Drugs 2003; 63 (15): 1549-1563
0012-6667/03/0015-1549/$33.00/0



# Neurotoxic Complications of Chemotherapy in Patients with Cancer

## Clinical Signs and Optimal Management

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## Contents

## Abstract

Neurotoxic side effects of chemotherapy occur frequently and are often a reason to limit the dose of chemotherapy. Since bone marrow toxicity, as the major limiting factor in most chemotherapeutic regimens, can be overcome with growth factors or bone marrow transplantation, the use of higher doses of chemotherapy is possible, which increases the risk of neurotoxicity.

Chemotherapy may cause both peripheral neurotoxicity, consisting mainly of a peripheral neuropathy, and central neurotoxicity, ranging from minor cognitive deficits to encephalopathy with dementia or even coma.

In this article we describe the neurological adverse effects of the most commonly used chemotherapeutic agents.

The vinca-alkaloids, cisplatin and the taxanes are amongst the most important drugs inducing peripheral neurotoxicity. These drugs are widely used for various malignancies such as ovarian and breast cancer, and haematological cancers. Chemotherapy-induced neuropathy is clearly related to cumulative dose or dose-intensities. Patients who already have neuropathic symptoms due to diabetes mellitus, hereditary neuropathies or earlier treatment with neurotoxic chemotherapy are thought to be more vulnerable for the development of chemotherapy--induced peripheral neuropathy.

Methotrexate, cytarabine (cytosine arabinoside) and ifosfamide are primarily known for their central neurotoxic side effects. Central neurotoxicity ranges from acute toxicity such as aseptic meningitis, to delayed toxicities comprising cognitive deficits, hemiparesis, aphasia and progressive dementia. Risk factors are high doses, frequent administration and radiotherapy preceding methotrexate chemotherapy, which appears to be more neurotoxic than methotrexate as single modality.

Data on management and neuroprotective agents are discussed. Management mainly consists of cumulative dose-reduction or lower dose-intensities, especially in patients who are at higher risk to develop neurotoxic side effects. None of the neuroprotective agents described in this article can be recommended for standard use in daily practise at this moment, and further studies are needed to confirm some of the beneficial effects described.

Neurotoxicity caused by chemotherapeutic agents is a frequently observed side effect. Both peripheral neurotoxicity and central neurotoxicity can occur. Vinca-alkaloids, cisplatin and the taxanes are among the most important agents to induce peripheral neurotoxicity, whereas methotrexate and ifosfamide, for example, mainly induce CNS toxicity.

This article provides a current update on both chemotherapy-induced CNS and peripheral nervous system toxicities for the most commonly used cytostatic agents in current oncological practice. A literature search was performed via Medline using a combination of keywords relating to chemotherapy and central and peripheral neurotoxicity. Data on management and neuroprotective agents are discussed when possible. However, none of the described neuroprotective agents can be recommended for standard use in daily practice at the moment, and further studies are warranted.

Nevertheless, it is important for clinicians who prescribe chemotherapeutic agents to be aware of the possibility of neurological adverse effects and the impact of these effects on quality of life for patients.

Table I shows an overview of the compounds described that cause peripheral and/or central neurotoxicity.

## 1. Platinum Compounds

### 1.1 Cisplatin

The mechanism of action of cisplatin (*cis*-Diamminedichloroplatinum; CDDP) is related to platinum binding to DNA, producing inter- and intrastrand cross-links, thus impairing DNA synthesis. Cisplatin is used in the treatment of ovarian, bladder, testicular, lung, and head and neck cancer. Cisplatin is administered intravenously, mostly in a dosage range of 50–100 mg/m$^2$ three times weekly.

#### *1.1.1 CNS*

Cisplatin penetrates the blood-brain barrier only to a minor degree but adverse effects to the CNS can occur, especially when it is administered directly into the carotid artery in patients with brain tumours.[1] Headache, encephalopathy, cortical blindness, focal deficits, stroke and seizures have all been described following cisplatin treatment, both in children and adults, and are usually reversible. Encephalopathy may be induced by a direct toxic effect of cisplatin but may also be caused by cisplatin-induced electrolyte disorders (e.g. hypocalcaemia, hypomagnesaemia and hyponatraemia as a result of inappropriate antidiuretic hormone secretion and renal toxicity).

#### *1.1.2 Peripheral Nervous System*

Peripheral neuropathy is a common adverse effect of cisplatin and may be dose limiting in patients. Sensory symptoms such as paresthesias and numbness usually follow cumulative doses of cisplatin >400 mg/m$^2$,[2] and often symptoms occur only after completion of treatment.[3] Off-therapy deterioration may occur for 2.5–5.5 months after withdrawal of cisplatin.[4] Sensory large fibres are predominantly affected, leading to loss of proprioception, which may result in an ataxic gait. Patellar and ankle reflexes usually disappear. Pin and temperature sensation are only slightly affected. Motor function is spared.

Nerve conduction studies show decreased sensory nerve action potentials and prolonged sensory distal latencies with cisplatin therapy. Sensory nerve conduction velocity is only mildly impaired[3-5] (table II).

The mechanism of action attributed to cisplatin-induced peripheral neuropathy is not clear, although in a postmortem study, the highest concentration of cisplatin was found in the dorsal root ganglia cells.[6] Therefore, cisplatin probably causes axonal changes secondary to the neuronal damage.

Cranial nerve impairment may follow infusion of cisplatin in the carotid artery. Lhermitte's sign has been described during or shortly after treatment with cisplatin.[7] Finally, muscle cramps are commonly associated with cisplatin treatment but are transient.

#### *1.1.3 Management and Neuroprotection*

Dose intensity and cumulative dose influence the severity of cisplatin-induced neuropathy. Dose reduction or longer intervals between cisplatin admin-

**Table I.** Overview of peripheral and/or central neurotoxic complications associated with various chemotherapy drugs

| Drug | Neurotoxic complications | | Management[a] |
|---|---|---|---|
| | CNS | peripheral nervous system | |
| Cisplatin | Rare: encephalopathy, headache, stroke, seizures | Sensory PNP with frequent off-therapy worsening, Lhermitte's sign, muscle cramps | Amifostine might protect in PNP |
| Carboplatin | Rare: cortical blindness | Sensory PNP | Caution with high doses |
| Oxaliplatin | No adverse effects | Postinfusion paresthesias, sensory PNP | Avoid cold drinks postinfusion; carbamazepine might ameliorate PNP |
| Vincristine | Overdose: encephalopathy, seizures, ataxia, athetosis, parkinsonism. Intrathecal: lethal radiculo-myeloencephalopathy | Sensorimotor PNP, mononeuropathy, cranial nerve palsy, autonomic neuropathy | Reduce dose intensity; glutamic acid, ganglio-sides and NGF may protect in PNP |
| Paclitaxel | Rare: acute encephalopathy, seizures | Sensorimotor PNP, myalgia, proximal muscle weakness | Reduce dose intensity; longer infusion time; amitriptyline for pain; NGF, glutamine, glutamate and amifostine may protect |
| Docetaxel | No adverse effects | Predominantly sensory PNP, Lhermitte's sign, proximal motor weakness | Dose reduction; pyridoxine for paresthesias |
| Methotrexate | Aseptic meningitis, transverse myelopathy, stroke-like syndrome, leukoencephalopathy, seizures | Lumbosacral radiculopathy | Caution with high doses; when possible, administer methotrexate before radiotherapy |
| Cytarabine | Aseptic meningitis, myelopathy. Rare: encephalopathy, seizures, and cerebellar dysfunction | Rare: painful sensory PNP, brachial plexopathy | |
| Fluorouracil | Rare: cerebellar dysfunction, inflammatory leukoencephalopathy | Rare: PNP | |
| Ifosfamide | Encephalopathy | Painful axonal PNP | Dose reduction; avoid use in combination with phenobarbital; methylene blue might reduce encephalopathy |
| Cyclophosphamide | Rare: blurred vision, confusion | No adverse effects | Dose reduction |
| Nitrosoureas | Rare: ocular toxicity, encephalopathy | | |
| Procarbazine | Rare: drowsiness, stupor | Sensory PNP, ataxia, orthostatic hypotension, intrinsic hand muscle weakness | |
| Etoposide | Headache, seizures, somnolence | Sensory PNP | Dose reduction |

a Thus far, neuroprotective agents are not widely used in everyday clinical practice; the agents mentioned in the table are studied *in vitro*, *in vivo* and in clinical trials.

**NGF** = nerve growth factor; **PNP** = peripheral neuropathy.

istrations may be of benefit for patients who develop neuropathy during the chemotherapy treatment. Patients who have been treated earlier with cisplatin are thought to be more vulnerable if retreated with platinum compounds. Recently, however, a study showed that retreatment with cisplatin did not result in substantial neurotoxicity.[8]

The addition of neuroprotective agents might prevent or ameliorate cisplatin-induced neurotoxicities and allow dose escalation of the cytostatic agent.

Org-2766, a synthetic adrenocorticotrophin [ACTH]-(4-9) analogue that is thought to stimulate the recovery of damaged neurons, was investigated in a randomised, double-blind, placebo-controlled study of patients with ovarian cancer receiving cisplatin. Vibratory perception threshold did not increase in the group receiving high-dose Org-2766, and clinical signs were less prominent.[9] However, this beneficial effect could not be confirmed in a later study of 131 patients with ovarian cancer.[10]

Glutathione showed a neuroprotective effect in patients with advanced gastric cancer treated with cisplatin; sensory nerve conduction was also significantly less impaired in the glutathione-treated patients.[11]

Amifostine, a thiol prodrug, may protect against cisplatin-induced neuropathy after dephosphorylation to WR-1065, its active metabolite. WR-1065 and, to a lesser extent, amifostine prevent cisplatin-DNA adduct formation, suggesting that the optimal time to administer amifostine is shortly before cisplatin administration. In a randomised, controlled trial of 242 patients with advanced ovarian cancer, amifostine caused a significant reduction in cisplatin-induced peripheral neuropathy.[12] However, in contrast, two recent clinical studies did not show a neuroprotective effect of amifostine. In one randomised study, repeated low dosages of amifostine (500 mg/day) in combination with paclitaxel, ifosfamide and cisplatin followed by high-dose carboplatin, etoposide and thiotepa in patients with germ cell tumour did not significantly reduce peripheral neurotoxicity.[13] The other study showed that the combination of amifostine (910 mg/m$^2$) and cisplatin in patients with progressive metastatic breast carcinoma did not reduce the incidence of peripheral neuropathy.[14]

## 1.2 Carboplatin

Carboplatin is a cisplatin analogue that is less neurotoxic than the parent compound. Carboplatin also crosses the blood-brain barrier poorly, although higher concentrations in the cerebrospinal fluid (CSF) are reached than with cisplatin.[15]

### *1.2.1 CNS*

When given intra-arterially, retinopathy is the only reported CNS adverse effect of carboplatin. Cortical blindness and cortical infarcts leading to coma have been reported occasionally.[16]

### *1.2.2 Peripheral Nervous System*

Carboplatin is less neurotoxic to the peripheral nervous system than cisplatin.[17] However, high-dose carboplatin may cause a severe sensory neuropathy.

## 1.3 Oxaliplatin

Oxaliplatin is a new platinum compound and is employed in the therapy of colorectal cancer. The most frequently encountered nonhaematological adverse effects associated with oxaliplatin treatment are gastrointestinal symptoms and peripheral neuropathy.[18]

### *1.3.1 Peripheral Nervous System*

Oxaliplatin induces two different types of neurotoxicity. Acute neurotoxicity typically occurs 30–60 minutes after infusion and disappears after a few days; however, it often reappears after every infusion. In a recent phase I study, all patients experienced acute, reversible symptoms consisting of paresthesias, cold hypersensitivity, jaw and eye pain, ptosis, leg cramps, and visual and voice changes after oxaliplatin treatment. Signs of hyperexcitability in motor nerves where shown in nerve conduction studies[19] (table II). Later in the course of treatment,

**Table II.** Nerve conduction abnormalities in peripheral neuropathy associated with various chemotherapy drugs

| Drug | Nerve conduction abnormalities in peripheral neuropathy |
|---|---|
| Cisplatin | Reduced sensory nerve action potentials, prolonged sensory distal latencies, mildly decreased sensory nerve conduction velocity |
| Oxaliplatin | Acute neuropathy: hyperexcitability in motor nerves |
| | Cumulative neuropathy: reduced sensory nerve action potentials, decreased sensory nerve conduction velocity |
| Vincristine | Reduced distal motor and sensory nerve action potentials, mildly decreased motor and sensory nerve conduction velocities |
| Paclitaxel | Reduced sensory nerve action potentials, sometimes reduced motor nerve action potentials, sometimes decreased sensory and motor nerve conduction velocities |
| Docetaxel | Reduced motor and sensory nerve action potentials, moderately decreased motor nerve conduction velocity |

after a certain cumulative dose, patients develop symptoms and signs identical to cisplatin-induced neuropathy. Nerve conduction studies show slowing of sensory nerve conduction with reduced amplitude in patients with this cumulative neuropathy[19] (table II).

The mechanism of action of oxaliplatin-induced acute neurotoxicity is different than that of other platinum compounds. Oxaliplatin seems to interfere with axonal ion conductance and neural excitability.[20]

#### 1.3.2 Management and Neuroprotection

Oxaliplatin-induced neuropathy is usually reversible after discontinuation of therapy. As a precaution in case of acute neurotoxicity, the patient should avoid cold drinks immediately after infusion of oxaliplatin. Oxaliplatin-induced cumulative neuropathy may also be managed by temporary cessation of treatment. Administration of amifostine before oxaliplatin counteracted oxaliplatin-related neuropathy in 10 of 15 patients without compromising the antitumour efficacy.[19]

Administration of carbamazepine, a sodium channel antagonist, led to a reduction of oxaliplatin-induced neuropathy in a pilot study.[21] However, no beneficial effect of carbamazepine was observed in oxaliplatin-induced acute neurotoxicity.[19]

## 2. Vinca-Alkaloids

The vinca-alkaloids comprise two natural alkaloids, vincristine and vinblastine, and several semisynthetic compounds, such as vindesine and vinorelbine. Vinca-alkaloids arrest cell division by inhibition of microtubule formation in the mitotic spindle. Vincristine is used especially in non-Hodgkin's lymphoma, Hodgkin's disease and leukaemia. The current dose intensity used is 2–4mg every 3–4 weeks.

The most important dose-limiting adverse effect of vinblastine is bone-marrow suppression, which usually precedes neurotoxicity. Vindesine and vinorelbine produce mild neurotoxicity, consisting of loss of deep tendon reflexes.[22,23]

### 2.1 Vincristine

#### 2.1.1 CNS

Accidental massive overdose with vincristine may cause CNS toxicity and may lead to death. Fatal myeloencephalopathy may follow intrathecal administration of vincristine.[24] Encephalopathy and seizures have been reported in an 8-year-old child with acute lymphoblastic leukaemia.[25] Cortical blindness, athetosis, ataxia and parkinsonian-like symptoms are infrequent and usually reversible.

#### 2.1.2 Peripheral Nervous System

Peripheral neuropathic symptoms and signs are frequently observed with vincristine therapy and are thought to be caused by inhibition of fast axonal transport by microtubules. Paresthesias in fingers and toes are usually the initial symptoms. Loss of ankle reflexes is the first change. Vibration sense is rarely impaired, but weakness, usually of the extensor muscles of the wrist and dorsiflexors of the toes, can occur.[26] Mononeuropathies (such as peroneal and femoral neuropathy) and cranial nerve palsies (vocal cord paresis,[27] diplopia, facial nerve palsy, ophthalmoplegia[28] and sensorineural hearing loss[29]) have been described.

Autonomic neuropathy is frequently seen with vincristine treatment, especially gastrointestinal adverse effects such as constipation,[30] sometimes leading to paralytic ileus or megacolon. Other autonomic adverse effects are bladder atony, impotence, orthostatic hypotension and disturbed heart rate.

Nerve conduction studies show decreased distal motor and sensory nerve action potentials with vincristine therapy. Only a slight reduction of motor and sensory nerve conduction velocities was found (table II). Sural nerve biopsy in vincristine-treated patients showed axonal degeneration with segmental demyelination.[31,32]

#### 2.1.3 Management and Neuroprotection

In general, smaller doses of vincristine per interval or longer intervals are associated with less neurotoxicity. When patients experience muscle weakness, treatment is usually interrupted.[33]

Patients with hepatic insufficiency are more likely to develop a severe neuropathy with vincristine

treatment, even with low doses.[28] Age does not seem to influence the development of neuropathy.[26,34] Unusually severe motor neuropathy has been described in a patient with Charcot-Marie-Tooth syndrome.[35] After discontinuation, vincristine-induced neuropathy usually resolves within a few months, and long-term effects were not troublesome in 40 patients 4 to 77 months after treatment with vincristine.[34]

Many attempts have been pursued to prevent or ameliorate vincristine-induced neurotoxicity. In a pilot study, Org-2766 seemed neuroprotective but a significant age difference between the study groups might have influenced the results.[36] Glutamic acid seemed also be able to reduce vincristine-induced neurotoxicity in an oral dose of 1.5 g/day.[37] However, no neuroprotective agent has been shown to be suitable for clinical practice.

## 3. Taxanes

### 3.1 Paclitaxel

Paclitaxel blocks cells in the late G2 mitotic phase of cell cycle by polymerisation and stabilisation of microtubules. Paclitaxel is effective in ovarian, breast and lung cancer, and is administered over 3, 6, 24 or 96 hours, usually once in 3 weeks or once weekly.

#### *3.1.1 CNS*

Chemotherapy using paclitaxel at a very high dose (>600 mg/m$^2$) can cause severe acute encephalopathy.[38] A sensation of light flashing across the visual field has been reported by some patients during paclitaxel infusion.[39]

#### *3.1.2 Peripheral Nervous System*

Whereas the vinca alkaloids prevent polymerisation from soluble dimers into microtubules, paclitaxel promotes the formation of microtubules and prevents their depolymerisation, which results in an abundance of rigid microtubules. These defective microtubules inhibit axonal transport.

Sensory symptoms and signs, the most predominant adverse effects associated with paclitaxel treatment, may develop shortly after treatment (within 48 hours), usually after a cumulative dose of 100–200 mg/m$^2$.[40] Symptoms begin with paresthesias, numbness and sometimes pain in the feet and hands. Difficulties with daily life activities, such as writing and buttoning, can occur. Furthermore, unsteadiness when walking, especially in the dark, is a frequently occurring symptom. Muscle weakness may develop but it is usually mild. Deep tendon reflexes disappear and vibratory perception threshold increases in the feet more than in the hands.[41] When paclitaxel >250 mg/m$^2$ is administered in combination with granulocyte colony-stimulating factor to rescue myelotoxicity, neuropathy becomes the dose-limiting factor.[42]

A few patients receiving paclitaxel also develop proximal muscle weakness that spontaneously resolves.[43] Acute arthralgia and myalgia in the legs may occur 2–3 days after administration of paclitaxel; this lasts for 2–4 days.[44] Autonomic neuropathy occurs infrequently with paclitaxel treatment.[45]

Nerve conduction studies show a reduction of sensory nerve action potentials in patients who have received paclitaxel. Sural sensory nerve potentials are nearly always reduced or absent in symptomatic patients.[46] In a few patients, abnormal motor nerve action potentials, diminished sensory and motor nerve conduction velocity, and denervation on needle aspirate examination have been described (table II). Histological examination of the sural nerve after paclitaxel treatment showed fibre loss, lack of axonal sprouting and axonal atrophy, with secondary demyelination and remyelination.[46]

#### *3.1.3 Management and Neuroprotection*

Paclitaxel-induced neuropathy is usually reversible after discontinuation, although there are some reports of permanent neuropathy.[47]

High-dose cycles, high cumulative doses, diabetes mellitus and pre-existing neuropathy are risk factors for the development of paclitaxel-induced neuropathy. Paclitaxel induces mild neuropathy at a dose of 135 mg/m$^2$; only 2% of patients developed grade 1 neurotoxicity.[48] When 175 mg/m$^2$ is given, dose-limiting neurotoxicity may occur, especially in patients with diabetes.[39] Significant neurotoxicity

occurs with doses >200 mg/m$^2$.[49] Shorter infusion times of high-dose paclitaxel may also lead to more pronounced neuropathy, an effect not observed with lower doses (135 vs 175 mg/m$^2$) in 3- versus 24-hour infusion times.[50]

Neuropathic pain or myalgia induced by paclitaxel treatment may improve with the administration of amitriptyline or antihistaminergic drugs.[51]

Several neuroprotective agents have been studied in combination with paclitaxel treatment. Nerve growth factor prevented toxic neuropathy in mice.[52] The ACTH(4-9) analogue Org-2766 prevented paclitaxel-induced neurotoxicity *in vivo*,[53] and glutamate significantly delayed the onset of neuropathy in paclitaxel-treated rats.[54] Glutamine significantly reduced high-dose paclitaxel-induced neuropathy in patients in a nonrandomised, non-placebo-controlled study.[55] In a phase I study, amifostine allowed paclitaxel to be safely administered at a high-dose intensity.[56] However, in a randomised phase II study, no protection from amifostine for paclitaxel-related neurotoxicity was observed.[57]

### 3.2 Docetaxel

Docetaxel is a more potent inhibitor of cell replication than paclitaxel. It promotes the *in vitro* assembly of stable microtubules and induces microtubule bundle formation in cells. Docetaxel is administered three times weekly (sometimes twice or once weekly) as a 1-hour intravenous infusion, usually at a dose of 100 mg/m$^2$.

#### *3.2.1 Peripheral Nervous System*

Neuropathy due to docetaxel treatment is usually mild to moderate, involving paresthesias, loss of deep tendon reflexes and vibration sensation. More severe clinical and electrophysiological abnormalities were observed after high cumulative doses (≥400 mg/m$^2$).[58] A predominantly sensory neuropathy develops, with low amplitude of motor and sensory nerve action potentials, and moderately slow motor conduction velocities exhibited on electrophysiological examination (table II). A peroneal nerve biopsy showed loss of large myelinated fibres and occasionally axonal degeneration.[58]

Some patients receiving docetaxel may experience Lhermitte's sign,[59] as well as proximal motor weakness.[43]

#### *3.2.2 Management and Neuroprotection*

The development of docetaxel-induced neuropathy is dose dependent and usually improves after discontinuation of therapy, although off-therapy worsening may occur.[59] Pyridoxine may ameliorate docetaxel-induced paresthesias.[60]

## 4. Antimetabolites

The antimetabolites can be subdivided into antifolates, cytidine analogues, fluorinated pyrimidines and purine antimetabolites.

### 4.1 Methotrexate

Methotrexate is an antifolate that is the most widely used antimetabolite in cancer therapy. Antifolates inhibit dihydrofolate reductase, and cause inhibition of purine and thymidine biosynthesis. Methotrexate acts against leukaemias, lymphomas, breast cancer, and head and neck cancer. Intrathecal administration is used for prophylaxis or treatment of leptomeningeal spread of tumour.

#### *4.1.1 CNS*

Acute toxicity consisting of an aseptic meningitis following intrathecal administration of methotrexate has been described.[61] Headache, stiff neck, nausea, vomiting and fever occur 2–4 hours after methotrexate injection and last for 12–72 hours. CSF analysis shows pleocytosis but cultures are negative. Transverse myelopathy is a rare complication of intrathecal methotrexate treatment and usually occurs after several injections. Patients report back pain, sometimes radiating into the legs, followed by sensory loss, paraplegia, and bowel and bladder dysfunction.[62]

Case reports describe subacute neurological toxicities consisting of hemiparesis, confusion, ataxia and seizures occurring 5–10 days after a moderate dose of systemic methotrexate.[63,64]

Delayed toxicity consists of leukoencephalopathy and is the most devastating complication of methotrexate. Delayed neurotoxicity is usually re-

ported in children treated with methotrexate; however, 26% of long-term adult survivors with primary cerebral lymphomas who were treated with high-dose methotrexate and radiotherapy showed late neurological complications at 68 months after diagnosis. Progressive dementia, gait disturbances, hemiparesis, aphasia and death were reported despite continuous remission of lymphoma. Post-operative radiotherapy followed by chemotherapy was a significant risk factor for the development of late neurotoxicity.[65]

Magnetic resonance imaging (MRI) scans reveal cerebral atrophy, diffuse white matter hyperintensities, ventricular enlargement and sometimes cortical calcifications in patients treated with methotrexate. MRI changes may precede neurological symptoms.[66] Recently, a histopathological study showed methotrexate-related multifocal axonal injury but the exact pathophysiology of methotrexate neurotoxicity is not clear thus far.[67]

#### 4.1.2 Peripheral Nervous System

Anterior lumbosacral radiculopathy, consisting of a progressive paraparesis, with gadolinium enhancement of anterior lumbosacral spinal nerve roots on MRI, has been demonstrated after intrathecal chemotherapy with methotrexate in children with leukaemia.[68]

#### 4.1.3 Management and Neuroprotection

Risk factors for the development of acute aseptic meningitis related to methotrexate treatment are use of a high dose, more frequent installation and the presence of leptomeningeal tumour.[61]

No effective treatment exists to prevent or treat leukoencephalopathy. Combination treatment (radiotherapy followed by methotrexate chemotherapy) appears to be more neurotoxic than methotrexate as single modality.[69] Therefore, radiotherapy should not precede methotrexate chemotherapy when possible.

Administration of folinic acid (leucovorin), an antidote to methotrexate-induced gastrointestinal or bone marrow toxicity, does not prevent or reverse neurotoxicity.

### 4.2 Cytarabine (Cytosine Arabinoside)

Cytarabine (cytosine arabinoside, ara-C) is a pyrimidine analogue that inhibits DNA polymerase α, which is incorporated into DNA and terminates DNA chain elongation. The drug is used in the treatment of leukaemia and lymphoma.

#### 4.2.1 CNS

Aseptic meningitis,[70] and rarely myelopathy,[71] may follow intrathecal administration of cytarabine, which is clinically similar to methotrexate. One patient developed a 'locked in syndrome' 48 hours after receiving intrathecal cytarabine in combination with intravenously administered cytarabine, cisplatin and doxorubicin.[72]

Encephalopathy and seizures are rare adverse effects of intrathecal cytarabine treatment.[73]

Cerebellar dysfunction occurs at a cumulative cytarabine dose of at least 36 g/m$^2$, mostly in older patients.[74] Dysarthria, nystagmus, gait ataxia and sometimes confusion and somnolence have been reported.[74] These symptoms have also been described in a few cases after administration of only 3 g/m$^2$.[75] Resolution of signs often occurs within 2 weeks of cessation of cytarabine.

MRI scans show cerebellar atrophy and reversible white matter changes following cytarabine treatment. The CSF is normal.

Other neurological adverse effects, described occasionally, are blurred vision and burning eye pain, blindness,[76] (pseudo)bulbar palsy,[77] Horner's syndrome and anosmia.[78]

#### 4.2.2 Peripheral Nervous System

Peripheral neurotoxicity is rare with cytarabine treatment but may present as a painful sensory neuropathy,[79] especially when high doses are given or when administered in combination with daunorubicin and asparaginase.[80]

Brachial plexopathy and lateral rectus muscle palsy have been reported occasionally with cytarabine therapy.[81]

There is one histology report of axonal degeneration and scattered demyelination following cytarabine treatment.[82]

#### 4.2.3 Management and Neuroprotection

The mechanism of cytarabine neurotoxicity is unknown. Cytarabine might kill neurons by interfering with cytidine-dependent neurotrophic signal transduction. There is no specific treatment but most patients recover spontaneously in the following days to months. Cerebellar dysfunction occurs more frequently in older patients and with high doses of cytarabine.[74]

Cicloheximide (cycloheximide) prevented cytarabine-induced apoptotic cell death of differentiating rat cerebellar granule neurons in an *in vitro* setting; this use needs further research.[83]

### 4.3 Fluorouracil

Fluorouracil (5-FU) is a pyrimidine analogue that binds thymidylate synthase. A metabolite of 5-FU, 5-fluoro-2′-deoxyuridine monophosphate, binds to and inhibits thymidylate synthase, leading to interference with DNA synthesis. 5-FU is effective in treating gastrointestinal tumours, head and neck cancer and breast cancer.

#### 4.3.1 CNS

5-FU rarely causes neurotoxicity except in patients with a deficiency of the enzyme dihydropyrimidine dehydrogenase, which is responsible for the rate-limiting metabolic clearance of 5-FU. CNS toxicity in these patients may include encephalopathy and coma.[84]

Rarely occurring adverse effects of 5-FU treatment are cerebellar ataxia, extraocular muscle abnormalities,[85] optic nerve neuropathy and extrapyramidal syndromes.[86] These symptoms may occur in patients with relatively normal 5-FU clearance and are related to the schedule of administration.

Combination therapy of 5-FU with allopurinol can cause acute and subacute cerebellar dysfunction, visual disturbances and, rarely, seizures.[87] When 5-FU is administered in combination with levamisole, an inflammatory multifocal leukoencephalopathy may develop.[88]

#### 4.3.2 Peripheral Nervous System

Peripheral neuropathy has been described in three patients after 5-FU chemotherapy in combination with folinic acid and eniluracil.[89]

### 4.4 Ifosfamide

Ifosfamide, an alkylating agent used in the treatment of sarcomas, lung cancer and testicular cancer, is a prodrug that requires hydroxylation by the liver to active metabolites. Ifosfamide and some of its metabolites cross the blood-brain barrier.

#### 4.4.1 CNS

Ifosfamide may cause acute, but usually reversible, encephalopathy when high doses are administered; the encephalopathy is characterised by cerebellar and extrapyramidal symptoms, hallucinations, seizures and sometimes coma.[90] Symptoms usually start within 24 hours of the drug infusion and resolve in 3–4 days.

#### 4.4.2 Peripheral Nervous System

A severe, painful axonal peripheral neuropathy associated with high-dose ifosfamide has been described in patients treated for bone and soft tissue sarcomas.[91]

#### 4.4.3 Management and Neuroprotection

Risk factors for the development of ifosfamide-induced encephalopathy include high doses, rapid infusion, renal impairment, hepatic impairment, low serum albumin levels, hypocalcaemia and previous cisplatin therapy.[92]

Drugs such as phenobarbital, which can increase the metabolic breakdown of ifosfamide to the active metabolites, may increase neurotoxicity.[93]

In a recent study, 12 of 52 (23%) patients who were treated with ifosfamide developed an encephalopathy. Eight of these patients received methylene blue to treat their encephalopathy. These patients showed a milder encephalopathy than patients not receiving methylene blue treatment.[94]

### 4.5 Cyclophosphamide

Like ifosfamide, cyclophosphamide requires metabolism by the liver to form active metabolites, and is used in the treatment of lymphatic leukaemia,

Hodgkin's lymphoma and different disseminated solid tumours. Cyclophosphamide has little or no neurotoxic side effects, although reversible blurred vision, dizziness and confusion have been described in a few patients receiving high-dose therapy.[95,96]

## 5. The Nitrosoureas

The nitrosoureas carmustine (BCNU) and lomustine (CCNU) cross the blood-brain barrier easily. Carmustine and lomustine are used to treat primary brain tumours, melanoma and lymphoma. Nitrosoureas rarely cause neurotoxicity in conventional doses, however, patients with brain tumours who have received previous radiotherapy and are treated with high-dose or intra-arterial carmustine may develop ocular toxicity, encephalopathy and seizures.[97,98]

Sudden blindness due to optic neuropathy is a rare complication of oral lomustine therapy combined with cranial radiotherapy.[99]

## 6. Procarbazine

Procarbazine is used in haematological malignancies and brain tumours.

### 6.1 CNS

CNS toxicity ranges from drowsiness to confusion or stupor. In patients treated with combination therapy of procarbazine, lomustine and vincristine for recurrent brain tumour (in most cases after radiotherapy), CNS adverse effects, such as focal neurological deficit, cognitive disturbances and cerebral atrophy shown by MRI may occur. Some of these features are (partly) reversible.[100]

### 6.2 Peripheral Nervous System

Peripheral neuropathy with paresthesias and loss of deep tendon reflexes occurred in 17% of patients and was usually reversible.[101] Ataxia, orthostatic hypotension and weakness of intrinsic hand muscles are recognised findings.

## 7. Etoposide

Etoposide (VP-16) is a podophyllotoxin, and is used in the treatment of lung cancer and leukaemia. Sensory neuropathy has been described in patients receiving intensive therapy with etoposide and melphalan.[102] Etoposide administered in high doses may cause headache, seizures and somnolence in patients who have received bone marrow transplantation.[103]

## 8. Chemotherapy and Cognitive Function

Recent studies have focused on cognitive functioning and neuropsychological sequelae in patients receiving chemotherapy. Both standard-dose chemotherapy and high-dose chemotherapy may cause cognitive impairment, consisting of problems with memory and concentration.[104,105]

Patients with breast cancer treated with high-dose cyclophosphamide, thiotepa and carboplatin had an elevated risk for cognitive impairment 2 years after chemotherapy compared with a nontreated control group.[104] In addition, patients treated with conventional cyclophosphamide, methotrexate and 5-FU showed a higher risk of cognitive impairment.[104]

These results were also obtained in another study with long-term survivors of breast cancer and lymphoma, who were treated with standard-dose chemotherapy. Cognitive deficits were identified on average 10 years after chemotherapy. Therefore, persistent cognitive deficits may occur long after treatment.[105]

## 9. Conclusions

Chemotherapy may cause neurological adverse effects, and both central and peripheral neurotoxicities have been described for many of the chemotherapeutic agents.

Peripheral neuropathy may be the dose-limiting toxicity when paclitaxel, vincristine and/or cisplatin are administered to patients. Therefore, the assessment of peripheral neuropathy and its impact on quality of life should be included in (potentially) peripheral neurotoxic chemotherapy regimens.

CNS toxicities such as seizures, drowsiness, cognitive deficits or even coma are observed less frequently. However, these adverse effects should always be taken into account when starting clinical chemotherapeutic trials in which higher doses or shorter intervals between doses are evaluated.

Neuroprotective agents ideally should reduce the chemotherapy-induced neurotoxicities without reducing the antitumour effect of the cytostatic agent. Unfortunately, data on neuroprotection in chemotherapy-related peripheral neurotoxicity are still controversial at this time. In our view, no neuroprotective agent can be recommended for standard use in daily clinical practice. Additional studies are needed.

Therefore, the management of neurotoxicity mainly consists of the reduction of dose of the cytostatic agent or the use of longer intervals between cycles. Furthermore, patients with diabetes, patients with hereditary neuropathies and patients who have received previous neurotoxic chemotherapy are more likely to develop peripheral neuropathy; therefore, these patients should be evaluated carefully when potentially neurotoxic chemotherapy is administered.

## Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

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