et al., 1997).

Erythropoietin has demonstrated promising results in cisplatin and docetaxel models of CIPN (Bianchi et al., 2007; Cervellini et al., 2010). It is considered as a multifunctional

trophic factor with potent activity during erythropoiesis and with a neurotrophic action on several neural cells in the central and peripheral nervous systems. In fact, erythropoietin's receptor is upregulated after injury to nervous tissue. The use of erythropoietin as a neuroprotectant in oncological practice, however, is currently prevented by concerns of safety, such as embolic adverse events (Dicato & Plawny, 2010). The efforts to establish a neuroprotective agent against cisplatin-induced CIPN have been unsuccessful, therefore randomised controlled clinical trials are needed for candidates that can prevent this debilitating side effect.

## 10.2 Antioxidants

Free radicals and oxidative stress are factors implicated in CIPN, although their effects have not been demonstrated beyond doubt (Carozzi et al., 2010). Nevertheless, several antioxidants, such as glutathione, vitamin E,  $\alpha$ -lipoic acid, and N-acetylcysteine, have been tested as neuroprotectants in different experimental models of CIPN. Due to the tolerability and safety of most of these agents, several have been tested in small clinical trials (Hausheer et al., 2006).

Glutathione and vitamin E have been tested in platinum or taxane treatments, but despite some evidence of activity by these agents, these trials were not adequately powered to offer conclusive evidence of neuroprotection, and their results will require further confirmation (Argyriou et al., 2005; Bove et al., 2001; Cascinu et al., 1995, 2002). Reduced glutathione (GSH) has a high affinity for heavy metals and prevented the accumulation of platinum in the DG (Cascinu et al., 2002; Schmidinger et al., 2000). Several studies with experimental models have shown a preventive role of the administration of GSH in cisplatin-induced CIPN. Moreover, several reports of placebo-controlled trials of GSH to prevent cisplatin and oxaliplatin-induced CIPN have been performed but were underpowered to obtain solid conclusions. In a study by Cascinu et al. (2002) nine of 21 patients in a group treated with GSH and 15 of 19 patients in a placebo group developed oxaliplatin-induced CIPN. The authors used NCI-CTC to assess CIPN with the known interobserver variability, which is considered an important limitation of this study. This study, as previous studies, was too underpowered to obtain a useful conclusion. As a consequence of these data, GSH has not been approved in the US or in most European countries.

## 10.3 Anticonvulsants and antidepressants

The use of anticonvulsant or antidepressant drugs (such as carbamazepine, lamotrigine, gabapentine or pregabalin, and venlafaxine) has also been attempted in patients with cancer, generally in small groups of individuals. The primary endpoint of these studies was a reduction rather than a prevention of the severity of CIPN-associated sensory symptoms and neuropathic pain (Cavaletti & Marmiroli, 2010; Hausheer et al., 2006). Regardless of the aim of the studies, though, the results were not clinically relevant.

Gabapentine has been examined in phase II and III trials to determine its potential role as a treatment for mitigating pain and other symptoms associated with CIPN. None of these studies have detected any significant benefit in reducing intensity of pain or sensory neuropathy (Wong et al., 2005). Gabapentine has been also evaluated as an agent for lowering the incidence and severity of oxaliplatin-induced CIPN, but this drug has failed to

lower either (Mitchell et al., 2005). Carbamazepine antagonises the effect of oxaliplatin in experimental models with rat DG neurons incubated with this anticancer agent (Adelsberger et al., 2000). Oxaliplatin increases the amplitude and duration of compound action potentials and lengthens the refractory period of peripheral nerves, suggesting an interaction with voltage-gated sodium channels. Clinical studies with carbamazepine, though, have given conflicting results for the ability of carbamazepine to prevent oxaliplatin-induced CIPN or mitigate symptoms (Hausheer et al., 2006; Lersh et al., 2002; Wilson et al., 2002). Venlafaxine is an antidepressant with clinical activity against oxaliplatin-induced acute CIPN (Durand et al., 2011). A study by Durand et al. (2011) tested the efficacy of this drug to prevent and relieve oxaliplatin-induced CIPN. From October 2005 to May 2008, 48 patients with oxaliplatin-induced acute CIPN were randomised in a double-blind study to receive either a placebo or 50 mg venlafaxine one hour prior to oxaliplatin infusion followed by an extended release of 37.5 mg venlafaxine twice daily from day 2 to day 11. Neurotoxicity was evaluated using the numeric rating scale (NRS) for pain intensity and experienced relief under treatment, the Neuropathic Pain Symptom Inventory, and the oxaliplatin-specific neurotoxicity scale. The primary endpoint was the percentage of patients with 100% relief under treatment. Twenty of 24 patients in arm A (venlafaxine) and 22 of 24 patients in arm B (placebo) were assessed for neurotoxicity, and based on the NRS, full relief was more frequent in the venlafaxine arm: 31.3% versus 5.3% ( $P = 0.03$ ) without grade 3–4 events (Durand et al., 2011). These findings are very important because this drug has shown clinical activity against the most disturbing and dose-limiting toxicity of oxaliplatin, which is a very common anticancer agent currently used in clinical practice (Durand et al., 2011).

#### 10.4 Amifostine

This product was approved by the FDA in 1996 for reducing the cumulative toxicity of repeated dosages of cisplatin on the kidney. It has been also studied as a potential preventer of CIPN, mainly induced by cisplatin and paclitaxel, but findings were inconsistent. The American Society of Clinical Oncology has developed guidelines for recommending the current clinical use of this agent, although it has generally failed to demonstrate any benefit (Hensley et al., 1999).

A phase II study of patients diagnosed with gynecologic tumours evaluated the potential efficacy of amifostine in the prevention or alleviation of clinically disturbing neuropathy associated with paclitaxel administered every 3 weeks combined with cisplatin (Moore et al., 2003). The baseline and subsequent evaluations were performed with the NCI-CTC scale, the FACT/GOG-Ntx neurotoxicity questionnaire, and the Vibration Perception Threshold (VPT). Twenty-seven patients were evaluated, but the study closed prematurely because the prospectively defined limit for neuropathy was exceeded when four patients developed grade 2–4 CIPN according to the NCI-CTC scale (Moore et al., 2003). Amifostine efficacy was thus insufficient to warrant a phase III clinical trial. Others found that VPT results were less sensitive to detect CIPN than were patients' questionnaires (Moore et al., 2003). One study attempted to evaluate the efficacy of amifostine in preventing CIPN in patients treated with paclitaxel in monotherapy with conventional dosages administered every three weeks or combined with doxorubicin or carboplatin (Leon et al., 2003). Other studies used higher dosages of amifostine (250 mg/m<sup>2</sup> every three weeks) (Gelmon et al., 1999), patients treated

with cisplatin as monotherapy at high dosages ( $120 \text{ mg/m}^2$  every four weeks) (Gradishar et al., 2001), or amifostine combined with docetaxel, but none provided any evidence for a protective or mitigating role of amifostine in CIPN (Makino, 2004).

### 10.5 Glutamine and glutamate

The administration of glutamate has been evaluated for preventing CIPN induced by paclitaxel, cisplatin, and vindesine. Evidence of a neuroprotective efficacy for glutamate with no negative impact on anticancer activity has been demonstrated in rat models, but the mechanism behind these results is unknown (Hausheer et al., 2006). Glutamine has also been evaluated in experimental and clinical studies. A study by Vahdat et al. (2001) reported a reduction in paclitaxel-induced CIPN but no reduction in numbness or paraesthesias in neurophysiologic evaluations. This study, though, had several limitations to clear results, such as small sample size and absence of a placebo-control arm, among others, which rendered definitive conclusions difficult (Hausheer et al., 2006). All these agents should be tested in a double-blind, placebo-controlled, clinical trial.

### 10.6 Tavocept (disodium 2,2'-dithiobisethane sulfonate, BNP7787, dimesna)

Tavocept is an investigational agent designed to prevent and mitigate clinically important toxicities associated with taxane and platinum-type chemotherapeutic agents, including CIPN (Hausheer et al., 1998). The mechanism of action, safety, effectiveness, and potential for tumour protection of this agent have been extensively evaluated using *in vitro* and *in vivo* models (Parker et al., 2010).

Preclinical studies conducted in rat models show that, under the applied experimental conditions, this agent exerts a protective effect against the neurotoxicity induced by multiple administration of cisplatin or paclitaxel (Cavalletti et al., 1999; Hausheer et al., 1999). Studies conducted in human tumour xenografts demonstrated that the agent does not interfere with the efficacy of chemotherapy (Boven et al., 2002). Masuda et al. (2011) conducted a phase I trial of BNP7787 (disodium 2,2'-dithio-bis-ethane sulfonate, Tavocept™) primarily to determine its safety and potential efficacy to prevent and mitigate paclitaxel- and cisplatin-induced toxicities. Twenty-two patients with stage IIIB/IV non-small-cell lung cancer (NSCLC) received BNP7787 alone one week before co-administration of BNP7787 with paclitaxel followed by cisplatin. The authors found that the appropriate dose was  $18.4 \text{ g/m}^2$  of BNP7787, although no dose-limiting toxicity was observed up to  $41.0 \text{ g/m}^2$ . Mild discomfort at the intravenous site, thirst, and nausea were the most common symptoms of toxicity. Co-administration of paclitaxel and cisplatin did not appear to influence the pharmacokinetics of BNP7787 and mesna. In conclusion, the authors recommended a dose for phase II/III studies of  $18.4 \text{ mg/m}^2$  of BNP7787 in combination with paclitaxel and cisplatin. Further studies are warranted to assess whether BNP7787 prevents and mitigates common and serious paclitaxel- and cisplatin-related side effects.

BioNumerik Pharmaceuticals, Inc. and ASKA Pharmaceutical Co. (Tokyo, Japan) have announced the results of a phase III trial of this agent in patients with advanced NSCLC. The results indicated no statistically significant benefit in preventing or reducing the severity of CIPN (primary endpoint). This study was a multicentre, double-blind, randomised, placebo-controlled phase III trial, conducted by ASKA in Japan, and included

182 patients who received the chemotherapeutic drugs paclitaxel and cisplatin as first-line therapy for advanced NSCLC every 3 weeks. The number of patients reporting either severe sporadic or cumulative neuropathy was approximately 50% lower in the Tavocept arm, compared with placebo, according to BioNumerik, but this result did not reach statistical significance ( $P = .1565$ ). BioNumerik and ASKA believe the lack of statistical significance is likely due to the relatively small size of the trial. A surprising observation was an increase in median survival of approximately 40 days for patients receiving Tavocept, compared with the placebo group. For patients with adenocarcinoma, the median survival was increased by approximately 138 days in the Tavocept patients, compared with the placebo group. These findings are very encouraging, but more studies are needed to obtain confident conclusions.

#### 10.7 Calcium and magnesium infusions for acute oxaliplatin neuropathy

Infusions of calcium and magnesium have been studied for the management of the acute form of oxaliplatin-induced peripheral neuropathy. A study by Gamelin et al. (2002) on patients diagnosed with advanced colorectal cancer tested the efficacy of calcium/magnesium infusions in patients treated with oxaliplatin. Sixty-three patients were treated and received 1 g calcium gluconate and 1 g magnesium sulfate before and after administration of oxaliplatin, and 38 patients did not receive these treatments. Patients treated with infusions of calcium and magnesium achieved a higher cumulative dose of oxaliplatin, had fewer treatment discontinuations due to CIPN (5% versus 56%), had a lower incidence of CIPN of any grade (27% versus 75%), had a lower incidence of laryngopharyngeal dysaesthesia, and were more likely to endure the treatment compared to the other population. All these positive effects were presented without an adverse impact on anticancer activity.

The N04C7 trial prospectively evaluated the activity of intravenous calcium and magnesium as neuroprotectant agents against cumulative oxaliplatin-related sensory neurotoxicity. Patients with colon cancer undergoing adjuvant therapy with FOLFOX were randomised to intravenous calcium and magnesium treatment (1g calcium gluconate plus 1g magnesium sulfate pre- and post-oxaliplatin) or a placebo in a double-blinded manner. The study was closed in view of preliminary reports from another trial suggesting that calcium and magnesium decreased the efficacy of anticancer treatment (Hochster et al., 2007). Despite the early discontinuation, this study demonstrated the activity of these agents as neuroprotectants against oxaliplatin-induced CIPN in adjuvant colon cancer. Before considering these infusions as standard components of oxaliplatin-based chemotherapies, further studies will be needed to refute the notion that these agents decrease the efficacy of anticancer therapies (Grothey et al., 2011; Nikcevich et al., 2008). In contrast to the previous study, a study by Gamelin et al. (2004) found no differences in objective response rate or in progression-free or overall survival. They also found a significantly lower frequency and severity of oxaliplatin neurotoxicity. The authors continue to propose infusions of calcium and magnesium for reducing oxaliplatin neurotoxicity in FOLFOX regimens, provided that the compounds are delivered sequentially and not concurrently. The temptation to reduce the frequency of infusions for outpatients could lead to the administration of some compounds at the same time and in the same delivery apparatus, which could lead to lower drug stability and thus reduced activity.



### 10.8 Xaliproden

Xaliproden is a non-peptidic neurotrophic drug that has recently been used in oxaliplatin-treated patients experiencing CIPN. This drug acts as a 5HT<sub>1A</sub> agonist. It has neurotrophic and neuroprotective effects *in vitro* (Appert-Collin et al., 2005; Duong et al., 1999; Labie et al., 1999) and has been proposed for use in the treatment of several neurodegenerative conditions, including amyotrophic lateral sclerosis (Meininger et al., 2004) and Alzheimer's disease (Lemaire et al., 2002).

Xaliproden remains under investigation for treatment of CIPN (Susman, 2006; Wolf et al., 2008). Researchers from Scotland recently conducted a phase III clinical trial to evaluate xaliproden for the prevention of oxaliplatin-associated CIPN. They have reported that xaliproden (SR57746A) reduces the risk of grade 3-4 and incidence of oxaliplatin-induced CIPN in patients with colorectal cancer (Cassidy et al., 2006).

### 10.9 Acetyl-L-carnitine

Acetyl-L-carnitine (ALC) is an additional intervention method used to treat CIPN. A study by Flatters et al. (2006) examined the potential efficacy of ALC to prevent and treat pain induced by paclitaxel. Rats received intraperitoneal injections of paclitaxel with daily administration of ALC. Authors concluded that the association of ALC prevented the development of paclitaxel-induced pain. This effect lasted for at least three weeks after the last dose of ALC. In a separate experiment, daily administration of ALC to rats with established paclitaxel-induced pain produced an analgesic effect which was quickly dissipated after ALC treatment was withdrawn.

### 10.10 Others

Other compounds with different mechanisms of action, such as carboxypeptidase II inhibitors or calpain inhibitors, have been investigated in preclinical and clinical studies, although their routine use in clinical practice has not been well established (Cavaletti & Marmiroli, 2010). Nimodipine, a calcium-channel antagonist, has been evaluated in conjunction with cisplatin, but the trial stopped prematurely due to significantly increased gastrointestinal toxicity (McWhinney et al., 2009). A cytokine called LIF, or leukaemia-inhibiting factor, was shown to have a role in diminishing peripheral neurotoxicity in animal models, but this effect was not confirmed in clinical samples.

## 11. Future

While the pharmaceutical research industry attempts to discover new, less-neurotoxic analogues of the currently available drugs (such as the thalidomide derivative Lenalidomide) (Cundari & Cavaletti, 2009), treatment modification or withdrawal are the only options currently available to oncologists for reducing neuropathy. Such a limited choice is a worrying issue since symptomatic treatment of CIPN is largely ineffective, particularly on long-lasting or permanent symptoms and signs of impairment that are frequent in platinum- or taxane-treated patients. The unfavourable outcome of CIPN is indeed becoming more worrying due to the increasing incidence of long-term cancer survival. This fact makes patient QOL a key concern since the potential effects of CIPN on

the lives of these people can be devastating. Close monitoring of individuals for early signs of CIPN will improve the long-term neurologic al outcome, highlighting the importance of early recognition that should be achievable through a close collaboration between oncologists and neurologists. With improved long-term survival, however, comes the importance of addressing QOL issues.

### 11.1 Markers of neurotoxicity

In addition to efforts to identify a successful neuroprotective agent, several studies have attempted to establish the role of various phenotypic markers for CIPN. An accurate marker of neurotoxicity that would enable a quantitative monitoring of the progress of neurotoxicity or provide a prediction of the ultimate severity would prove valuable in controlling this toxicity.

Cavaletti et al. (2004) indicated a highly significant correlation between the decrease in circulating levels of nerve growth factor (NGF) and the severity of CIPN in patients treated with cisplatin and paclitaxel. The correlation, however, did not predict final neurological outcome. In addition, nerve electrophysiological studies have been used to detect the progression of CIPN. Further studies to evaluate the effectiveness of both blood markers and electrophysiology in the detection of neurotoxic progression, though, must be performed to conclude that these provide any sufficient benefit to the patient.

The most recent step in this research is the introduction of genome-wide studies, which are an effective tool for identifying specific regions of the genome that are associated with either drug response or drug toxicity. This research could enhance the identification of putative candidate genes and ultimately the particular genomic signatures related to a drug response and the development of toxicity (Potti et al., 2006). Moreover, genome-wide studies of polymorphisms describe variability between individuals and associate these with response and toxicity. All these efforts are needed to determine genetic linkages as a cause of platinum-based toxicity and the toxicities of other anticancer treatments. Ultimately, the goal is to diminish these effects and increase the beneficial antitumour therapies (Mileshkin et al., 2006).

## 12. Conclusions

CIPN is a common and very serious toxicity secondary to several anticancer agents that presents diagnostic and therapeutic challenges. This distressing complication interferes with the QOL of patients, with the administration of anticancer treatments, and subsequently with prognoses. Thus, much remains to be done to know better understand the pathogenic mechanisms, clinical features, and the best tools for measuring the severity of neuropathic toxicity. The present situation is very unsatisfactory. Improving our understanding of CIPN is a difficult but achievable goal requiring an effective, open-minded collaborative network of neurologists and medical oncologists to focus on this severe adverse effect of anticancer agents.

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