

# Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention

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Peripheral neuropathies induced by chemotherapy (CIPN) are an increasingly frequent problem. Contrary to hematologic adverse effects, which can be treated with hematopoietic growth factors, neither prophylaxis nor specific treatment is available, and only symptomatic treatment can be offered. Neurotoxic drugs are becoming a major dose-limiting factor. The epidemiology is still unclear. Several drug-dependent pathogenetic mechanisms exist. CIPN are predominately sensory, length-dependent neuropathies that develop after a typical cumulative dose. Usually, the appearance of CIPN is dose dependent, although in at least 2 drugs (oxaliplatin and taxanes), immediate toxic effects occur. The most frequent substances causing CIPN are platin compounds, vinka alkaloids, taxanes, and bortezomib and thalidomide. The role of synergistic neurotoxicity caused by previously given chemotherapies and concomitant chemotherapies and the role pre-existent neuropathy on the development of a CIPN is not clear. As the number of long-term cancer survivors increases and a new focus on long-term effects of chemotherapy-induced neuropathies emerge, concepts of rehabilitation need to be implemented to improve the patients' functions and quality of life.

**Keywords:** cancer treatment, chemotherapy induced neuropathy, long-term effects, neurotoxicity.

Anticancer drug-induced peripheral neurotoxicities (CIPNs) are predominately sensory, length-dependent neuropathies that develop after a cumulative dose. Rarely, motor, autonomic, or cranial nerve involvement occurs. Typically, the appearance of CIPN is dose dependent, although in at least 2 drugs, immediate effects appear. The most frequent substances

causing CIPN are vinca alkaloids, taxanes, platin derivatives, and bortezomib and thalidomide. Little is known about synergistic neurotoxicity caused by previously given or concomitant chemotherapies. Although the individual biological effects of all neurotoxic substance classes is known, the precise mode of action on the peripheral nerves is not always clear. Many efforts have to be made to develop strategies of prevention and treatment of CIPN. As the number of long-term cancer survivors increases, long-term effects are becoming important.

## Epidemiology

The epidemiology of anticancer drug-induced peripheral neurotoxicity (CIPN) is still unclear.<sup>1</sup> Several confounding factors and also improper assessment play a role, and data obtained from oncology clinical trials must be carefully evaluated. Platinum drugs are frequently associated with CIPN. Literature data suggest that a threshold for the earliest signs of cisplatin-induced CIPN is 250–350 mg/m<sup>2</sup>,<sup>2</sup> with increasing incidence and severity with higher doses.<sup>3</sup> Cisplatin liposomal formulation (lipoplatin) and carboplatin seem to be less neurotoxic. The presence of other known risk factors for CIPN (e.g., alcohol consumption, diabetes, high serum creatinine levels, or age) has not been demonstrated to remarkably influence the incidence and severity of cisplatin-induced CIPN.<sup>4</sup>

Oxaliplatin presents 2 different clinical features. Acute, transient, cold-related paresthesias; jaw spasms; and cramps occur in virtually all the patients but are reversible. CIPN is frequently persistent and dose-dependent, with a threshold dose of 500–600 mg/m<sup>2</sup>.<sup>5</sup> Predictors for severe chronic oxaliplatin-induced CIPN have been suggested.<sup>6</sup>

The toxicity profile of the different antitubulins is different in clinical presentation, incidence, severity, and

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outcome. Vincristine is the most neurotoxic. The severity of vincristine-induced CIPN is dose-related, ensuing in most patients after the administration of 4 mg/m<sup>2</sup> of the drug. Sensory signs are the earliest; with doses >6–8 mg/m<sup>2</sup>, distal motor weakness is not uncommon,<sup>7</sup> as well as neuropathic pain<sup>8</sup> and autonomic dysfunction.<sup>9</sup> Vinblastine, vinflunine, and vinorelbine are less neurotoxic.

Taxanes and epothilones act on the cytoskeleton by enhancing tubulin polymeration. Among taxanes, paclitaxel is slightly more neurotoxic than is docetaxel.<sup>10</sup> The neurotoxic threshold is around 1000 mg/m<sup>2</sup> for paclitaxel and 400 mg/m<sup>2</sup> for docetaxel.<sup>11</sup> The risk of developing severe taxane-induced CIPN is related to treatment interval. The use of an albumin-bound paclitaxel formulation (abraxane) seems to be less neurotoxic.<sup>12</sup>

The number of subjects treated with epothilones is relatively small, and most of them were exposed to ixabepilone. In these studies, the incidence of clinically relevant sensory neuropathy was variable, from 6% to 71%.<sup>13</sup>

The thalidomide dose and incidence of CIPN have been reported, with studies evidencing a cumulative dose relationship.<sup>14</sup> The thalidomide analogs lenalidomide and pomalidomide are less neurotoxic. Bortezomib, a proteasome inhibitor, is used in multiple myeloma treatment. Sometimes bortezomib is used in combination chemotherapy with thalidomide, with a possible cumulative effect of CIPN.<sup>15</sup> Bortezomib-induced CIPN occurs in about half of the patients receiving treatment with this drug,<sup>16</sup> and the cumulative dose of bortezomib has been associated with an increased severity. Several risk factors include pre-existing neuropathy, age, and comorbidities.

The use of biological agents has also been occasionally associated with CIPN. An example is brentuximab vedotin (Adcetris) which can be associated with mild, mostly non-clinically relevant sensory neuropathy.<sup>17</sup>

## Pathogenesis

The dorsal root ganglia (DRG) are the main target of platinum drug-induced CIPN.<sup>18</sup> Although most of the presented results were obtained in cisplatin models, it is likely that the pathophysiology of chronic CIPN induced by carboplatin and oxaliplatin is similar.<sup>19</sup> The body of the experimental evidence points toward 2 different putative mechanisms, not necessarily mutually exclusive, because both can eventually produce DRG neuron apoptosis: (i) the formation of platinum intra-strand adducts and inter-strand crosslinks, which influence the tertiary structure of the nuclear DNA,<sup>20</sup> altering cell-cycle kinetics,<sup>21</sup> and (ii) the interaction with mitochondrial DNA, leading to oxidative stress<sup>22</sup> and, possibly, to p53 increased activity and mitochondrial release of cytochrome-c pathway, independent of fas receptor activation,<sup>23</sup> as well as activation of p38 and ERK1/2.<sup>24</sup> These mechanisms do not explain the acute, transient symptoms induced by oxaliplatin that have been reported to be secondary to oxalate-induced

dysfunction of nodal axonal voltage-gated Na<sup>+</sup> channels.<sup>25</sup> The affinity for tubulin among vinca alkaloid compounds has been linked to their variable neurotoxicity.<sup>26</sup> Vinca alkaloids exert their antineoplastic effect by inhibiting microtubule dynamics, and this may lead to loss of axonal microtubules and alteration in their structure, causing axonopathy through axonal transport impairment.<sup>27</sup> Taxanes and epothilones share several fundamental characteristics. Perturbation of axonal transport secondary to excessive tubulin polymeration has been advocated to explain the neurotoxicity of taxanes and epothilones.<sup>28</sup> Pathologic changes in DRG neuron cellular bodies have also been described.<sup>29</sup> The exact mechanisms of the neurotoxic effects of thalidomide are not known. It is likely that the anticancer and the neurotoxic effects of thalidomide are secondary to ≥1 of the several species-specific enzymatic and non-enzymatic hydrolysis products from its metabolism.<sup>30</sup>

The established mechanism in bortezomib that is responsible for its anticancer activity (i.e., inhibition of the 20S proteasome) has not yet been firmly linked to the pathogenesis of CIPN. Experimental evidence suggests that the drug acts both on the DRG and on the peripheral nerves, with interference with transcription, nuclear processing, and cytoplasmic translation of mRNAs in DRG neurons,<sup>31</sup> leading to damage of large and C-fibers with abnormal vesicular inclusion body in unmyelinated axons.<sup>32</sup> Other effects, including mitochondrial and endoplasmic reticulum damage and activation of the mitochondrial-based apoptotic pathway, have also been proposed.<sup>33</sup> New experimental approaches to reveal the pathogenesis of antineoplastic drug-induced CIPN have been intended. Among them, the use of pharmacogenetic studies has been considered to be a reliable tool.

Most of the studies reported were based on the hypothesis that the same genes relevant in the treatment of cancer cells might be similarly relevant also for neurotoxicity. This is an unproven assumption that led to focus the investigation mostly of key genes for intracellular detoxication, DNA repair, and drug cellular influx or efflux. Glutathione S-transferase-1 (GST1) is one of the most important oxidative stress agent scavengers, acting by catalyzing the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione and has been examined in oxaliplatin-treated patients. GSTP1 Ile105Val single nucleotide polymorphism (SNP) has been targeted by >20 trials, which reported a positive correlation with CIPN in about half of the studies. Other oxidative stress scavengers, such as glutathione S-transferase M1 and M3 (GSTM1 and GSTM3), were investigated, with negative results.

Another mechanism investigated by pharmacogenetic studies is DNA repair. Among the possible genes, most of the studies focused on excision repair cross-complementing group 1 (ERCC1) gene. ERCC1 Asn118Asn SNP was investigated, but despite the earliest results indicating a positive correlation, all the subsequent confirmatory studies failed to disclose any significant relationship with the course or severity of CIPN. Similar conflicting associations were reported

for alanine-glyoxylate aminotransferase (AGXT) Ile340Met and Pro11Leu SNPs, for ATP-binding cassette sub-family B member 1 Ala893Ser/Thr SNP, and for different cytochrome P4502C8 and cytochrome P4503A5 polymorphisms in platinum drug- and/or taxane-treated patients. The only study that also included neurological examinations investigated integrin B3 (an integral cell-surface protein known to participate in cell adhesion and in cell surface-mediated signaling) Leu33Pro polymorphism in a small series of oxaliplatin-treated patients with colorectal cancer, reporting a marginal association of the T/T genotype with more severe toxicity ( $P = .044$ ).<sup>34</sup>

In patients with myeloma, thousands of SNPs have been investigated using high throughput systems applied to DNA specimens to assess their value in the prediction of disease outcome and subsequently re-analyzed for CIPN occurrence and severity. These patients were treated with different chemotherapy schedules, based on bortezomib, thalidomide, and/or vincristine. Associations were found with different genes in each trial, thus raising doubts of the reliability of the results.<sup>35</sup>

## Symptoms, Signs, and Investigations

### *Clinical Symptoms*

Most chemotherapy-induced neuropathies are sensory. Tingling or numbness in the feet or fingers is often an early sign. Patients report various positive sensory symptoms including paresthesia; dysesthesia; tingling; itching; and burning, tight, stabbing, sharp (lightning like), or aching pain. Sensory loss in the feet and legs can cause sensory ataxia and gait disorders. Loss of dexterity in the hands is often perceived as “clumsiness”. Some patients report Lhermitte’s phenomenon. Pruritus, Raynaud’s phenomenon, and muscle pain are less frequent. Myalgias have been described with gemcitabine and taxane therapies. Smell and taste abnormalities have been reported with platinum compounds; vestibular dysfunction and hearing loss occur.

Examination reveals diminished sensory perception for touch, pinprick, and vibration. Reflexes, especially at the ankles, are often absent. Testing sensation with Semmes Weinstein monofilaments is useful. Tests of coordination, such as finger to nose, knee to shin, and Romberg test may become abnormal when proprioceptive sensation is diminished. Stereotactic recognition of traced figures, coins, and keys may be helpful.

Vinca alkaloids may cause distal weakness, including foot drop. Bortezomib for the treatment of myeloma may cause weakness in some patients. Autonomic signs are rare but can be seen in vinca alkaloids, taxanes, and platinum compounds. Several drugs cause muscle cramps or weakness.<sup>36</sup> Raynaud’s syndrome has been observed in long-term survivors of testicular cancer.<sup>37</sup>

### *Scales and Quality of Life*

The evaluation by scales and scores of CIPN is an important issue that goes beyond the common National Cancer Institute toxicity scale (NCI-CTC). A progress was the use of the total neuropathy score,<sup>38</sup> and a careful analysis of instruments has been done by Perinoms et al.<sup>39</sup> Increasingly, quality of life instruments are used as CIPN 20<sup>40</sup> and the FACT/GOG-Ntx.<sup>41</sup>

## Diagnosis

### *Nerve Conduction Velocities (NCV)*

Measurement of sensory and motor nerve conduction velocity (NCV), sensory nerve action potential (SNAP), and compound muscle action potential (CMAP) together with needle electromyography (EMG) are standard neurophysiological tests used. Diminished amplitude of SNAP NCV is thought to reflect axonal loss from sensory nerves. The correlation of changes in NCV with clinical findings has caveats: It is weaker (i) in drugs affecting the DRG, such as platinum derivatives, and (ii) when small sensory fibers are involved.

### *Skin Biopsy*

The role of skin biopsy in CIPN is evolving.<sup>42</sup>

### *Nerve Biopsy*

Sural or other whole nerve biopsies are rarely indicated in the evaluation of CIPN.

### *Clinical Course and Development*

Most CIPNs are length- and dose-dependent neuropathies (Table 1). Symptoms commonly begin after 3 or 4 cycles. For some drugs, there is an apparent slowing of progression after the fourth or fifth cycle.<sup>43</sup>

## General Phenomena

### *Factors Predisposing to CIPN*

Preexisting neuropathy, such as diabetes mellitus, alcohol, or inherited neuropathies, may predispose to more severe neuropathy. Age-related axonal loss may also predispose to more severe symptoms from CIPN. Prior chemotherapy can also be predisposing towards CIPN.<sup>44</sup>

### *Coasting*

Coasting is a phenomenon particularly associated with the use of cis- and oxaliplatin. It is less common with carboplatin.

**Table 1.** Cumulative doses

Drug	Cumulative dose	Large series	Acute effects	Other effects
Cisplatin	300–400 mg/m <sup>2</sup>	+		Coasting
Carboplatin	600 mg/m <sup>2</sup>	+		
Oxaliplatin	800 mg/m <sup>2</sup>	Acute toxicity more often described than cumulative	Acute toxicity	
Ifosfamide	?			Painful
Gemcitabine	?			Myalgia
Vincristine	5–15 mg/m <sup>2</sup>	+		CN, mononeuropathies, autonomic, muscle
Paclitaxel	200 mg/m <sup>2</sup>	+	Acute toxicity likely	Myalgia, Myopathy
Docetaxel	400–600 mg/m <sup>2</sup>	+	?	
Bortezomib	1–1,3 mg/m <sup>2</sup>	+		Painful, rarely demyelinating
Thalidomide	20 g (total)	+		

Cumulative dose per m<sup>2</sup> associated with CIPN is known for a number of drugs from studies of large series of patients. Two drugs (paclitaxel and oxaliplatin) are associated with acute symptoms.

### Reversibility and Long-Term Effects

The reversibility of CIPN is increasingly becoming important, as active chemotherapies prolong survival and the number of long-term cancer survivors increases steadily. Although there are few long-term studies, it must be assumed that CIPN is not always completely reversible.

## Drugs Commonly Associated with CIPN

### 1.1 Platinum derivatives

Three members of the drug family are currently used: cisplatin, carboplatin (mainly in lung, breast, and ovarian cancer), and oxaliplatin (in metastatic colon cancer and other gastrointestinal malignancies).

#### Clinical Features of Platinum Derivates

##### 1.1.1 Cisplatinum

CIPN is closely related to total cumulative drug dose for cisplatin.<sup>45</sup> The neuropathy is predominantly sensory, with initial complaints of numbness or paresthesias in the distal parts of the extremities. Loss of large fiber sensory function with sensory ataxia is common. Lhermitte's phenomenon can occur. Coasting is a unique feature. Many patients experience residual neuropathic pain after improvement in their neuropathy. Ototoxicity can result in hearing loss and dizziness.

##### 1.1.2 Carboplatin

Carboplatin is less neurotoxic.<sup>46</sup> In higher cumulative doses, however, carboplatin also produces a sensory neuropathy similar to that of cisplatin. Overall, 40% of patients receiving cisplatin and taxol develop CIPN.<sup>47</sup>

### 1.1.3 Oxaliplatin

In addition to the cumulative dose-dependent neuropathy, about 80% of patients develop cold-induced paresthesiae and dysesthesiae in the throat, mouth, face, and hands. The symptoms settle a few days after the infusion is completed. Oxcarbazepine has been shown to be modestly effective in prophylaxis against the transient symptoms.<sup>48</sup> The dose-related sensory neurotoxicity resembles cisplatin-induced neuropathy.

#### Laboratory studies

Platinum compounds predominantly cause reduction or loss of SNAP.

**1.2 Other alkylating agents** such as nitrosoureas, procarbazine, and thiotepa, are generally not associated with CIPN, except for ifosfamide, in which neuropathy occurs in about 8%.<sup>49</sup> The onset is gradual with paresthesias and pain in the feet. Neuropathic pain can occur.

### 1.3 Cytotoxic antibiotics

Several antibiotics have antineoplastic effects, the most prominent being doxorubicin, which is widely used in a variety of chemotherapy regimens. Although it affects dorsal root ganglion neurons in culture models, it does not produce CIPN in humans.

### 1.4 Mitotic spindle inhibitors

Drugs affecting microtubule structure induce apoptosis in cancer cells by disrupting mitotic spindle formation. Microtubules are essential for axonal transport. Disruption of structure or function of microtubules results in axonal injury and CIPN.

#### 1.4.1 Vinca alkaloids

Vinca alkaloids produce a dose-related sensorimotor neuropathy. Vincristine and vindesine have more

severe neurotoxicity than do vinblastine and vinorelbine. The combination of vinorelbine with taxanes in patients previously treated with paclitaxel has been reported to induce severe CIPN.<sup>50</sup>

### Clinical features

Early symptoms are painful paresthesias and pain in the hands and feet. Weakness can occur in wrist extensors and dorsiflexors of the toes.<sup>51</sup> Autonomic changes can result in gastrointestinal symptoms, including paralytic ileus and bladder atony, impotence, orthostatic hypotension, and cardiac problems.

### Laboratory studies

Nerve conduction studies show axonal neuropathy with reduced amplitude of motor and sensory action potentials with mildly reduced conduction velocities.

### Prognosis and treatment

There are no pharmacologic treatments to reduce or prevent CIPN induced by the vinca alkaloids. A decreased risk of neuropathy and a more rapid recovery may exist in African Americans with at least 1 CYP3A5\*1 allele.<sup>52</sup>

## 1.5 Taxanes

Both paclitaxel (taxol) and docetaxel (taxotere) are widely used alone and in combination with other agents for the treatment of breast, ovary, lung, and other forms of cancer. Paclitaxel can produce a more severe neuropathy than docetaxel.<sup>53</sup>

### Clinical features

Sensory symptoms are common and dose related<sup>54</sup>. Both drugs induce paresthesiae, loss of sensation, and dysesthetic pain in the feet and hands. Gait unsteadiness may result from proprioceptive sensory loss. Weakness is absent or mild, although a motor neuropathy can occur.<sup>55</sup> Treatment with taxanes can result proximal weakness. CK is normal and the weakness improves after cessation of therapy. Myalgia/arthritis can occur with paclitaxel.

### Laboratory studies

Electrophysiological testing demonstrates that sural nerve potentials are reduced or absent.

### Prognosis and treatment

The sensory symptoms can be troublesome but often remit within several weeks after treatment. However long-term follow-up examinations describe a prolonged

effect of CIPN in some individuals, with a negative effect on their quality of life.<sup>56</sup>

## 1.6 Epothilones

Epothilones include epothilone A, epothilone B,<sup>35</sup> and epothilone D. In phase III clinical trials, they have been reported to produce a distal sensory and motor neuropathy, similar to the taxanes.<sup>57</sup>

**1.7 Eribulin** (eribulin mesylate) is a non-taxane microtubule dynamics inhibitor with tubulin-based anti-mitotic activity. It is used in the treatment of patients with locally advanced or metastatic breast cancer.<sup>58</sup> Peripheral neuropathy can occur.

## 1.8 Proteasome Inhibitors

Bortezomid is a polycyclic derivative of boronic acid that inhibits the mammalian 26S proteasome. In addition, the secretion of cytokines in the bone marrow is suppressed. It also enhances oxidative stress by upregulation. Carfilzomib is a new proteasome inhibitor in clinical trial with reportedly fewer neurotoxic adverse effects.<sup>59</sup>

### Clinical features

The neuropathy is dose related and cumulative. It is predominantly sensory, distally accentuated, and length dependent. It often causes neuropathic pain, probably because of small fiber involvement. Autonomic changes with postural hypotension occur. Increased age is a risk factor. CIPN occurs in 37%–44% of patients with multiple myeloma.

### Laboratory studies

Electrophysiological changes demonstrate axonal loss.

## 1.9 Thalidomide and Lenalodimide

Thalidomide has been used in the treatment of multiple myeloma, Waldenström's macroglobulinemia, myelodysplastic syndromes, acute myeloid leukemia, and several other cancer types. It is a potent VEGF inhibitor.

The neuropathy is predominantly sensory. The neuropathy develops in 20%–40% of patients.<sup>60</sup> The frequency of neuropathy increases with age and the cumulative dose.<sup>61</sup> Lenalodimide (alpha-3-amino-phthalimidoglutaramide) is an analogue of thalidomide that seems to be less neurotoxic.

## 1.10 Suramin

Suramin is a polysulfonated naphthylurea. It has been used experimentally as a cancer chemotherapeutic agent. It causes nephropathy and peripheral neuropathy. Two types of CIPN have been described: a mild distal

axonal neuropathy and an acute form resembling an acute polyradiculoneuropathy.<sup>62</sup>

### Drugs Less Commonly or not Associated with CIPN

Podophyllins are both spindle and topoisomerase inhibitors. Etoposide (VP 16) and teniposide (VM 26) are chemotherapy agents derived from podophyllin. Peripheral toxicity occurs occasionally.

Antimetabolites are compounds that inhibit synthesis of key intermediary metabolites. Most of the antimetabolites are either analogs of nucleotide bases or interfere with folic acid metabolism.

Methotrexate (MTX) is a folate antagonist that inhibits dihydrofolate reductase. It is used alone or in combination chemotherapy for solid tumors and hematological malignancies. Peripheral neurotoxicity is rare.

Cytosine arabinoside (Ara-C) is a pyrimidine antagonist. Peripheral neurotoxicity is rare.

Gemcitabine is a deoxycytidine analog structurally related to Ara-C. It causes in 10% sensory neuropathy with paresthesias. Muscle symptoms appear as myalgias.

Fluorouracil (5-FU) and capecitabine is a pyrimidine antagonist. It is used as a single agent or in combination regimes for the treatment of many tumors. A small number of cases of CIPN have been reported after treatment with 5-FU.<sup>63</sup>

Topoisomerase inhibitors interfere with repair of DNA damage and facilitate apoptosis. Type I topoisomerase inhibitors are the camptothecins, irinotecan, and topotecan. Rarely, CIPN occurs.

#### Biologicals

A number of biological agents that are highly selective for their targets based on antibody specificity have been introduced as anti-cancer agents over the past few years. They are often used in combination with neurotoxic drugs.

#### Antibodies

Brentuximab vedotin (SGN-35) is a anti-CD30 monoclonal antibody used in combination with monomethyl auristatin E (an antitubulin agent). It is used in the treatment of Hodgkin's lymphoma. Sensory neuropathies have been described.<sup>64</sup>

Other antibodies, such as bevacizumab and trastuzumab do not appear to be commonly associated with CIPN.

Interferon- $\alpha$  is being used in the treatment of leukemia and lymphoma and in the treatment of hepatitis C. It can cause distal symmetric sensory neuropathy with pain, paresthesia, and loss of pain and temperature perception.<sup>65</sup>

#### Hormones

A trial of using aromatase inhibitors (anastrozole and exemestane) in patients with ER-positive and/or

PgR-positive breast cancer showed grade 2 neuropathies occurring in 30% of patients receiving chemotherapy.<sup>66</sup> Focal neuropathies, such as carpal tunnel syndrome, may occur during aromatase therapy.<sup>67</sup>

### Long-Term Effects of CIPN

Increasing interest is expressed for persistent and late toxicity, in particular as the number of cancer survivors increases.<sup>68</sup> The common symptoms are various types of peripheral neuropathy, neuropathic pain syndromes, muscle cramps and fasciculations, disorders of smell and taste, vestibular and ototoxic effects and Raynaud's syndrome.

### Tumor Types

A high prevalence of neuropathic pain has been described in long-term survivors of breast cancer,<sup>69</sup> ovarian cancer, and germ cell tumors.<sup>70</sup> Although testicular cancer has an excellent oncological prognosis and a survival rate of 95%,<sup>71</sup> up to 20% of long-term survivors face the problem of late neurotoxicity.<sup>72</sup> Other tumors, colon cancers, and sarcomas have an increasing number of long-term survivors and the associated late toxicity issues.<sup>73</sup>

### Late Toxicity of Commonly Used Drugs

#### Platinum Compounds

CIPN usually develops during platinum drug treatment, but symptoms and signs may progress for 2–6 months after cessation of chemotherapy because of coasting. A cross-sectional study of patients with testicular cancer re-evaluated 23–33 years after finishing treatment showed that CIPN remains detectable in up to 20% of patients, being symptomatic in 10% of them.<sup>2</sup> Similar results were found in another study that evaluated cisplatin-treated patients after a median follow-up of 15 years: 38% and 28% of patients had asymptomatic and symptomatic neuropathy, respectively, which was disabling in 6%.<sup>74</sup> Clinical symptoms can also include persisting taste and smell disorders,<sup>75</sup> and oto- and vestibular toxicity.<sup>76</sup> Raynaud's phenomenon is severely disturbing and reduces the quality of life. In older individuals, persisting neuropathic syndromes can induce mobility disability.<sup>77</sup> Age is a risk factor.<sup>78</sup> Pain, in particular neuropathic pain, is often an issue.<sup>79</sup> Chronic oxaliplatin PN is partially reversible in about 80% of patients and completely resolved in about 40% at 6–8 months after treatment discontinuation.<sup>80</sup> Two studies have reported persistence of neuropathy in almost 35% of patients 5–6 years after cessation of oxaliplatin treatment.<sup>81,82</sup>

### FOLFOX (5-FU and Oxaliplatin)

The combination of 5-FU and oxaliplatin is frequently used in patients with gastrointestinal cancer, and 92% of patients develop sensory CIPN.<sup>83</sup> The median time to resolution of symptoms was up to 9 months. Persisting symptoms, such as numbness, dysesthesia, and cold pain, might be a long-term problem for long-term survivors.

### Platinum and Taxane Combination

This combination yielded a 15% persistent neurotoxicity 6 months after cessation of chemotherapy. After a median follow-up of 48 months, 23% of patients with chemotherapy-induced neurological toxicity had residual neuropathy.

Vincristine neuropathy is usually reversible when therapy is discontinued. The median duration of paresthesias and motor weakness after treatment discontinuation is 3 months.<sup>84</sup> Cramps in small hand but in particular small foot muscles occur.

### Taxane

Generally, symptoms of taxane-induced CIPN improve or resolve within the first 3–6 months after the discontinuation of treatment.

### Thalidomide

The overall incidence of CIPN ranges from 25% to 83%, with about 15% of the patients having to interrupt their therapy.<sup>85</sup> The thalidomide-induced neuropathies, in contrast to the bortezomib-induced neuropathies, can be irreversible.

### Bortezomib

Symptoms of bortezomib-induced PN usually improve or completely resolve 3–4 months following discontinuation of treatment. The APEX-study demonstrated that 64% of patients with at least NCI-CTC grade 2 PN experienced improvement or resolution of symptoms, compared with baseline, at a median of 110 days.<sup>86</sup>

### Prevention

Preventive drugs can potentially counteract cancer therapy. This has been the problem with several previously used preventive therapies. Several drugs have been used, such as vitamin B and E, glutathione, alpha lipoic acid, acetylcysteine, amifostine, calcium and magnesium, diethyldithiocarbamate, dithiocarbamate, Org 2766, oxcarbazepine,<sup>87</sup> and erythropoietin.<sup>88</sup> For platinum drugs, a Cochrane review states that chemoprotective agents do not seem to prevent CIPN.<sup>89</sup>

## Symptomatic Treatment

The use of drugs directed against neuropathic pain with anticonvulsants, antidepressants, in severe cases opioids, and recently also topical local anaesthetics can be an option. CIPN, apart from sensory symptoms and pain, often causes loss of proprioception, which has a highly disruptive effect on activities of daily living and gait. These effects are often underestimated. It is likely that, by using physiotherapy and occupational therapy, compensate sensory deficits might be improved by systematic training.<sup>90</sup> Rehabilitation for patients with cancer is increasingly offered.<sup>91</sup>

## Summary

CIPN caused by cancer treatment is gaining importance because several effective therapies damage the peripheral nerves by various mechanisms. Despite different mechanisms of drugs, it is hoped that common mechanisms in the structure or function of peripheral nerves may help to develop preventive strategies. Although most CIPNs are of the length-dependent sensory type, several different manifestations can be observed and acute toxicities appear.

As the number of long-term cancer survivors increases, a new focus on long-term effects of chemotherapy-induced neuropathies has emerged. The symptoms can be related to the sensory system, neuropathic pain, and cranial nerve dysfunction, because smell and taste and symptoms related to ototoxicity can persist.

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