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REVIEW

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Chemotherapy-induced peripheral neuropathy

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Abstract The induction of peripheral neuropathy is a common factor in limiting therapy with chemotherapeutic drugs. Little is known about the mechanisms responsible for the development of neuropathy. Depending on the substance used, a pure sensory and painful neuropathy (with cisplatin, oxaliplatin, carboplatin) or a mixed sensorimotor neuropathy with or without involvement of the autonomic nervous system (with vincristine, taxol, suramin) can ensue. Neurotoxicity depends on the total cumulative dose and the type of drug used. In individual cases neuropathy can evolve even after a single drug application. A general predisposition for developing a chemotherapy-induced neuropathy has been observed in nerves previously damaged by diabetes mellitus, alcohol or inherited neuropathy. The recovery from symptoms is often incomplete and a long period of regeneration is required to restore function. Up to now, no drug is available to reliably prevent or cure chemotherapy-induced neuropathy.

Key words Neuropathy · Taxol · Cisplatin · Vincristine · Suramin

Introduction

Beside bone marrow suppression and renal toxicity the neurotoxic side-effects of the most common chemotherapeutic agents are very often the reason for stopping the anti-tumour therapy or changing the dose regimen. It is known that the neurotoxic effects can appear immediately during or shortly after administration of the drug. Depending on the drug used, these effects can also become evident with a long delay following cessation of chemotherapy (called "coasting", see below). In all cases the neurotoxicity can significantly interfere with function and compromise the quality of life. Most commonly, symptoms are indicative of a predominantly sensory or sensory-motor neuropathy which in some cases is accompanied by dysfunction of the autonomic nervous system. The degree of damage done by chemotherapy depends on the type of drug used, the duration of administration and the cumulative dose applied (for overview see table 1). In general, the peripheral nervous system (PNS) has a great capacity of regeneration in response to injury. For regeneration to occur, the cell body needs to be spared and a long period without damage following the drug administration allowed so that the PNS has sufficient time to accomplish repair. Depending on dosage and agent used, symptoms resolve completely in some cases. Unfortunately, in most instances, the chemotherapy-induced neuropathy (CIN) is only partly reversible and in the worst cases damage is completely irreversible. CIN therefore represents an important and persistent limitation of quality of life even when the tumour has been successfully treated by the drugs.

Most of the drugs causing neuropathy are substances which have been in use for a long time or are newer derivatives of these such as the platinum compounds, vinca alkaloids, taxols and suramin. Only few recently developed drugs have been reported to produce peripheral neuropathy. Many of the remaining chemotherapeutic drugs such as etoposid, methotrexate and Ara-C

JON 561

Table 1 Compound related signs and symptoms of chemotherapy-induced peripheral neuropathy

Compound	Neuro-toxic doses	Clinical symptoms			NCS findings	EMG findings	Morphological Changes
		Sensory	Motor	Autonomic			
Vincristine	> 4 mg cumulative doses	always *early manifestation of numbness and tingling of hand and feet, loss of achilles tendon reflex, pain*	rare *muscle cramps, severe weakness in distal muscles*	frequent *paralytic ileus, postural hypotension, urogenital dysfunction*	less frequent *slowing of sensory NCV with reduced amplitude*	rare *signs of denervation in distal muscle*	demyelination with axonopathy *demyelination, axonal loss of the dying back type and DRG damage*
Taxane (Taxol, Docetaxel)	> 175–200 mg/m^2 cumulative doses	frequent *distal symmetrical paraesthesia, pall-hypaesthesia, loss of joint position sense, painful dysaesthesia, Lhermitte's sign, pain*	less frequent *progressive distal and/or proximal paresis; myalgia, rare cases of myopathy*	rare *paralytic ileus, orthostatic hypotension, arrhythmia*	frequent *reduced amplitude of sensory and motor CAP, almost normal NCV*	less frequent *signs of denervation in distal muscles*	combined neurono- and axonopathy *severe nerve fiber loss, axonal atrophy and secondary demyelination,little axonal regeneration*
Platinum Analogues							
Cisplatin	> 300 mg/m^2 cumulative doses	frequent *paraesthesia, tingling of hand and feet, loss of tendon reflexes, impaired vibration and joint position sense, ataxia Lhermitte's sign*	absent *muscle weakness is extremely rare*	rare *orthostatic dysregulation*	frequent *slowing of sensory NCV with reduced amplitude, prolonged or absent H-reflexes*	none	axono- and neuronopathy *damage of large myelinated Ia fibres, damage to the cell bodies in the dorsal root ganglia*
Carboplatin	> 400 mg/m^2 cumulative doses	less frequent *paraesthesia, tingling of hand and feet, loss of tendon reflexes, impaired vibration and joint position sense, ataxia, Lhermitte's sign*	absent	unknown	less frequent only after high dosis and combination with other drugs *slowing of sensory NCV with reduced amplitude, prolonged or absent H-reflexes*	none	axono- and neuronopathy *damage of large myelinated Ia fibres, damage to the cell bodies in the dorsal root ganglia*
Oxaliplatin	no threshold doses for early signs > 300 mg/m^2 cumulative doses late onset CIN	always *almost instantaniously cold, triggered and/or aggravated paraesthesia, disesthesia and pain later typical signs as seen under cisplatin*	less frequent *muscle cramps, myotonia, tetanic spasms, rarely muscle weakness*	unknown	frequent *low threshold of sensory and motor nerves, rarely repetitive firering, slowing of sensory NCV with reduced amplitude*	less frequent *myotonic discharges, signs of denervation, complex repetitive discharges*	unknown
Suramin	> 350 mg max. plasma level	frequent *mild hypaesthesia and paraesthesia, tingling of hand and feet, loss of tendon reflexes, impaired vibration and joint position sense*	less frequent *severe paresis with a Guillain-Barré syndrome like picture*	unknown	less frequent *NCV slowing and conduction block*	rare *Signs of denervation*	demyelination with axonopathy *segmental demyelination in sural nerve biopsies*

are also capable of inducing polyneuropathy but they are less frequently used or administered at concentrations which will not cause neuropathy; they are considered negligible. The extent of neuronal damage during chemotherapy not only depends on the type of drug used and its dosage, but also on pre-existing nerve damage such as diabetic or/and alcohol neuropathy and inherited neuropathy. Pre-existing neuropathy may also be present as a paraneoplastic syndrome which can worsen with chemotherapy.

Assessment of chemotherapy induced neuropathy relies mainly on clinical examination since no technical method to detect and evaluate neuropathy at an early stage is available. Even when a neuropathy is present evaluation of its severity may yield varying results owing to the different rating scales used to classify the degree of damage (see table 2) [40, 41]. The classical methods of clinical neurophysiology, nerve conduction studies, NCV and electromyography (EMG) are on the one hand often insensitive in detecting early signs of neuropathy, even when the patients already suffer from sensory or motor symptoms, and on the other hand are not very well tolerated by the patient. Therefore, it would be desirable to have new and non-invasive methods at hand to detect and quantify early signs of neuropathy.

Little is known about the mechanisms responsible for the development of neuropathy. Most of the studies reported have focused on morphological changes under drug therapy. However, some of the drugs have also direct effects on nerve excitability by altering ion conductance of the axon and/or Schwann cells. The present review will place special emphasis on this aspect of CIN which has been largely neglected.

Vincristine

Vinca alkaloids act by binding on intracellular tubulin. Under normal circumstances they hardly cross the blood-brain barrier. Apart from infrequent central nervous system side effects (e. g. seizures) peripheral and autonomic neuropathy are regularly encountered. In the peripheral nervous system the drug rapidly induces alterations in the cellular micro-tubuli structure which leads to oedema of the fast and slow conducting axons. This might contribute to the vincristine-induced painful neuropathy which has been produced in an animal model [55]. Most of the patients treated with vincristine develop a dose-dependent (cumulative max. doses 30–50 mg), primarily sensory neuropathy [39, 42, 29]. Early symptoms and signs of neuropathy are paraesthesia and pain of the hands and feet, and distally accentuated hyperaesthesia. Tendon reflexes vanish early in the evolution of neuropathy. Muscle cramps and muscle weakness up to high-degree paresis of the distal muscles are characteristics of the advanced stage of this neuropathy. When vincristine is administered in childhood or given to a patient suffering from hereditary neuropathy, it can lead to rapidly evolving tetraplegia which can be misdiagnosed as acute Guillain-Barré syndrome (GBS) [5, 20]. More than one third of the patients develop signs of autonomic nervous system dysfunction characterised by orthostatic hypotension, constipation, paralytic ileus, urinary bladder dysfunction and erectile impotence. Some of the patients show disturbances of eye movements and paralysis of the vocal cords [7]. Most of these symptoms are reversible after months or years. In some cases, however, they remain permanently.

Table 2 Grading scales for chemotherapy-induced peripheral neuropathy.

Type	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO [33]	None	Paraesthesias and/or decreased tendon reflexes	Severe paraesthesias and/or mild weakness	Intolerable paraesthesias and/or mared motor loss	Paralysis
ECOG [37]	None	Decreased deep tendon reflexes, mild paraesthesias, mild constipation	Absent deep tendon reflexes, severe constipation, mild weakness	Disabling sensory loss, severe peripheral neuropathic pain, obstipation, severe weakness, bladder dysfunction	Respiratory dysfunction secondary to weakness, obstipation requiring surgery, paralysis confining patient to bed/wheelchair
NCIC-CTC [41]					
Sensory neuropathy	None	Loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function	Objective sensory loss or paraesthesia (including tingling) interfering with function, but not interfering with activities of daily living	Sensory loss or paraesthesia interfering with activities of daily living	Permanent sensory loss that interferes with function
Motor neuropathy	None	Subjective weakness but no objective findings	Mild objective weakness interfering with function, but not interfering with activities of daily living	Objective weakness interfering with activities of daily living	Paralysis

ECOG: Eastern Cooperative Oncology Group
NCI-CTC: National Cancer Institute common toxicity criteria

In individual cases symptoms progress even after cessation of therapy or appear some time following withdrawal of the drug. This phenomena is called "coasting" and it is frequently observed after discontinuing cisplatin treatment (see below).

Platinum compounds

The cytotoxic effects of platinum have been known for more than 35 years when Rosenberg et al. observed the inhibition of cell division in bacteria by electrolysis products from platinum electrodes [48]. Soon after, cisplatin (*Cis*-diamine-dichloro-platinium) was introduced as an anti-tumour agent which showed convincing therapeutic effects in various malignancies, particularly ovarian, bladder, lung and testis cancer [34]. However, in those early days of cisplatin treatment nephrotoxicity and gastro-intestinal disturbance used to be the principal side-effects limiting the use of this compound. Since then, these side-effects have been reduced to a minimum by appropriate hydration schedule and other manoeuvres so that cisplatin has become one of the most widely used cytotoxic drugs. The platinum derivatives in common use are cisplatin, carboplatin and the more recently introduced oxaliplatin. They act as anti-tumour agents by reacting with the DNA. DNA is damaged by intra- and interstrand crosslinks and this induces apoptotic cell death in rapidly dividing cell lines and cancer cells [28]. The platinum derivatives bind avidly to plasma proteins. They hardly cross the blood-brain barrier, but have a high affinity to the peripheral nervous system. The compound can be detected in dorsal root ganglion cells (DRG) and the sensory nerves themselves. Here they accumulate and induce shrinking of the nuclear and cytoplasmic compartments [21, 12]. The mechanism of toxicity is probably not due to direct damage of the DNA, but is based on a disturbance of cellular metabolism and the axo-plasmatic transport. It is unknown why platinum compounds affect sensory nerves more than motor nerves. A possible explanation could be the high affinity of the drug to accumulate in the DRG neuron which is known to exist for other metals like barium and thallium. Electrophysiological investigation of the effects of cisplatin on cultured dorsal root ganglion neurones revealed a reduction of voltage activated potassium currents by 50 % and calcium currents by 60 % [51]. This observation could explain a direct effect of cisplatin on nerve excitability. However, our own experiments with isolated peripheral nerves investigated in an organ bath showed little acute effects of cisplatin on excitability parameters of peripheral nerves in vitro and these effects differed considerably from the effects of oxaliplatin and taxol [22].

Histological examination of cisplatin neuropathy reveals loss of axons with secondary atrophy of the dorsal root. In an advanced stage of neuropathy reactive gliosis of the dorsal column develops as a consequence of the loss of the DRG. The platinum-induced neuropathy can therefore be categorized as a primary neuronopathy rather than an axonopathy [60].

The neurotoxicity of cisplatin and carboplatin is well documented. First signs of the predominantly sensory neuropathy appear about one month after initiation of therapy [30, 34, 58]. The extent of neuropathy can be correlated to the cumulative dose of the platinum compound but also depends on the single dose given at each administration. Neuropathy can follow exposure to amounts as low as 200 mg/m^2. Doses above 400 mg/m^2 will always lead to neuronal damage [23]. The clinical picture of the neuropathy is characterised by a predominantly sensory neuropathy with diminished vibration perception, loss of tendon reflexes and discomforting paraesthesia starting in the lower extremities [57]. The intensity of paraesthesia reported ranges from light tingling to extensive pain. In an advanced stage of the neuropathy the patient is ataxic with a pronounced gait disturbance due to impaired proprioception. Beside these frequent symptoms which also include muscle cramps, one can find Lhermitte's sign or a similar perception which is described as an electric sensation in the shoulder girdle. This is due to demyelination of the dorsal roots and columns [53]. Electroneurography detects a pure sensory axonal and secondary demyelinating neuropathy relatively late in the clinical manifestation of symptoms. The sural nerve as the most sensitive indicator for sensory neuropathy shows amplitude reduction and slowing of nerve conduction velocity reflective of both axonal loss and demyelination. Motor nerves are normally spared by the neuropathy. Therefore electromyography should be normal. Symptoms of neuropathy may start even after cessation of therapy and can persist over the following months [23]. This characteristic phenomenon of cisplatin induced neuropathy called coasting makes it very difficult to grade cisplatin induced neuropathy since even after discontinuing drug treatment the peak of symptoms might not be reached. The underlying mechanism is not well understood; however, it might be related to the ability of the drug to accumulate and persist over long time in the DRG.

Oxaliplatin is a new compound in the platinum family. It is employed in the therapy of colorectal cancer. There is no cross-resistance to other platinum compounds when used in combination. Oxaliplatin acts by cross-binding of DNA as well as by blocking DNA-synthesis [63]. The mechanism by which oxaliplatin evokes neuropathy has not been observed with other platinum compounds. Oxaliplatin seems to interfere with axonal ion conductance and thereby alters neural excitability. Evidence in support of this hypothesis comes from our in-vitro experiments where oxaliplatin elicited cellular hyperexcitability in a dose dependent manner [1]. This

observation offers a good explanation why oxaliplatin induces sensory symptoms 30 to 60 minutes after infusion, which the patients describe as paraesthesia and dysaesthesia aggravated by cold [18]. Apparently infusion time and the cumulative total dose of oxaliplatin play an important role in inducing this type of "early" neuropathy. Almost every patient who receives a total dose of > 540 mg/m^2 develops neuropathy. These early symptoms described above completely disappear within a few days to a couple of weeks. The symptoms consistently reappear after every new drug application. Apart from these early symptoms, patients develop the well known sensory disturbances caused by all members of the platinum family which consist of pronounced hypaesthesia of the distal part of the extremities. These symptoms are partly reversible in about 80 % of the patients and completely resolve after 6 to 8 months in about 40 % of all patients [18].

Taxol

Paclitaxel and docetaxel are new and effective chemotherapeutic drugs which have been used in the treatment of different tumours [49]. In contrast to vincristine, which leads to dissociation of microtubuli by binding to specific regions of tubulin, the taxanes paclitaxel and docetaxel act by aggregation of intracellular microtubules. The most restricting side-effect of these drugs is their neurotoxicity [47]. The mechanism by which these drugs affect neuronal tissue is still unknown despite a wealth of in-vitro and in-vivo studies. The effects of taxol were investigated in cell cultures, samples of peripheral human and animal nerves and with different electrophysiological methods in patients. Collectively, these studies demonstrated direct effects of the drug on Schwann cells, a loss of axons and a disturbed cytoplasmatic flow in the affected neurones [13, 49].

Our own in-vivo and in-vitro investigations applying new electrophysiological methods demonstrated an acute effect of taxol on the excitability of human peripheral sensory and motor nerves [50, 45]. In these experiments taxol induced an acute membrane depolarisation via an axonal membrane leak and a non-specific ion influx in peripheral nerves. These findings can explain some of the acute symptoms under taxol therapy which have not been described for other chemotherapeutic drugs. In contrast to previous observations taxol had no threshold dose in inducing neuropathy in our studies [50, 56, 24]. A few patients develop neuropathy even after a single administration of taxol, especially in combination with cisplatin. More than half of the patients treated with taxol > 250 mg/m^2 complain about par- and dysaesthesia which appear 24–72 hours after administration. These symptoms are followed by distal symmetrical hypaesthesia and hyperalgesia [43, 62] of the upper and lower extremities in a length dependent manner [14]. In contrast to cisplatin which predominantly affects the small and thinly myelinated axons (responsible for pain and temperature perception), taxol affects all sensory modalities preferring thick myelinated nerve fibres that conduct vibration perception and sense of position. Loss of tendon reflexes are an early sign in this type of neuropathy [27]. First reports about taxol induced neuropathy described a predominantly sensory or sensory autonomic neuropathy. More recent reports from larger trials, however, clearly produced evidence that the taxanes are also capable of inducing muscle weakness and motor neuropathy, which has in some cases been predominant and disabling [35].

NCV and EMG studies reveal damage of the motor nerves even in clinically asymptomatic cases. These measurements show a reduction of motor and sensory compound action potential (CAP) amplitude. The reduction of the motor and sensory CAP amplitude is an indicator of axonal loss which leads to secondary CV reduction as a result of the loss of fast conducting myelinated axons. EMG studies reveal pathological spontaneous activity in the distal muscles of the lower limbs. In individual cases pure proximal weakness and myalgia have been reported which showed typical myopathic changes in the EMG [47]. Muscle pain starts one to two days after taxol infusion and disappears without any specific treatment within four days up to one week. Risk factors for taxol-associated CIN are cumulative dose, high single doses, rapid infusion time (< 24 h), previous or simultaneous administration of other chemotherapeutic drugs and pre-existing neuropathy.

During taxol and docetaxel therapy progression of neuropathy as well as amelioration of neuropathic symptoms can be observed. In individual cases the course of the neuropathy is almost impossible to predict since continued aggravation of neuropathy has been reported even when taxol therapy was stopped several weeks previously [26].

Suramin

Suramin is an experimental chemotherapeutic agent which shared results as an anti-neoplastic drug in a number of clinical trials. It is used in the treatment of solid tumours as e. g. prostate and ovarian cancer as well as in lymphoma. Dose-limiting neurotoxicity remains the most serious complication of suramin treatment. The mechanism of suramin-induced cyto- and neurotoxicity is unclear [15]. A possible mechanism seems to be the inhibition of growth factors. Another known effect of suramin is its blocking effect on P2 purinergic receptors, which are divided into two subtypes: the metabotropic P2Y and the ionotropic P2X receptors.

These receptors are localised on many different cell types. However, in the PNS they are only found on the DRG neurons (P2X) and Schwann cells (P2Y) [54, 61]. Activation of P2 receptors has been reported to induce intracellular Ca^{2+} transients in intact peripheral nerves which play an important role in the intracellular signal transduction pathways [32]. Therefore, blockade of P2 receptors by suramin could seriously perturb these Ca^{2+} dependent intracellular pathways and consecutively lead to cell damage. Our own experiments on human sural nerve in vitro showed that suramin was only effective in blocking purinergic rise in intracellular Ca^{2+} in unmyelinated Schwann cells. This observation indicates that suramin is able to induce neuropathy only in unmyelinated nerve fibres. The clinical picture of suramin-induced neuropathy is, however, a mix of predominantly sensory and motor symptoms with higher dosage. About 40 % of patients with plasma peak levels higher than 350 µg/ml will develop sensorimotor neuropathy. In individual cases, neuropathy can be very severe, resembling subacute GBS with flaccid paralysis. In general suramin neuropathy has a good tendency to remit; however to prevent neuropathy plasma levels should be carefully monitored and treatment discontinued at the first signs of neurotoxicity.

Combination of different drugs

The combination of different chemotherapeutic agents is common practice in anti-tumour treatment. Their synergistic effect in inducing neuropathy is not well known. Especially the combination of taxol and cisplatin is frequently used since they are still effective when other chemotherapeutic drugs have failed [11, 14]. The combination of taxol and cisplatin can lead to a rapidly progressing neuropathy which exceeds the neuropathic symptoms known from cisplatin or taxol therapy alone [42, 49]. The taxol-cisplatin neuropathy is characterised by involvement of predominantly thick myelinated nerve fibres [14]. The principal symptoms are pain, paraesthesia, numbness of the fingers and toes, paralysis, involvement of the cranial nerves and autonomic dysfunction. Vincristine is frequently combined with other chemotherapeutic agents like procarbazin and CCNU. Little is known about a possible aggravation of vincristine neuropathy due to combination with other drugs [42].

When should chemotherapy be limited or even stopped?

There are no general rules when drug therapy should be changed or even stopped. Prevention or attenuation of CIN should be major goals of an adaptation of the drug regime. Whenever chemotherapy is able to cure the patient's cancer CIN should be tolerated as an undesirable side effect without changing the effective dose regime. In most instances, however, chemotherapy is used in the palliative treatment of cancer. Given the more pronounced efficacy of antineoplastic drug treatments that results in larger disease-free intervals, quality of life becomes a major issue. CIN considerably affects quality of life in most patients. However, clear guidelines how to use the grading systems given in Table 2 are lacking and these grading scales do not include assessment of quality of life [41]. In general, grade 2 (WHO or ECOG) will already affect quality of life in most patients. Grade 3 (WHO, ECOG and NCI-CTC) should be considered as a stage where limiting drug dose or alternative therapeutic approaches should seriously be considered. There are a few exceptions to this general view. Cisplatin induced neuropathy may start even after cessation of therapy and can persist over the following months (coasting) which makes general recommendation and guidelines concerning grading and dose limiting difficult. In contrast, oxaliplatin is known to induce rapidly sensory symptoms 30 to 60 min after infusion which the patients describe as paraesthesia and dysaesthesia aggravated by cold [18]. These symptoms soon severely compromise quality of life in most patients. However, since these early symptoms completely disappear within a few days to a couple of weeks and most of the symptoms can be attenuated or even abolished with sufficient carbamazepine pre-treatment, the drug dose should not be limited until severe and persisting signs of neuropathy (grade 3) are observed.

Therapy of CIN and prophylactic measures

Prophylaxis and therapy of CIN should not be a difficult task since the damage induced by the chemotherapeutic drugs is restricted to a limited time period and to a specific tissue. However, clinical experience shows that CIN is a difficult problem to manage. There are no effective drugs for prophylaxis or therapy of this neuropathy. Different strategies to prevent neuropathy have been developed in cell and animal models. Some have reached clinical application [for review 4]. Neurotrophic factors seem to provide an attractive approach to prevent and to treat CIN [2]. In animal models of cisplatin-, vincristine- and taxol-induced neuropathy nerve growth factor (NGF) and insulin-like growth factor (IGF) were able to reduce or even prevent neuropathy [3, 25, 16]. Furthermore, a recent report on potent analgesic effects of glia-derived neurotrophic factor (GDNF) in neuropathic pain states suggests this compound may be an option for future treatment of CIN [6]. Unfortunately these promising substances have not so far reached clinical application. One of the reasons is based on the difficul-

ties in drug administration, adverse effects and pharmacokinetics.

Furthermore, until now it is still unclear how nerve growth factors might effect tumour proliferation. Other approaches to prevent CIN are based on neuroprotective compounds like amifostine (chemically ethanethiol) and glutathion (an antioxidant). These substances are supposed to protect selected healthy tissue in different organ systems against the cytotoxic substances without reducing the effectiveness of the chemotherapeutic agents [4, 8, 9]. Amifostine (740–910 mg/m^2 intravenously over 15 min) is given about 30 min before the start of chemotherapy [17, 38]. Lower concentrations might also be effective but clinical trials on amifostine are still lacking. The neuroprotective effect of amifostine in preventing neuropathy during combined carboplatin/paclitaxel therapy is slightly significant [52, 38]. In contrast, glutathione (1,5 g/m^2 in 100 ml NaCl over 15 min, about 30 min before chemotherapy starts) appears to significantly reduce CIN [9]. This promising result has to be confirmed by future studies. Other neuroprotective drugs which are used in diabetic neuropathy might be also helpful in CIN. Alpha-lipoic acid which has proven efficacy in diabetic neuropathy could be one of the future candidates which could be administered before, during or after drug treatment [36]. To date, only anecdotal reports on the effectiveness of alpha-lipoic acid are available. Attempts to prevent CIN by the calcium channel blocker nimodipine failed [10]. Glutamate ameliorates experimental vincristine, cisplatin and paclitaxel neuropathy. Clinical trials, however, have not been conducted. One of the first attempts to prevent CIN was through administration of corticosteroids or ACTH-like substances during chemotherapy. Small clinical trials yielded promising results, but the use of these substances has not been generally recommended [19, 59]. In contrast, recent studies reported that under cisplatin and docetaxel therapy the administration of corticosteroids and ACTH-like substances worsened the neuropathy [44, 46]. The general idea of protecting neuronal tissue by closing the blood-nerve barrier by corticosteroids is appealing. However, CIN in most instances starts at the nerve endings, the dorsal root ganglion or at the nerve root, where the blood-nerve barrier is absent or incomplete.

All other therapeutic approaches are restricted to symptomatic treatment of paraesthesia and pain. Ion channel blockers like carbamazepine and gabapentin have shown efficacy. Carbamazepine (600–1200 mg) seems to be particularly effective in the treatment of early hyperpathic symptoms under oxaliplatin therapy [31]. As in neuropathic pain treatment, tricyclic anti-depressivants are also in first line. In general, during administration of platinum compounds, magnesium and calcium ions are able to attenuate the symptoms.

Conclusion

Chemotherapy induced neuropathy is a common adverse effect of chemotherapy which can be the dose limiting factor in cancer therapy. The neuropathy is often disabling and severely impairs the quality of life. To date no effective strategy to prevent or cure the symptoms is available. Therapy is restricted to the treatment of unpleasant dysaesthesia and pain by using membrane stabilising drugs and tricyclic antidepressants. It seems therefore important and mandatory to inform the patient of the risk to develop CIN, its nature, symptoms and prognosis. When anti-tumour therapy has been effective and sufficient time allowed for the regeneration of the damaged peripheral nervous system to occur, then in most cases CIN is reversible.

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