Characteristics of Chemotherapy-induced Neuropathy

Clinical Studies on Cisplatin and Docetaxel

Kenmerken van door chemotherapie veroorzaakte polyneuropathie;
klinische studies naar Cisplatin en Docetaxel

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Chapter 1

Chemotherapy-induced peripheral neuropathy

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Abstract

Peripheral neurotoxicity is an important side-effect of several chemotherapeutic agents. These agents may cause a usually axonal neuropathy, which may ultimately lead to severe and disabling symptoms and signs. Besides describing in this review the pathogenesis, the clinical presentation, the neurophysiological findings and the nerve biopsies, we also recount the relation between cumulative dosage/dosage per cycle and neuropathy for the cytostatic drugs for which neurotoxicity is an important side-effect: cisplatin, vincristine, paclitaxel, docetaxel and suramin. With the development of strategies to circumvent toxicities of other organs and with the use of combinations of neurotoxic agents such as cisplatin/paclitaxel, neurotoxicity is an important and dose limiting side-effect of many treatment regimens. Detailed knowledge of the neurologic side-effects of these drugs is essential for the management of their neurotoxicity. The review concludes with a short discussion of neuro-protective agents. Although several nerve growth factors, gluthation and ethiofos hold promise as possible neuroprotective factors, the clinical data on these drugs are still limited. New trials are needed to confirm the value of these drugs. If neurotoxicity can indeed be prevented or delayed, this may lead to more effective treatment regimens.

Introduction

Some of the chemotherapeutic agents are notorious for their toxic effects on the peripheral nerves. The severity of this complication may range from some loss of sensory function and mild paresthesias to neuropathic pain, severe ataxia and weakness leading to pronounced disability. The involvement of autonomic nerve fibres with orthostatic hypotension, impotence and incontinence may further reduce the quality of life. Many cytostatic agents have occasionally been reported to be neurotoxic, but in only a few drugs peripheral neuropathy is an important and dose limiting side-effect. The neurotoxicity of the older agents vincristine and cisplatin is well-known. In several of the newer and promising chemotherapeutic agents, i.e. paclitaxel (Taxol®), docetaxel (Taxotere®) and suramin, neuropathy is also a prominent side-effect. Due to their neurotoxicity treatment with these drugs must often be discontinued, which may prohibit an effective treatment.

In all these drugs, either the dose per cycle, or the cumulative dose, or the dose-intensity determines the severity of the neurotoxicity. If it were possible to prevent and/or modify the neurotoxic side-effects of these drugs, this would have important consequences for the efficacy of the treatment and the quality of life of these patients. A modification of dosing-schedules may be one possibility to prevent severe neurotoxicity. Others have tried to prevent chemotherapy-induced neuropathy with possible neuroprotective agents, some of which experiments showed promising results. This article reviews the drugs in which peripheral neurotoxicity is an important side-effect, and briefly discusses the possible role of (neuro)protective agents. As the taxanes are a new and important class of chemotherapeutic agents, some emphasis is put on these drugs.

Cisplatin

Cisplatin is an effective cytotoxic agent in various malignancies, particularly ovarian, testicular and bladder cancer. The anti-tumor effect is based mainly on the reaction with DNA, forming both intra- and interstrand crosslinks. Nephrotoxicity used to be the principal side-effect, but since the reduction of renal toxicity (by several measures such as a hydration schedule) and of gastro-intestinal side-effects neurotoxicity is regarded as a dose-limiting side-effect of cisplatin [1]. As in vitro studies on human cancer-cell lines and clinical trials show a steep dose-response relationship for cisplatin, more intensive dosing schedules of cisplatin have been used [2,3]. Neurotoxicity was a major toxicity in many studies on high-dose cisplatin [3-10]. Infrequently, other neurotoxic effects have been reported: autonomic neuropathy [2,11-13], optic neuropathy [14] and encephalopathic symptoms including cortical blindness and seizures [15-18].

Thus, in most cases neurotoxicity is limited to an axonal sensory neuronopathy and to ototoxicity. Ototoxicity mainly affects hearing in the high frequency range, the clinical spectrum of which varies between tinnitus and severe deafness [19]. The sensory neuropathy is due to damage of large myelinated Ia fibres, presumably at the level of the cell bodies of the sensory nerves located in the dorsal root ganglia [20-22]. Dorsal root ganglia are not protected by a blood-brain barrier, explaining a 10-fold higher cisplatin concentration at that site as compared to the brain and spinal cord [20]. Probably cisplatin binds or crosslinks proteins involved in microtubular structure and axonal transport [23].

The first symptoms of cisplatin neuropathy are paresthesias and numbness in a stocking and glove distribution, loss of tendon reflexes and a decrease in mainly thick fibre mediated sensory qualities such as vibration perception, fine touch perception and proprioception. This can lead to

difficulties in small motor coordination. As the neuropathy increases a disabling sensory ataxia may ensue. Muscle weakness is extremely rare [20,24-26]. Pain is not a symptom of cisplatin neuropathy. Some patients develop Lhermitte's sign or experience paresthesias and an electric shock sensation on stretching the arms or legs [27-32]. The neuropathy may continue to deteriorate up to three to four months after cessation of therapy. This phenomenon probably reflects a time-lag in clinical manifestations of neuronal injury related to ongoing pathological changes in axonal transport [6,8,33,34]. Thereafter a gradual but often incomplete recovery is the rule, leaving especially those patients with severe neuropathy with residual deficits [5,8,17,35,36].

Typically, nerve conduction studies (NCV) show a decrease or absense of sensory nerve action potentials, delayed sensory nerve conduction velocities and prolonged or absent H-reflexes. The motor nerve conduction and electromyography (EMG) are usually normal [11,20,22,24,29,37-39]. Sural nerve biopsies show a degeneration of large myelinated axons with signs of segmental demyelination and remyelination [20,24].

The main prognostic factor for the severity of neuropathy is the cumulative dose of cisplatin [17,24,25,40]. With conventional doses of cisplatin 50-75 mg/m^2 per cycle and cumulative doses exceeding 300 mg/m^2, the reported incidence of neuropathy varies between 24% and 92% [5,24,29,32,41,42]. In a large prospective Dutch study in which patients received a median cumulative dose of cisplatin between 500 and 600 mg/m^2, the overall incidence of any grade of neuropathy was 47% [25]. The incidence in long survivors was even higher (61%). Severe neurotoxicity leading to walking difficulties occurred in 4% of patients. Some authors have reported a relation between severity of neuropathy and age, gender or tumor type [3,43].

In some studies cisplatin-toxicity was reduced by modifying the dosing schedule. Decrease of cisplatin dose-intensities by dividing the total dose over

several days is associated with less ototoxicity [44], gastrointestinal toxicity and nephrotoxicity [45]. Other studies reported that a schedule with administration of cisplatin on day 1 and 8 was less toxic than the same total dose given over five days, so perhaps the accumulation of cisplatin is smaller when larger time intervals are used [46,47]. It is unclear if the severity of neuropathy is influenced by alterations in the dosing schedule. In a comparative study we found only the cumulative dosage and not the dose-intensity to be related to the development of neurotoxicity [36]. In contrast, in two other studies higher dose-intensities of cisplatin gave rise to increased neurotoxicity [5,41]. A subsequent study in our institute on retreatment with cisplatin in patients with recurrent ovarian cancer following earlier treatment with cisplatin gives support for the importance of the dose-intensity. No significant neurotoxicity was observed despite the administration of a total cumulative dosage over 800 mg/m^2 in most patients [48].

Vincristine

The vinca alkaloids are widely used in cancer therapy for both solid tumors and hematologic malignancies. These drugs bind microtubule associated proteins preventing the formation of microtubuli in the mitotic spindle, thereby interfering with cell division. Microtubules are also involved in axoplasmatic transport and much of the neurotoxicity is explained by disruption of this process [35,49,50].

Vincristine is the most frequently used vinca alkaloid due to its efficacy and relative lack of myelosuppression. However, it is also more neurotoxic than the other two, and this is the dose-limiting side-effect [35,50]. Vincristine neuropathy is of a mixed sensory-motor and autonomic nature. Rare manifestations of vincristine neurotoxicity are cranial nerve involvement [51-53], seizures, mental changes and confusion, and the syndrome of inappropriate

antidiuretic hormone secretion [35]. Paresthesias involving hands and feet are an early manifestation, often occurring within the first few weeks of therapy. Many patients complain about numbness but usually the sensory symptoms outweigh the objective sensory deficits. The earliest and most consistent finding of vincristine neuropathy is the suppression of the achilles-tendon reflexes. Later on other deep tendon reflexes also disappear [51,52,54,55]. Objective sensory loss is seldom severe. The neuropathy is painless, although severe pain in the region of the jaw or throat occasionally occurs after the first or second dose of vincristine [52]. Motor involvement is the most severe manifestation of neuropathy. It is often heralded by clumsiness of the hands and cramps in the legs, and may result in severe weakness. The distribution of weakness is unusual, characteristically the weakness impairs the extensors of the fingers and wrist and the dorsiflexors of the toes and ankle [51,52,54]. Autonomic neuropathy is another frequent and early side-effect of vincristine [35,50]. Often, this causes gastro-intestinal symptoms, with constipation, abdominal pain and paralytic ileus as the major manifestations [51,52,56]. Other less frequent manifestations of autonomic dysfunction include bladder atony with urinary retention, impotence and orthostatic hypotension [51]. Usually, recovery starts when the drug is withdrawn although symptoms and signs may first worsen to some extent. Even paresis is generally completely or partially reversible but recovery is often slow, requiring months. Sensory symptoms and hyporeflexia may persist but are not troublesome in most patients [57].

NCV studies show normal or near-normal sensory and motor nerve conduction velocities, with a reduction in the amplitude of the sensory nerve action potentials and compound motor potential. The EMG may show signs of denervation [54,58]. The H-reflex may be unimpaired despite the absence of achilles tendon reflexes. Guiheneuc et al. found a decrease of the ratio of the

amplitudes of the soleus muscle elicited by the achilles tendon reflex and the H-response the most sensitive early parameter [59]. These findings are compatible with an axonal degeneration of the 'dying back type'. The axonal nature of this neuropathy has been confirmed by nerve biopsies [50,58,60].

The incidence and severity of vincristine neuropathy are related to both the single and cumulative dose. Treatment within a dose range of 2-6 mg/m^2 per month causes usually no more than mild paresthesias and reflex depression. Vincristine is predominantly excreted via the biliary system, therefore liver impairment increases the susceptibility to neurotoxicity [51]. Concurrent neurotoxic medication may worsen the neuropathy. A pre-existing neuropathy may make patients more susceptible to vincristine neurotoxicity. Severe neuropathy in patients with (asymptomatic) Charcot-Marie-Tooth disease [61,62] and Guillain-Barre syndrome [63] has been reported. As stated, the other vinca-alkaloids like vinorelbine are less neurotoxic, due to their low affinity for axonal tubulin. Still, in one-third of paclitaxel pretreated patients vinorelbine caused a severe axonal sensori-motor neuropathy [64]. Whether this was due to the pre-existent neuropathy or to a synergistic toxic effect remains unknown.

Paclitaxel (Taxol®)

Paclitaxel (Taxol®) is the first of a new important class of anti-cancer agents, the taxanes. Paclitaxel was discovered in 1963 as part of a large scale program of the National Cancer Institute (USA) to screen plant extracts for cytotoxic activity. A crude extract from the bark of the Pacific yew Taxus brevifolia, a slow-growing and scarce American evergreen, was found to have cytotoxic activity against a broad range of tumors [65,66]. Clinical anti-tumor activity has been demonstrated against a variety of tumors [66]. In contrast to other anti-microtubule drugs such as vinca-alkaloids that induce the

disassembly of microtubules, paclitaxel promotes the polymerization of tubulin forming very stable and dysfunctional microtubules. It thus interferes with microtubule functions required for cell division and several vital interphase functions including maintenance of shape and intracellular transport [65-67]. The main side-effects of paclitaxel are hypersensitivity reactions, myelosuppression, cardiac disturbances and neurotoxicity [65,66]. As myelosuppression can in part be circumvented with granulocyte colony-stimulating factor (G-CSF), neurotoxicity is a dose-limiting side-effect [68,69]. Paclitaxel induced neuropathy is probably due to dysfunctional microtubuli in dorsal root ganglia, axons and Schwann cells [70,71]. The primary site of pathogenesis is not clear. The distal symmetric length-dependent neurological deficits in some patients suggest a dying-back neuropathy, which may have its origin both in the cell body and in the axonal transport. On the other hand, the simultaneous onset of symptoms in arms and legs in some patients, and the occasional trigeminal involvement are also compatible with a neuronopathy.

Autonomic neuropathic manifestations such as a paralytic ileus and symptomatic orthostatic hypotension have been observed but they are rare [72]. Other rare neurotoxicities include optic nerve disturbances [73], epileptic seizures [72] and encephalopathy [74]. The most frequent neurotoxic side-effect is a predominantly sensory neuropathy. Typically, signs and symptoms start shortly after the administration of paclitaxel and tend to improve before the next cycle [75]. Initial symptoms include numbness, paresthesias and a burning pain in a glove-and-stocking distribution. There is often a simultaneous onset in hands and feet, sometimes with facial involvement [70]. At examination distal loss of both large and small fibre mediated sensory qualities and loss of deep tendon reflexes can be found. In patients with more severe neuropathy motor involvement is not rare, usually as a mild distal weakness, but some patients

go on to develop a severe weakness [76,77]. The neuropathy may be extremely painful or accompanied by disabling dysesthesias. Some patients have transient myalgias 2-3 days after the administration of taxol, which resolve in a few days [78]. A myopathy has been described in patients with high doses of paclitaxel (300-350 mg/m^2) in combination with cisplatin [79]. In most patients the neuropathy improves after the end of treatment, but progressive detoriation of the neuropathy with severe weakness following the discontinuation of treatment has been described [76,80].

Nerve conduction studies usually show a predominantly axonal sensory, but in more severe cases both axonal degeneration and demyelination may be present with widespread denervation signs and severe conduction abnormalities. Sural nerve biopsies showed mainly axonal loss [70,76,81].

The severity of neuropathy is related to both the single and cumulative dose of paclitaxel. At lower dosages per cycle(135-200 mg/m^2) neuropathy is rare, occurring at a higher cumulative dosage (>1400 mg/m^2) and usually mild [75]. At a higher dosage per cycle (>250 mg/m^2) a more severe neuropathy is frequent, which often starts in the days following the first cycle [70,82]. Despite the frequent improvement before the next cycle, with more cycles the symptoms increase [75,82]. It has been suggested that the neuropathy may be more severe if paclitaxel is administered in three hours as compared to 24 hours, due to a higher area under the concentration-time-curve [82]. Other risk factors include prior exposure to other neurotoxic agents and antecedent medical disorders (alcoholism, diabetes mellitus) associated with peripheral neuropathy [77]. Especially in diabetes mellitus severe neuropathies have been described [80,83]. Amitryptiline may be useful to treat neuropathic pain in taxanes-induced neuropathy.

Docetaxel (Taxotere®)

Because the natural supply of the source of paclitaxel is limited, a synthetic pathway was sought. In 1986 this resulted in a semi-synthetic taxane, docetaxel (Taxotere®) for which a precursor extracted from a renewable source, the needles of the European yew (Taxus baccata), was used [65]. Structurally, docetaxel is closely related to paclitaxel and has the same mechanism of action: it inhibits tubulin depolymerization and promotes microtubule assembly, thereby stabilizing microtubules. In vitro docetaxel is twice as potent as paclitaxel [65]. In recent years docetaxel has been found to be one of the most active new anti-neoplastic agents. Phase I and II trials have shown significant clinical activity in ovarian cancer, breast cancer, melanoma, non-small-cell lung cancer and small-cell lung cancer [84]. Neutropenia is the dose-limiting toxicity in most studies. Other side-effects are hypersensitivity reactions, a fluid retention syndrome with peripheral edema, gastro-intestinal toxicity, cutaneous toxicity, onchylysis and a peripheral sensory neuropathy [84]. The precise mechanism of docetaxel-induced neuropathy is unknown, but based on the resemblance with paclitaxel it may also be due to the formation of dysfunctional microtubules.

In phase II trials of docetaxel treatment with a dose of 100 mg/m^2 every 3 weeks, after 3 or 4 cycles 37%-54% of the patients developed a usually mild but occasionally severe dose dependent sensory neuropathy with numbness and paresthesias in a glove-and-stocking distribution [85-88]. In a study conducted in our institution 20 out of 41 evaluable patients treated with cumulative doses ranging 150-1100 mg/m^2 developed a usually mild neuropathy [89]. However, of the 15 patients treated with a cumulative dose above 600 mg/m^2 11 developed a neuropathy, which was considered moderate or severe in 4 [89]. Symptoms started with paresthesias and numbness in hands and feet and loss of tendon reflexes and vibratory perception were

early signs. With the progression of the neuropathy the paresthesias became disabling or painful, suggesting involvement of small unmyelinated nerve fibres. Due to the numbness with loss of joint position sense several patients developed loss of dexterity and unsteadiness of gait. Although signs and symptoms were dominated by a sensory neuropathy, in one patient severe weakness was observed [89,90]. New et al. found evidence of motor weakness in half of the patients with docetaxel neuropathy [91]. Another series reported a predominantly proximal weakness in 7 out of 60 docetaxel treated patients [92]. Similar to in cisplatin induced sensory neuropathy, Lhermitte's sign was observed [93]. In most patients symptoms tend to improve following the discontinuation of the treatment, but in some patients the symptoms first increase to improve again after 4-8 weeks [89-91]. NCV studies show a predominantly axonal sensory neuropathy, in more severe cases conduction abnormalities may be present and the EMG may show denervation signs [90,94].

In our experience the neuropathy is related to the cumulative dose, with more severe symptoms and signs in patients treated with a cumulative dosage over 600 mg/m^2. Liver function disturbances interfere with the metabolism of docetaxel, and they have been related to more severe side-effects [84]. This may also account for individual susceptibility for neurotoxicity as encountered in some patients [90]. The dosage per cycle is also important, since we have observed an ameloriation of docetaxel neuropathy despite a continuation of treatment at a lower dosage (75 mg/m^2 per cycle instead of 100 mg/m^2) [93]. Steroids reduce several side-effects of docetaxel like the fluid retention syndrome, but we observed no reduction of docetaxel induced neuropathy by steroid co-medication during treatment [95].

Discontinuation of treatment in taxanes induced neuropathy

Although infrequent, sometimes the only significant toxicity of taxanes is the neuropathy. Especially in a patient with a tumor response to the treatment this poses a difficult problem. On the one hand continuation of the treatment may result in a severe neuropathy, whereas discontinuation means the cessation of an effective drug. No studies have yet addressed this clinical issue. In general, symptoms and signs of taxane-induced neuropathy diminish once the treatment is discontinued but this is not always the case [76,80,89-91]. Some patients detoriate after discontinuation, and they may even develop severe weakness. Also, in occasional patients the residual symptoms have a great influence on the quality of life. In general, we discontinue the treatment once signs and symptoms interfere with daily functions such as tightening buttons and walking, or when patients develop motor signs. Invariably, NCV studies in patients treated with taxanes show an axonal sensory neuropathy. We also consider discontinuation of the treatment once NCV studies show an axonal motor neuropathy or significant motor conduction disturbances. It is unknown if treatment must always be discontinued, since we have observed the amelioration of docetaxel induced neuropathy following dosis reduction [93].

Combination treatment with taxanes and cisplatin

Cisplatin and taxanes act against the same tumors, like ovarian carcinoma and head/neck cancer. Taxanes have been effective in patients with platinum resistant tumors, and in ovarian cancer the combination of cisplatin and paclitaxel was found to be more effective than the standard treatment with cisplatin/endoxan [96]. As a result, many patients are now treated either with both drugs at the same time or in succession. Although by a different

mechanism, both drugs are neurotoxic and thus a cumulative neurotoxicity may be expected [97]. Indeed, pre-treatment with cisplatin has been related to an increase in neurotoxicity of a subsequent treatment with either paclitaxel or docetaxel [98,99]. Unfortunately, no well-designed studies have addressed this issue, and in studies on docetaxel neurotoxicity no evidence for increased neurotoxicity was apparent in cisplatin pre-treated patients [41,94]. In a large study on 1000 patients with platinum refractory ovarian cancer treated with 135 mg/m^2 paclitaxel per cycle, only 2% of the patients developed a moderate or severe neuropathy [100]. Thus, there is no reason to refrain from taxanes-based chemotherapy in cisplatin pre-treated patients or vice versa, although it certainly justifies a more careful approach.

As expected, a combination chemotherapy of taxanes and cisplatin induces a sensory neuropathy in a significant number of patients. In phase I trials on a combination chemotherapy of cisplatin and paclitaxel, sensory neuropathy was a dose limiting toxicity [69,80,101]. The neuropathy seemed mainly due to the dose per cycle and cumulative dosage paclitaxel. Neuropathy was rare in patients receiving less than 200 mg/m^2 paclitaxel per cycle, but frequent in those treated with >200 mg/m^2 per cycle. This is no surprise, as at this dosage paclitaxel is neurotoxic by itself. A phase III trial on combined paclitaxel/cisplatin chemotherapy employing 135 mg/m^2 paclitaxel administered over 24 hours underscores this, since no increase in neurotoxicity was observed compared to the treatment with cisplatin/endoxan [96]. Conflicting results were reported on the treatment with cisplatin 75 mg/m^2 and paclitaxel 135-175mg/m^2 administered over 3 hours. With this treatment, one study observed frequent neurotoxicity which was severe in one-fifth of the patients [102]. In contrast, others observed no significant neurotoxicity, and comparison to a control group treated with cisplatin and cyclophosphamide showed similar neurotoxicity of the latter

regimen [103]. In our experience, neurotoxicity is a dose limiting toxicity of this schedule. In a dose finding phase I study on docetaxel/cisplatin chemotherapy, we observed a neuropathy in 24 out of 35 patients treated with a cumulative dosage over 200 mg/m^2 of both cisplatin and docetaxel. The neuropathy was considered moderate in 10, and severe in one patient. The combination appeared to be more neurotoxic than either drug alone at the same dosage level, thus these drugs may have a synergistic effect on neurotoxicity [104,105]. It is often possible to decide which agent causes the neuropathic symptoms, as the clinical picture (onset of symptoms, pain) is different between the two drugs. This may allow dose reduction. Even in patients with a severe neuropathy due to this combination chemotherapy, signs and symptoms are usually, at least partially, reversible.

Suramin

Suramin is a polysulfonated naphtylurea which has been used since the 1920s as an antiparasite agent [106]. Recently, suramin has received attention as a potential anti-neoplastic agent, because of its capacity to disrupt several systems important to tumor proliferation, in particular the inhibition of several cellular growth factors. In clinical trials the drug appeared to have clinical activity in prostate cancer [107,108], ovarian cancer [109], and non-Hodgkin lymphoma [107]. The inhibition of growth factors by suramin, in particular the fibroblast growth factor and nerve growth factor, may play a role in the peripheral nerve damage. In in-vitro studies the high dose nerve growth factor was able to ameliorate suramin-induced dorsal root ganglia damage [110].

Toxicities reported in these trials include myelosuppression, renal toxicity and adrenal insufficiency. Peripheral neuropathy was a main and dose-limiting side-effect. Many patients developed a mild neuropathy (NCI-criteria : grade I and II) with mainly sensory symptoms but with a higher dosage as

many as 11-23 % of patients developed a severe sensori-motor neuropathy. This toxicity was directly proportionally related to plasma suramin levels with a 40% probability of developing a severe neuropathy for those whose plasma peak levels exceeded 350 μg/ml [108,111].

LaRocca reported in detail on the clinical, electrophysiological and histological features of severe suramin-induced sensori-motor neuropathy in four out of 38 suramin-treated patients [112]. In two of these patients the clinical syndrome resembled that of a subacute Guillain-Barré syndrome with progression to complete flaccid paralysis with bulbar and ventilatory involvement. Two other patients developed a flaccid paresis of the limbs. All four patients demonstrated an elevated CSF protein in the acute phase of their neuropathy. The EMG and NCV showed evidence of conduction block, and sural nerve biopsies showed segmental demyelination. Recovery was complete in two, but the other two patients were left with severe residual weakness [112].

Suramin-induced neuropathy appears to be a potentially serious toxicity that requires careful monitoring of plasma drug levels and cessation of treatment upon achieving plasma suramin concentrations of 300 μg/ml [112].

Other chemotherapeutic agents

Cytosine Arabinoside (Ara-C): This antimetabolite, used for the treatment of hematological malignancies, is associated with central nervous system toxicity. Peripheral neuropathy is a rare complication of Ara-C treatment. To date only a few cases have been reported [113]. The clinical syndrome varied: a pure sensory neuropathy, a rapidly progressive ascending polyneuropathy with ventilatory dependency, a sensorimotor polyneuropathy and a bilateral brachial plexopathy have all been reported [113,114]. No clear correlation with the cumulative dose and the number of cycles seems present.

Procarbazine: This is a weak monoamine oxidase inhibitor used for the treatment of lymphomas, SCLC and primary brain tumors. A mild peripheral neuropathy has been reported in 10-20% of the patients, manifested by paresthesias, depressed deep tendon reflexes and myalgia [35,115]. These symptoms tend to occur only after several weeks of continuous oral therapy and they are reversible after discontinuation of the drug.

Ifosfamide: The neurological toxic effects of this cyclophosphamide analog mainly comprise central nervous system side-effects. Severe, short-lasting exacerbation of a pre-existing mild peripheral neuropathy has been reported in four patients receiving high-dose intravenous ifosfamide. Patients developed a sudden onset of severe paresthesias and extreme pain in their hands and/or feet. The symptoms lasted for a few hours, then gradually improved over a few days and eventually returned to base-line over a few weeks. A rechallenge with ifosfamide led to the recurrence of the exacerbation [116].

Neuroprotective agents

Presently, no therapeutic options are available once a patient develops a chemotherapy induced neuropathy. One can only try to diminish symptoms with symptomatic treatment, such as amitryptiline in case of a painful taxanes induced neuropathy. The prevention of toxic neuropathies by administration of rescue-drugs would have great clinical significance, as this would also allow a more intense cytostatic treatment with agents in which neuropathy is a dose limiting toxicity [1,23,117,118]. A prerequisite for the use of any such drug is, that it does reduce antitumor activity of the cytostatic agent. Both neurotrophic factors (the ACTH analogue 4-9, insulin like growth factor and nerve growth factor) and sulfahydryl group containing

drugs (ethiofos or WR-2721 and glutathion) have been investigated for this purpose. Most of the research has been done in either in-vitro models or animal models, in which it was investigated whether a co-drug prevented or ameliorated the effect of the neurotoxic drug in the model. As in-vitro models cultures of embryonic rat dorsal root ganglia cells and schwann cells were often used, with outgrowth of neurites, cell survival or migration of cells as outcome parameters [23,119]. In animal models, usually motor and sensory nerve conduction studies, tests for sensory pathways as the tail-flick test, and the determination of sensory neurotransmitters as substance P and calcitonine gene related peptide were used as outcome parameters [71,120-124]. Only a few drugs have been tested in clinical trials (the ACTH analogue 4-9, ethiofos and glutation).

As cisplatin has a steep dose-response curve, attempts have been made to deliver higher doses of cisplatin with the use of other drugs as a chemoprotective agent. The nucleophilic sulfur containing compounds ethiofos or amifostine (WR2721) and reduced gluthathione have showed a selective protection of normal tissues in preclinical and clinical studies against the platinum compounds [117,125,126]. Amifostine is an organic thiophosphate that protects against cisplatin-induced nephrotoxicity, haematologic toxicity and neurotoxicity in animal models [1,117,118]. The drug probably accumulates more easily in normal cells than in tumor cells, and it rescues normal cells from cisplatin toxicity by binding to active cisplatin [126]. Clinical studies combining cisplatin and WR-2721 have revealed promising results [5,117,127-129]. The analysis of a randomised trial also suggests a neuroprotective effect, but the small number of patients, the relatively low dose of cisplatin used (420 mg/m^2) and the small number of patients with long-term follow-up hamper a meaningful analysis [126]. Gluthathion was developed as a nephroprotectant, but in a clinical study it also seemed to

reduce neurotoxicity [125,130]. Thereafter, it was found to reduce cisplatin induced neurotoxicity in rats [121]. A randomised trial suggested this drug is indeed neuroprotective, but the duration of the follow-up was too short to observe the usual increase of cisplatin neuropathy following the end of the treatment [125].

The observation that ACTH and the ACTH(4-9) analogue org 2766 can exert trophic effects on neural tissue has led to several studies on the prevention of chemotherapy-induced polyneuropathy. In in-vitro models Org 2766 was effective in modifying cisplatin neurotoxicity [23,119]. In a rat model Org 2766 prevented cisplatin-induced reduction of sensory nerve conduction velocities [131-133]. In a subsequent placebo controlled study the treatment with Org 2766 indeed prevented the occurrence of cisplatin-neuropathy [134]. Based on these studies, further trials in cisplatin neuropathy were performed but they either could not confirm these results or were less convincing [75,135,136]. As expected, we were also unable to demonstrate a beneficial effect of org 2766 on cisplatin neuropathy of longstanding duration [137]. Org 2766 has also been studied in vincristine and paclitaxel neuropathy. In a snail model, org 2766 partially prevented the vincristine induced decrease of microtubules [138]. A preliminary clinical study on vincristine neuropathy showed promising results [139]. Although in in-vitro studies org 2766 seemed not effective in taxol induced neuropathy, in a rat model org 2766 prevented taxol induced SNCV slowing [119,140]. Unfortunately, the lack of a clear benefit of Org 2766 in cisplatin induced neuropathy has led to a complete cessation of trials with Org 2766 in toxic neuropathies (Vecht, personal communication).

Nerve growth factor (NGF) is necessary for the development of dorsal root ganglions and the maintenance of the normal ganglion function in adults [122].

A neuroprotective effect of nerve growth factor was suggested by several in-

vitro studies on cisplatin, paclitaxel and suramin neurotoxicity [23,110,141,142]. In animal models, NGF prevented the taxol and cisplatin induced decrease of the compound motor action potential, and the increase of the threshold of thermally induced pain [71,122]. Clinical trials have to be waited.

The actions of the neurotrophin family members such as NGF are mediated by Trk tyrosine kinase receptors. Large dorsal root ganglions cells with myelinated axons involved in proprioception express the neurotropin-3 receptor TrkC. These are the sensory neurons most affected by cisplatin. Neurotropin-3 was found to reverse cisplatin induced peripheral sensory neuropathy in rats [124]. No clinical trials have yet been carried out. Insulin-like growth factor-1 is a factor probably involved in regulating body growth during development. It has a variety of other actions, including a stimulation of motor and sensory nerve regeneration. In animal experiments, it prevented the development of both vincristine and paclitaxel induced neuropathy [123,143]. It is currently being tested in clinical trials with cisplatin and taxol.

In conclusion, in the past years a number of interesting possible neuroprotective drugs have been investigated, but the evidence obtained in clinical trials is still meagre. This holds for both the safety and the efficacy data. It is most important for such trials (especially those concerning cisplatin chemotherapy) that the follow-up period is long enough to observe the usual increase of neuropathic symptoms and signs in the period after the end of the treatment. Also, the value of observations obtained from studies employing a dosage causing none or only minor neuropathic symptoms in the majority of patients is unclear.

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Chapter 2

Clinical course and risk factors of neurotoxicity following cisplatin in an intensive dosing schedule

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Abstract

An intensive weekly regimen of cisplatin was administered to 66 patients with solid cancer in doses varying from 70-85 mg/m^2. The occurrence of sensory neuropathy was prospectively examined by the assessment of neuropathic signs and symptoms and measurement of the Vibration Perception Threshold (VPT). The evaluation was performed before initiation of the therapy and during the follow-up until 3 to 12 months after the last cycle of cisplatin. A mild or moderate neuropathy developed in 47% of patients at 2 weeks after the treatment. This neuropathy continued to deteriorate until approximately 3 months after cessation of chemotherapy leading to a mild or moderate neuropathy in 71% of the patients and a severe neuropathy in 9% of the patients. Thereafter we observed a gradual but incomplete recovery. The high incidence of neuropathy we found may be explained by the prolonged observation period compared to earlier reports.

The only factor correlating with the severity of the neuropathy was the cumulative dose of cisplatin, while there was no association with either the pre-treatment VPT, age, sex, tumor-type or co-treatment with etoposide. The progressing course up to approximately 3 months after the end of the treatment underscores the need for a prolonged follow-up in future studies on cisplatin neuropathy.

Introduction

Cisplatin is a cytotoxic agent effective against a wide spectrum of solid tumors. Neuropathy is one of its dose-limiting side-effects. This neuropathy is purely sensory and characterised by paresthesias, the loss of tendon reflexes and a decrease of mainly thick-fiber mediated sensory qualities as vibration perception, fine-touch perception and propriocepsis. In some patients a disabling sensory ataxia may develop [1-4]. The reported incidence, time of onset and severity vary considerably between different studies, depending on the criteria for neuropathy, the extensiveness of the neurological examination and the cumulative dose of cisplatin administered [2,3,5-12].

A dose-response relationship for cisplatin has been shown in studies on human cancer-cell lines and has also been suggested by data from several clinical trials [5,8,12]. Because potentially severe side-effects like nephrotoxicity and hyperemesis can now be reduced by vigorous hydration, the use of hypertonic saline and potent anti-emetics, more intensive dosing schedules of cisplatin have become feasible, leaving neurotoxicity as the dose-limiting factor. It is uncertain whether apart from the cumulative dose of cisplatin other factors determine the severity of neuropathy development.

A large phase II study with an intensive weekly schedule of cisplatin for patients with locally advanced or metastatic solid tumors was performed in our institution. In these patients the incidence, severity and course of cisplatin-induced neuropathy were assessed prospectively. The size of the study enabled us to investigate the prognostic value of these factors on the severity of the neuropathy. The Vibration Perception Threshold (VPT) was used as the main quantitative measure of the severity of the neuropathy.

Patients and methods

For this study, patients were required to have metastatic or locally advanced cancer for which no other appropriate therapy was available. Other inclusion criteria were age 18-75 years, WHO performance status of 0-2 and a life-expectancy of more than 3 months. Cisplatin was dissolved in NaCl 3% and administered in a 3-hour infusion with standard pre- and post-hydration. The administration took place in a weekly regimen of doses varying from 70-85 mg/m^2. In some patients one week off-therapy was allowed after the third cycle. In most patients the cisplatin was combined with etoposide in a daily dose of 50 mg orally 2 or 3 weeks per month, which was continued after cessation of cisplatin with a dose of 50 mg/m^2 daily at days 1 to 21 every 4 weeks for a maximum of 4 cycles. All patients participating in this trial who had received at least 4 cycles of cisplatin were considered evaluable for the assessment of neurotoxicity. Excluded were patients with diabetes mellitus, alcohol abuse, earlier treatment with cisplatin and brain or leptomeningeal metastases.

The severity of the neuropathy was evaluated by a questionnaire for neurological symptoms, by neurological examination and by VPT measurements before the start of treatment, at 2 weeks after the last dose of cisplatin and every 3 months up to 12 months thereafter. The questionnaire established separately the absence (0) or presence (1) of paresthesias, numbness, loss of dexterity, unsteadiness of gait, Lhermitte's sign and pain. On sensory examination position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tight-rope walking were each scored as normal (0) or abnormal (1). A sum-score for these signs and symptoms was calculated (minimum 0, maximum 12). Patients with a sum-score of 2 to 6 were considered to have a mild or moderate neuropathy and with a sum-score of 7 or more to have a severe one. The VPT was

measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type III (Somedic AB, Stockholm, Sweden) and recorded in micrometers (μm) of skin displacement. The Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The method of limits was used to obtain the mean VPT and this was repeated three times. This method has been shown sensitive and reproducible [13]. The VPT has been shown to be a reliable technique to monitor cisplatin neuropathy and shows a satisfactory correlation with the sum-score of neuropathic signs and symptoms as observed previously [14-17].

The mean sum-score and mean VPT for the whole group pre-treatment and at several time-points post-treatment were calculated. The maximum sum-score post-treatment per patient was determined. Because of the skewed distribution of VPT, the natural logarithm was used for statistical analysis. The mean and standard deviation of the VPT are reported in original units, but were derived from the mean and standard deviation of log(VPT). By this procedure the means are less sensitive to outliers. Spearman rank correlation-coefficients between clinical parameters and the VPT were calculated. Analysis of variance (ANOVA) was applied to study the relationship of the pre-treatment VPT with age, sex and tumor-type. Linear regression analysis was applied for comparison of several prognostic factors with maximum post-treatment VPT.

Results

Sixty-six patients were entered in the study. Patient characteristics and tumor type are shown in table 2.1. Three patients received 4 cycles, 6 patients 5 cycles and 57 patients 6 cycles of weekly cisplatin. The cumulative dose of cisplatin was 420 mg/m^2 in 34 patients, less than 420 mg/m^2 (280-400 mg/m^2) in 10 patients and more than 420 mg/m^2 (450-510 mg/m^2) in 22 patients.

Forty-three patients were co-treated with etoposide. All patients were examined before the start and at least once after cessation of the treatment. The length of the follow-up was 3 months for 19 patients (29%), 6 months for 18 patients (27%), 9 months for 18 patients (27%) and 1 year or more for 11 patients (17%).

Table 2.1
patient characteristics and tumor type

number of patients		66
sex	male/female	51/15
age	mean years	55
	(range)	(34-71)
tumor type		
	head and neck	15
	pleural mesothelioma	13
	colorectal	12
	melanoma	9
	non-small cell lung	8
	other	9

Before the start of the treatment 16 patients (24%) had a mild or moderate neuropathy (sum-score 2-6). Table 2.2 shows the maximum sum-score for signs and symptoms after the treatment. Forty-six patients (71%) had a mild to moderate neuropathy and 6 (9%) a severe one. Thirteen patients (20%) did not develop any neurotoxicity.

Table 2.2
Severity of cisplatin neuropathy and maximal sum-score of signs and symptoms post-treatment

neuropathy	N[1)] (%)	max.sum-score post-treatment	N
no	13 (20%)	0	8
		1	5
mild to moderate	46 (71%)	2	12
		3	10
		4	8
		5	10
		6	6
severe	6 (9%)	7	3
		8	1
		9	1
		10	1

[1)] *N indicates number of patients; data on 1 patient incomplete*

A significant correlation was found between the pre-treatment VPT and age (Spearman rank-correlation = 0.50; p = < 0.001). No correlation was observed between the pre-treatment VPT and gender or tumor-type. The VPT values correlated significantly with the sum-score for signs and symptoms measured at the same evaluation (Spearman rank-correlation = 0.56; p = < 0.001).

Regression analysis showed that the maximum post-treatment VPT correlated significantly with the cumulative dose of cisplatin (p = < 0.001) and the pre-treatment VPT (p = 0.003). Table 2.3 shows the pre-treatment VPT, the maximal post-treatment VPT and the relative increase of the VPT in relation to the cumulative dose of cisplatin. The post-treatment VPT was increased compared to the pre-treatment value in 63 of 66 patients (96%)

with an average increase of 222%. The relative increase of the VPT was exponentially higher in patients receiving higher cumulative doses of cisplatin. No difference in the maximal post-treatment VPT was found between patients co-treated either with or without etoposide. The pre-treatment VPT of patients who developed a severe neuropathy did not differ from other pre-treatment values.

Table 2.3
pre-treatment VPT, maximal post-treatment VPT and relative increase of VPT in relation to cumulative dose of cisplatin

cum.dose cisplatin (mg/m^2)	N (%)	pre-treatment VPT mean ±SD	post-treatment max.VPT mean ±SD	relative increase[1] mean ±SD
< 420	10(15%)	0.7 ±0.8	1.5 ±1.2	105% ±78%
= 420	34(52%)	0.8 ±0.5	2.1 ±1.4	153% ±177%
> 420	22(33%)	0.7 ±0.3	3.8 ±2.9	470% ±507%
	66(100%)	0.8 ±0.5	2.4 ±1.9	222% ±271%

1) relative increase = 100x(postVPT - preVPT)/preVPT

Figure 2.1 presents the mean VPT fitted against time by the cumulative-dose group. It clearly shows that the magnitude of the post-treatment VPT value depends on the cumulative dose of cisplatin. It also shows that the maximal VPT values occur in the period around 3 months after the last cisplatin administration with subsequent improvement thereafter.

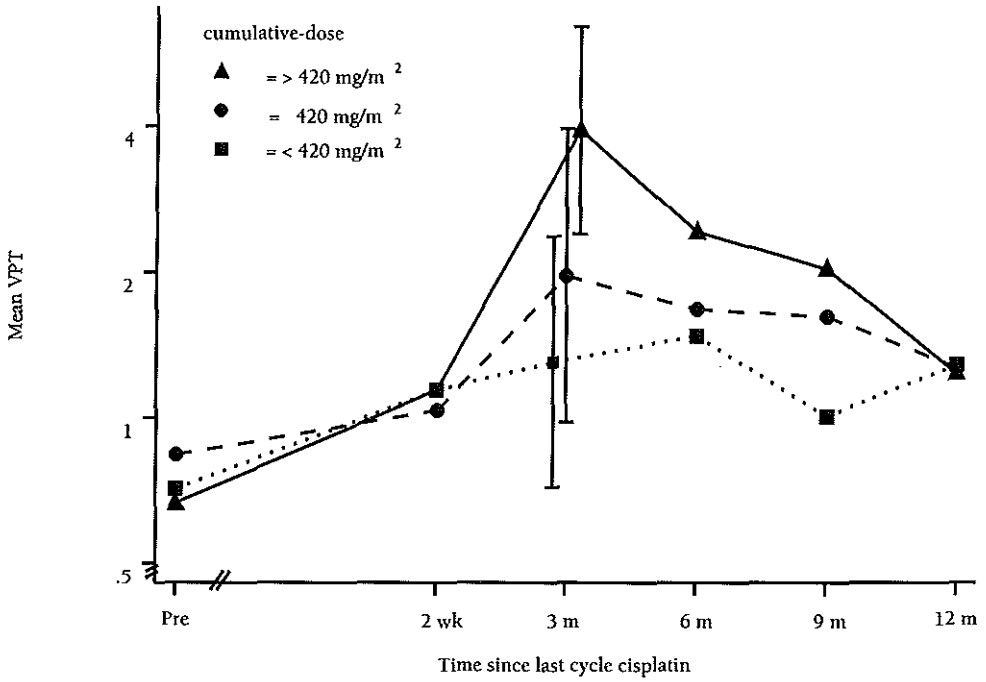

Figure 2.1
Mean Vibration Perception Threshold (VPT) fitted against time by cumulative-dose group. Standard deviations of mean values at 3 months after the last cycle of cisplatin.

Table 2.4 expresses this course of neuropathy. It shows a similar pattern of increase in the frequency of paresthesias and other signs and symptoms and of the VPT scores achieving a maximum at around 3 months after the treatment and gradual but incomplete improvement thereafter.

Table 2.4

Paresthesias, sum-score of signs and symptoms and pre- and post-treatment

	paresthesias	sum-score mean ±SD	sum-score 0-1 2-6 6-12	VPT mean ±SD
pre-treatment	3%	1.0 ±1.4	76% 24% 0%	0.8 ±0.5
post-treatment				
2 weeks	12%	1.7 ±1.5	53% 47% 0%	1.1 ±0.7
3 months	55%	3.4 ±2.4	23% 68% 9%	2.4 ±2.0
6 months	47%	2.7 ±2.0	29% 64% 7%	1.9 ±1.5
9 months	39%	2.4 ±2.3	44% 48% 7%	1.7 ±1.0
12 months	18%	1.2 ±1.2	64% 36% 0%	1.3 ±0.4

Discussion

The interpretation of data on the incidence and severity of cisplatin neuropathy is complicated because of differences in criteria for neuropathy, cumulative dose of cisplatin and prior or concurrent chemotherapy. With conventional doses of cisplatin 50-75 mg/m^2 per cycle and cumulative doses exceeding 300 mg/m^2, the reported incidence varies between 24% and 92% [2,6,10,11,18,19]. In one large study in which patients received a median cumulative dose of cisplatin between 500 and 600 mg/m^2, the overall incidence of any grade of neuropathy was 47%. Severe neurotoxicity characterized by a disability to walk occurred in 4% of the patients [3]. Although neurotoxicity has emerged as one of the major complications in most studies on high-dose cisplatin [7,9,10,12,17,20-22], in some studies surprisingly either no or a low incidence of neuropathy is mentioned [8,23-25].

The patients in our study participated in a trial on the feasibility of an intensive dosing schedule with a weekly administration of cisplatin, as reported previously [26]. A mild or asymptomatic neuropathy was observed in 16 out of 66 patients (24%) before the initiation of the treatment, which is similar to other reports on the incidence of neuropathy in cancer-patients [27-29]. Following cisplatin exposure we found a mild to moderate neuropathy in 71% and severe neurotoxicity in 9% of the patients.

We found a progression of the neuropathy after cessation of the therapy for a period of approximately 3 months, with subsequent but incomplete recovery thereafter. This phenomenon, also designated as "coasting", had previously been described and may reflect a time-lag in clinical manifestations of neuronal injury possibly related to pathological changes in axonal transport [17,20,30,31]. The long-term follow-up may explain the high incidence of neuropathy we observed.

The main prognostic factor in our study for the severity of the neuropathy was the cumulative dose of cisplatin as reported before [2,3,14,32]. In contrast to others we did not find any relation between the severity of the neuropathy and age, gender or tumor type [33,34]. The pre-treatment VPT or the co-treatment with etoposide had no effect on the development of neuropathy either.

We conclude that the severity of cisplatin neuropathy depends primarily on the cumulative dose. The observed progression of the neuropathy after cessation of the therapy implies the need for a prolonged follow-up up to at least 3 months after cisplatin exposure in future trials on cisplatin neuropathy.

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Chapter 3

Effect of increased dose-intensity of cisplatin administration on neurotoxicity

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Abstract

It is uncertain whether intensive dosing schedules of cisplatin intended to attain a higher anti-tumor efficacy would lead to a change in severity of cisplatin-induced neuropathy. We assessed the development of neuropathy in three groups of patients treated with cisplatin in different dosing schedules. The severity of the neuropathy was determined by measurement of the Vibration Perception Threshold (VPT) before the treatment and during the follow-up until 2 to 12 months after the last cycle.

Sixty-six patients were treated with an intensive weekly regimen of doses varying from 70-85 mg/m^2 in one day (trial A), 21 patients with a three-weekly combination chemotherapy containing cisplatin 75 mg/m^2 in one day (trial B) and 20 patients with a three-weekly regimen containing cisplatin 20 mg/m^2 for five consecutive days (trial C). The mean dose-intensity achieved was 59 mg/m^2/week in trial A, 21 mg/m^2/week in trial B and 33 mg/m^2/week in trial C.

The maximum post-treatment VPT correlated significantly with the pre-treatment VPT ($p < 0.001$) and with the cumulative dose of cisplatin ($p < 0.001$). Following the correction for these two variables the maximum post-treatment VPT did not show a statistically significant association with dose-intensity.

These results suggest that neuropathy is not related to dose-intensity of cisplatin. This implies that a treatment with more intensive dosing schedules employing equal cumulative doses of cisplatin does not result in a concomitant increase of neurotoxicity within a cumulative dose range of 280-675mg/m^2.

Introduction

Cisplatin is a cytotoxic agent effective against a wide spectrum of solid tumors. In vitro studies on human cancer-cell lines and a number of clinical trials have suggested a dose-response relationship for cisplatin [1-3]. The administration of more intensive dosing schedules of cisplatin have become feasible, because potentially severe side-effects like vomiting and nephrotoxicity can now be reduced by potent anti-emetics, vigorous hydration and the use of hypertonic saline as a vehicle for cisplatin.

Peripheral neuropathy is an important and dose-dependent side effect of cisplatin. This sensory neuropathy is characterized by paresthesias, numbness, loss of tendon reflexes and a decrease in mainly thick-fiber mediated sensory qualities as vibration perception, fine-touch perception and proprioception. In some patients a disabling sensory ataxia may develop [4-7]. The neuropathy continues to deteriorate up to approximately three months after the cessation of the therapy ("coasting"), with subsequent but incomplete recovery thereafter [8-10]. It is presently uncertain if the severity of the neuropathy is influenced by alterations in cisplatin dosing schedules. In studies on the effect of dosing schedules and dose-intensity of cisplatin conflicting results on the development of neurotoxicity have been reported[11,12].

We studied the development of neuropathy in three prospectively studied groups of patients treated with different dosing schedules of cisplatin. The Vibration Perception Threshold (VPT) was used as a quantitative measure of neuropathy. The VPT has been shown to be a reliable technique to monitor cisplatin neuropathy and other toxic neuropathies [9,13-15].

Patients and Methods

Three different studies on the effect of cisplatin were performed in our Institution during the same period of time. For inclusion, WHO performance status had to be 0-2 and life expectancy more than three months. Patients participating in these trials who had received at least four cycles of cisplatin were considered eligible for assessment of neurotoxicity. Excluded were patients with diabetes mellitus, alcohol abuse, earlier treatment with cisplatin and brain or leptomeningeal metastases.

Patients in trial A participitated in a phase II study on the effect of weekly cisplatin on locally advanced or metastatic solid tumors (Chapter 2). Cisplatin was dissolved in 3% NaCl and administered in a 3-hour infusion with standard pre- and post-hydration. The administration took place in a weekly regimen in doses varying from 70-85 mg/m^2 in six intended cycles. In some patients one week off-therapy was allowed after the third cycle. In most patients cisplatin was combined with etoposide in a daily dose of 50 mg orally two or three weeks per month which was continued after the cessation of cisplatin with a dose of 50 mg/m^2 daily at days 1-21 every four weeks for a maximum of four cycles. Trial B consisted of patients with ovarian cancer who were treated with cisplatin in a three-weekly schedule of 75 mg/m^2 in one day in combination with cyclofosfamide 750 mg/m^2 for six intended cycles. Trial C consisted of patients with testicular cancer or adenocarcinoma of unknown primary, who were treated in a schedule of 20 mg/m^2 on five consecutive days every three weeks for four intended cycles. They were co-treated with etoposide 120 mg/m^2 for three days every three weeks and bleomycin 30 mg weekly or ifosfamide 1.2 g/m^2 for five days three-weekly. Patients in trials B and C participated in two double-blind placebo-controlled studies on the effect of Org 2766, an ACTH(4-9) analogue, on preventing cisplatin neuropathy. Only patients who received the placebo during

chemotherapy were used for comparison in this study. Nine patients from trial B received Org 2766 during the follow-up period starting one month after the last cycle of cisplatin. In trials B and C cisplatin was dissolved in NaCl 0.9% and administered in a 4-hour infusion with standard pre- and post-hydration. None of the patients in trial A,B and C received chemotherapy or other neurotoxic drugs during the follow-up period.

The dose-intensity of cisplatin was calculated as the total amount of cisplatin administered divided by the total number of treatment weeks and was expressed in mg/m^2/week. Measurements of the VPT were performed before the start of the treatment, at 2 weeks after the last dose of cisplatin and every 3 months up to 12 months thereafter. All patients had to have measurements of the VPT before the start of the treatment and during the follow-up until at least 2 months after the cessation of cisplatin treatment in order to be eligible for assessment of neurotoxicity. The VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type III (Somedic AB, Stockholm, Sweden) and recorded in micrometers (μm) of skin displacement. The Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The method of limits was used to obtain the mean VPT and this was repeated three times [16].

Because of the skewed distribution of VPT, the natural logarithm was used for statistical analysis. The mean and standard deviation of VPT are reported in original units, but were derived from the mean and standard deviation of log(VPT). In this way they are less sensitive to outliers. The maximum VPT post-treatment per patient was calculated. Analysis of variance (ANOVA) was applied to study the relationship of the pre-treatment VPT with age, and regression analysis was used for the comparison of several prognostic factors with the maximum post-treatment VPT. Analysis of co-

variance was used to study the association of dose-intensity and the maximum post-treatment VPT taking into account both total cumulative dose and the pre-treatment VPT.

Results

Sixty-six patients were treated in a weekly schedule (trial A), 21 patients in a three-weekly schedule (trial B) and 20 patients in a three-weekly schedule with administration divided over five consecutive days (trial C). Patient characteristics and the tumor type of the patients in these three groups are shown in table 3.1. The average age in group C is lower because of the tumor type (mainly younger males with testicular cancer).

Table 3.1
Patient characteristics and tumor types in trials A, B and C

		group A	group B	group C
number of patients		66	21	20
sex	male/female	51/15	0/21	20/0
age	mean years	55	58	29
	(range)	(34-71)	(28-73)	(18-41)
tumor type				
	head and neck	15		
	pleural mesothelioma	13		
	colorectal	12		
	melanoma	9		
	non-small cell lung	8		
	ovarian		21	
	testicular			16
	adenocarcinoma of unknown primary			4
	other	9		

Table 3.2 shows the dosing schedule, cumulative dose and dose-intensity of cisplatin and the pre- and post-treatment VPT in groups A, B and C. There is a difference in values for the mean pre-treatment VPT between these three groups. This difference is primarily due to the difference in age distributions of the patients in the three trials. Age shows a strong correlation with the pre-treatment VPT (Spearman rank-correlation 0.65) as has been shown by others (16). The calculated dose-intensity of cisplatin achieved with each schedule is often lower than the scheduled dose-intensity because of dosage delay in some patients either by pre-scheduled interruption of chemotherapy or for reasons of toxicity.

Table 3.2
Dosing schedule, cumulative dose and dose-intensity of cisplatin and pre- and post-treatment VPT in trials A,B and C

		group A	group B	group C
dosing schedule	(mg/m^2)	70-85	75	5x20
	time-period	weekly	3-weekly	3-weekly
cumulative dose	mean (mg/m^2)	430	486	435
	(range)	(280-510)	(375-675)	(400-900)
dose-intensity	(mg/m^2/week)	59	21	33
	(range)	(26-82)	(15-25)	(26-34)
pre-treatment VPT	mean ±SD	0.8 ±0.5	0.6 ±0.3	0.3 ±0.1
max.post-treat.VPT	mean ±SD	2.4 ±1.9	3.6 ±3.7	1.3 ±1.7

The variation in the cumulative dose within each trial is due to the variation in the number of courses between patients within the trials. One patient in trial C was treated with a very high cumulative dose of 900 mg/m^2. All other patients received doses between 280 and 675 mg/m^2. Some patients in trial B had been treated with Org 2766 after the cessation of chemotherapy. The maximum post-treatment VPT of these patients was apparently not different from the other patients. The variation in the cumulative dose and dose-intensity, both between and within the trials was exploited to analyse the association of the maximum post-treatment VPT with the cumulative dose, dose-intensity, age and pre-treatment VPT. Age ($p< 0.001$) or similarly the pre-treatment VPT ($p< 0.001$), and cumulative dose ($p< 0.001$) turned out to be strongly associated with the post-treatment VPT, explaining 40% of the variation. Given these factors, dose-intensity or treatment schedule showed no statistically significant association with the maximum post-treatment VPT and, moreover, inclusion of these factors did not alter the regression coefficient for the cumulative dose.

Figure 3.1 shows the relation of the maximum post-treatment VPT, adjusted for the pre-treatment VPT, and the cumulative dose of cisplatin with the regression line for the three schedules pooled. Exclusion of the outlier with the high cumulative dose in group C did not affect this line. Regression lines for each of the trials separately (not shown for clarity) were close to and not statistically significantly different from the line shown.

This implies that in this study-population the level of neurotoxicity, as measured by the maximum post-treament VPT, depends primarily on the pre-treatment VPT or correspondingly the age of the patient, and the cumulative dose of cisplatin and not so much on the schedule employed or dose-intensity achieved.

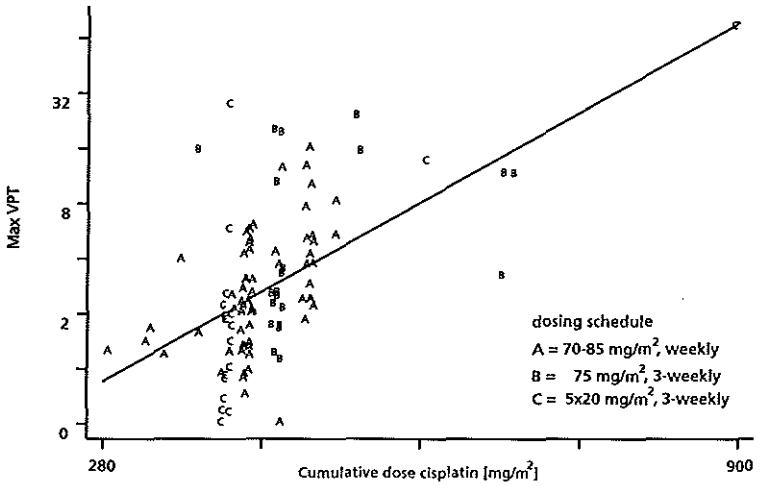

Figure 3.1

Maximum post-treatment VPT versus cumulative dose of cisplatin adjusted for pre-treatment VPT. A,B and C indicate 3 trials with different dosing schedule.
A = 70-85 mg/m² weekly; B = 75 mg/m² 3-weekly; C = 5x20 mg/m² 3-weekly

Discussion

The observation that the co-administration of hypertonic saline and a vigorous

hydration can minimize cisplatin-induced nephrotoxicity has led to the use of higher doses and more intensive dosing schedules of cisplatin aiming at better tumor-control [2,3,17,18]. However, one of the major complications in most studies on high-dose cisplatin is neurotoxicity [3,11,17,19-22], and the main factor for the severity of the neuropathy is the cumulative dose [5,6,13,23].

In the present study, we assessed prospectively neurotoxicity in patients treated with cisplatin in different dosing schedules with a follow-up until at least two but in the majority of cases until three to six months after the last cycle. We were able to confirm that the cumulative dose of cisplatin is the main prognostic factor for the severity of the neuropathy.

Several authors have attempted to reduce toxicity by modifying the dosing schedule of cisplatin. Short infusion schedules resulted in severe ototoxicity while schedules dividing the same total dose over five days did not, suggesting that ototoxicity is related to high peak levels of cisplatin [24]. A low incidence of gastrointestinal toxicity and nephrotoxicity with high-dose cisplatin in a five day continuous infusion has been observed [25]. Other studies reported that a schedule with an administration of 100 mg/m^2 cisplatin on day 1 and 8 was less toxic than when the same total dose was given over five days (5x40 mg/m^2). Less accumulation of cisplatin by employing larger time intervals seems one possible explanation [26,27].

A limited number of studies on the effect of dosing schedules of cisplatin on the development of neurotoxicity have been reported. Mollman et al. found an increased incidence of neuropathy in patients treated with high-dose cisplatin (200 mg/m^2 given over 5 days every 3 weeks) even with lower cumulative doses, as compared to patients treated with conventional dosing schedules (50mg/m^2 every 4 weeks) suggesting that higher dose-intensities of cisplatin give rise to increased neurotoxicity [11]. In contrast, Cavaletti et al. found a lower incidence of neuropathy in patients treated with 50 mg/m^2 cisplatin given every week in 9 cycles than in patients treated with 75 mg/m^2 cisplatin every 3 weeks in 6 cycles [12].

To determine the influence of dose-intensity on the severity of the neuropathy, we compared patients from three trials treated with dosing schedules differing in the dose-intensity of cisplatin administration. Compared to patients in groups A and B, the value for the mean pre-treatment VPT was lower in patients of group C because of younger age. The difference in the pre-treatment VPT between groups A and B may reflect a higher incidence of pre-existing neuropathy in patients in group A, who all had advanced disease. The cause of this cancer-associated neuropathy is

uncertain but probably related to a-specific factors as cachexia, malnutrition and tumor progression [28,29]. Following correction for the pre-treatment VPT and the cumulative dose of cisplatin no significant difference in post-treatment neuropathy was observed between patients in these three groups, suggesting that dose-intensity is not a factor of major importance for the development of neuropathy. It is well-known that the VPT increases with age [16] and we confirmed this in our study. The patients in group C indeed had a lower mean post-treatment VPT, but they also had much lower pre-treatment VPT values, because of younger age. We found a strong significant correlation between the pre-treatment VPT and post-treatment VPT values, indicating that the change in the VPT may be a better measure for neuropathy than its absolute value.

One reason for the discrepancies between studies on the influence of the dosing schedule [11,12] may be the length of the observation after the cessation of cisplatin cycles. As the neuropathy commonly continues to deteriorate up to approximately three months after the last cycle ("coasting") longer follow-up periods are required, as employed in this study. Our results imply that the use of more intensive dosing schedules are not associated with an increased risk on neurotoxicity in the cumulative dose range used in our patients. These observations, however, should still be interpreted carefully, as patients from trial A received hypertonic saline as a vehicle for cisplatin administration and patients from trials B and C normal saline. Hypertonic saline has been shown to attenuate nephrotoxicity, but it is unknown whether a preventive effect on neurotoxicity exists and this may warrant further study. We would consider it improbable that the use of Org 2766 after the cessation of cisplatin treatment in 9 patients from trial B has influenced the results, since we did not find a difference in the post-treatment VPT between patients either with or without Org 2766. Another point for

consideration is that the dose-range in this study population is limited and that the numbers of patients treated in trial B and C are rather small. The fact that the regression lines of the maximum post-treatment VPT versus the cumulative dose for the three schedules were not statistically significantly different indicates that there are at least no large differences. Larger studies, however, would be required in order to be able to detect small differences.

We conclude that the severity of cisplatin neuropathy is mainly determined by the cumulative dose and seems not to be influenced by an increased dose-intensity of cisplatin administration. These results suggest that the anti-tumor effects of cisplatin may possibly be increased by the use of more intensive dosing schedules without a simultaneous risk on enhanced neurotoxicity in the cumulative dose range used in our study.

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Chapter 4

Peripheral neurotoxicity induced by docetaxel

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Abstract

Docetaxel, a new semi-synthetic taxoid used as an antineoplastic agent, induced a predominantly sensory neuropathy in 20 out of 41 patients. We assessed neurotoxicity in all patients participating in four phase II trials conducted in our institution. The neuropathy was evaluated by a clinical sum-score for symptoms and signs and by measurement of the Vibration Perception Threshold (VPT). The severity of the neuropathy was graded according to the National Cancer Institute's 'Common Toxicity Criteria'.

Neuropathic symptoms were mild in most patients. However, at cumulative doses above 600 mg/m2, three out of 15 patients developed a moderate neuropathy and one out of 15 patients a severe one. There was a significant correlation between the cumulative dose of docetaxel and the post-treatment sum-score ($p = 0.002$). We found no correlation between the post-treatment VPT and the clinical sum-score or between the post-treatment VPT and the cumulative dose of docetaxel.

We conclude that docetaxel produces a mild and predominantly sensory neuropathy in a high proportion of patients treated. This neurotoxicity appeared to be dose-dependent and may be severe and disabling at higher dose levels. Determination of the VPT is not a reliable method to monitor docetaxel-induced neuropathy.

Introduction

Docetaxel (Taxotere®, Rhône-Poulenc Rorer) is a new semi-synthetic taxoid prepared from a precursor, extracted from the needles of the European yew, Taxus baccata. Docetaxel has the same mechanism of action as paclitaxel (Taxol), and both represent a unique class of chemotherapeutic agents. They inhibit tubulin depolymerization and promote microtubule assembly, thereby stabilizing microtubules. In contrast to paclitaxel, which is derived from the bark of the pacific yew, Taxus brevifolia, docetaxel comes from a renewable source. In vitro, docetaxel is more potent than paclitaxel [1].

In preclinical studies, docetaxel has demonstrated anti-tumor activity against a wide variety of solid tumors [1]. Phase I and II trials have shown significant clinical activity in ovarian carcinoma [2,3], breast cancer [4-8], melanoma [9], non-small-cell lung cancer [10,11] and small-cell lung cancer [12]. Neutropenia is the dose-limiting toxicity in most studies. Other side-effects are hypersensitivity reactions, cumulative fluid retention syndrome mainly characterized by peripheral edema, gastrointestinal toxicity, skin toxicity and onchylysis.

Lipton et al. reported neuropathy as a dose-dependent side-effect of the treatment with paclitaxel [13]. Mild peripheral neurotoxicity induced by docetaxel was present in phase I and phase II studies but there have been no attempts to further characterize the neuropathy. Our institution participated in four multicentre phase II trials on the activity of docetaxel as first or second line chemotherapy in metastatic or locally advanced solid tumors. We assessed neurotoxicity prospectively in all our patients entered in these trials.

Patients and methods

Patients were required to have metastatic or locally advanced cancer for which no appropriate therapy was available. Other inclusion criteria were age 18-75 years, WHO performance status 0-2, normal organ functions and a life expectancy of more than three months. All patients granted informed consent according to institutional rules. Patients with symptomatic peripheral neuropathy grade 2 or more according to the "National Cancer Institute (NCI) criteria" and patients with brain or leptomeningeal metastases were excluded.

Docetaxel was supplied by Rhône-Poulenc Rorer. In three trials it was administered as a one-hour infusion at a dose of 100 mg/m^2 every three weeks. In one trial for patients with breast cancer the dose per cycle was divided and given on day one and day eight every three weeks. Only in the latter study patients were randomized to receive premedication with methylprednisolone. No other neurotoxic drugs were used during the study or follow-up period.

The severity of the neuropathy was evaluated by a questionnaire for neurological symptoms, by standardized neurological examination and by measurements of the Vibration Perception Threshold (VPT) before the start of the treatment, after every two cycles, at two weeks after the last dose of docetaxel and every three months thereafter. The questionnaire established separately absence (0) or presence (1) of paresthesias, numbness, loss of dexterity and unsteadiness of gait. On sensory examination position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tendon-reflexes of the legs were each scored as normal (0) or abnormal (1). A sum-score for these signs and symptoms was calculated (minimum 0, maximum 11). The severity of paresthesias was graded on a 5-point scale (0=no, 1=temporary, 2=continuous & light, 3=severe, 4=unbearable). Sensory loss was defined as an abnormal test on either

position sense or vibration sense or pin-prick sense. Patients were asked whether they experienced Lhermitte's sign or pain. The distal muscle strength in the lower extremities was tested. Motor signs were defined as the presence of objective weakness. The severity of the neuropathy was scored according to the NCI Common Toxicity Criteria (CTC) for sensory neuropathy (0=no symptoms or signs, 1=mild paresthesias,loss of deep tendon reflexes, 2=moderate paresthesias,objective sensory loss, 3=severe paresthesias,sensory loss interfering with function). The VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type IV (Somedic AB, Stockholm, Sweden) and recorded in micrometers (μm) of skin displacement. This Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The method of limits was used to obtain the mean VPT and this was repeated three times [14]. The VPT has been shown to be a reliable technique to monitor cisplatin neuropathy and shows a good correlation with the sum-score of neuropathic signs and symptoms as observed previously [15-17]. It has been employed to quantify paclitaxel-induced neuropathy [18].

As only nine patients were evaluated on two or more occasions post-treatment, the first post-treatment evaluation was used as a primary endpoint for the assessment of the neurotoxicity. Cycles of docetaxel given after the last neurological evaluation, which occurred in a few patients, were not counted in the analysis and excluded from the calculation of the cumulative dose.

The mean sum-score and mean VPT for the whole group pre-treatment and post-treatment were calculated. Because of the skewed distribution of the VPT, the natural logarithm was used for statistical analysis. The mean and standard deviation of the VPT are reported in original units, but were derived from the mean and standard deviation of log(VPT).

Analysis of variance (ANOVA) was applied to study the relationship of the pre-treatment VPT with clinical parameters, for example with previous treatment with cisplatin. This technique was also applied to study the association between the cumulative dose of docetaxel and the post-treatment sensory sum-score or VPT or the difference with the pre-treatment scores. In addition Spearman rank-correlations were calculated to determine the strength of the association between ordinal variables as the cumulative dose, VPT and sum-score.

Results

Fifty-five patients from our institution were entered in the clinical trials on docetaxel. Fourteen of these 55 patients were excluded from the assessment of neurotoxicity because of lack of a pre-treatment evaluation (n=3), treatment with less than two cycles (n=7) or lack of evaluation after the second cycle (n=4).

Patient characteristics, tumor-type and previous chemotherapy of 41 patients evaluable for the present analysis are shown in table 4.1. Twelve patients had not been treated previously with chemotherapy. Nine patients had received prior anti-tumor treatment with cisplatin. The other patients had been treated with non-neurotoxic chemotherapy. One patient had diabetes mellitus and one patient reported alcohol abuse.

Twenty-five patients received 2-4 cycles of docetaxel, 10 patients 6-8 cycles and six patients 9-11 cycles before their last evaluation. All patients started treatment at a dose of 100 mg/m^2 docetaxel per cycle, but some patients required dose-reduction because of adverse effects. In the 11 breast cancer patients this cycle dose was administered in the day 1-8 schedule. The cumulative dose of docetaxel was less than 300 mg/m^2 (range 150-300 mg/m^2) in 14 patients, 300-600 mg/m^2 in 12 patients and more than 600

mg/m^2 (range 600-1100 mg/m^2)in 15 patients. The median duration of the follow-up after the last cycle was 27 days (range 7-310 days).

Table 4.1
Patient characteristics and tumor type

number of patients		41
sex	male/female	14/27
age	mean years	53
	(range)	(28-73)
tumor type		
	breast	11
	ovarian	10
	sarcoma	7
	head and neck	5
	bladder	5
	melanoma	2
	colorectal	1
previous treatment		
	cisplatin	9
	other chemotherapy	20

Before the start of the treatment four patients had a mild neuropathy which was due to previous chemotherapy with cisplatin. In the other five patients with previous cisplatin treatment as well as in the patients with diabetes mellitus or alcohol abuse no neuropathic symptoms and no or only minor signs could be detected.

Table 4.2 shows the incidence of neuropathic signs and symptoms at the first post-treatment evaluation. At the first post-treatment evaluation paresthesias were encountered in 21 patients (51%): in the hands (n=5), in

the feet (n=2), in both hands and feet (n=14). Eight patients suffered from pain in either hands or feet, which was felt to be secondary to neuropathy. Numbness developed in 13 patients (34%) and loss of dexterity in 14 patients (35%). In nine patients (23%) the sensory neuropathy led to unsteadiness of gait. Lhermitte's sign developed in two patients not pre-treated with cisplatin during the treatment with docetaxel, in one patient accompanied by severe sensory neuropathy after seven cycles of docetaxel and in the other as the only symptom after one cycle. Objective sensory loss was detected in 11 patients (30%) and objective loss of motor strength in two patients (5%). Loss of ankle jerk was found in 18 patients (51%), loss of both ankle and knee jerks in 16 patients (41%).

Table 4.2

Neuropathic signs and symptoms at first post-treatment evaluation

	N	(%)
paresthesias	21/41	(51)
grade 1	10[1]	
grade 2	11[2]	
grade 3	0	
grade 4	0	
pain	8 /40[3]	(20)
numbness	13/38	(34)
loss of dexterity	14/40	(35)
unsteadiness of gait	9 /40	(23)
Lhermitte's sign	2 /40	(5)
sensory loss	11/37	(30)
motor signs	2 /38	(5)
Romberg's sign	1 /37	(3)
loss of knee jerk	16/40	(41)
loss of ankle jerk	18/35	(51)

[1]) *Excluding 1 patient with pre-existing paresthesias grade 1*
[2]) *Including 1 patient with pre-existing paresthesias grade 1*
[3]) *Patients with this sign or symptom at pre-treatment evaluation or missing data are excluded*

Table 4.3 shows the mean increase in the sensory sum-score, the mean relative increase in the VPT value, the severity of paresthesias and the CTC-neurosensory-grade at first post-treatment evaluation classified by cumulative dose. According to CTC criteria, 20 patients developed a sensory neuropathy. In the groups with a cumulative dose below 600 mg/m^2 nine out of 26 patients showed a mild sensory neuropathy. Out of 15 patients who had received a cumulative dose above 600 mg/m^2, 11 patients developed a sensory neuropathy which was graded mild in nine patients and moderate in two patients. In this group with high cumulative doses, four out of seven patients with prior cisplatin treatment developed a neuropathy in contrast to seven out of eight patients without previous cisplatin treatment. In three patients treatment with docetaxel had to be discontinued because of neurotoxicity and in five patients because of other toxicities.

Table 4.3

Severity of neuropathy in relation to cumulative dose docetaxel

	< 300 mg/m^2 N = 14	300-600 mg/m^2 N = 12	>600 mg/m^2 N = 15
sensory sum-score increase[1]			
mean (±SD)	1.5 ±1.2	2.9 ±2.5	3.9 ±2.7
VPT relative increase (%)[2]			
mean (±SD)	35 ±89%	7 ±38%	34 ±87%
paresthesias[3]			
grade 1	5	3(2)[4]	2(1)
grade 2	1	3(5)	7(6)
grade 3	-	-	-(2)
grade 4	-	-	-(1)
CTC neurosensory[3]			
grade 1	2	7	9(7)
grade 2	-	-	2(3)
grade 3	-	-	-(1)

[1]) *difference between first post-treatment and pre-treatment score.*
[2]) *relative difference between first post-treatment and pre-treatment score.*
[3]) *incidence at first post-treatment evaluation; in case of pre-existing graded toxicities only higher grades are counted.*
[4]) ( ) = *numbers when maximum scores post-treatment are considered.*

Nine patients had two or more post-treatment evaluations. In four of these patients neuropathy worsened during the follow-up, of which two patients developed a moderate neuropathy and one patient a severe one.

A clear correlation between the pre-treament value of the VPT and the pre-treatment sum-score was found (Spearman rank-correlation $R_s = 0.64$, $p < 0.001$). This association was primarily due to higher scores on both the VPT and sum-score in patients with previous cisplatin treatment. Following docetaxel treatment no correlation was found between the relative increase in the VPT and the increase in the sum-score ($R_s = 0.08$, $p > 0.20$). The cumulative dose of docetaxel showed a statistically significant correlation with the increase in the sum-score ($R_s = 0.39$, $p = 0.01$), but the change in the VPT showed no correlation with the cumulative dose ($R_s = 0.08$, $p > 0.20$). Some increase in the VPT was seen after cumulative doses of more than 600 mg/m^2, but this is far from statistically significant. Moreover, there is no trend apparent in the increase of the VPT with increasing dose (Table 4.3). In contrast, the sensory sum-score showed an increase even at lower cumulative doses of docetaxel (Figure 4.1). The increase in sensory sum-score was higher in the patients treated with the day 1-8 schedule in comparison to the other patients, but this difference was not statistically significant.

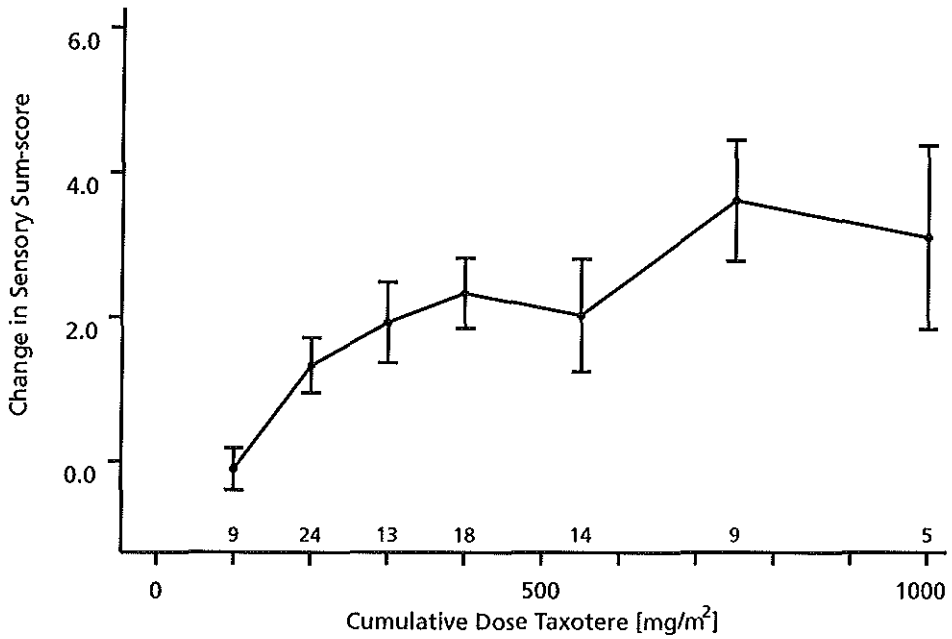

Figure 4.1

The mean change (± SE) in sensory sum-score after treatment with docetaxel (Taxotere) in relation to the cumulative dose docetaxel (mg/m²). The numbers above the horizontal axis indicate the number of patients evaluated.

Discussion

All patients were treated with docetaxel at a cycle dose of 100 mg/m², but differed in the total cumulative dose they received. Forty-nine percent of the patients showed a sensory neuropathy at the first post-treatment evaluation. In four patients the neuropathy worsened during the follow-up. As we saw only nine patients more than once post-treatment, the neurotoxicity may have been underrated. The neuropathy was mild in most patients, but at cumulative dose levels above 600 mg/m², three out of 15 patients developed a moderate neuropathy, and one out of 15 a severe sensory neuropathy interfering with function. Two of these patients also showed severe motor involvement. The neuropathy was the dose-limiting toxicity in three patients.

The most extensively studied taxoid, paclitaxel, causes a predominantly sensory, both axonal and demyelinating, neuropathy which is related to both the single dose and cumulative dose of paclitaxel [13,18]. Its pathophysiologic

mechanism is presumably related to the promotion of microtubule aggregation in neurons, axons and Schwann cells, possibly initiated at the level of the dorsal root ganglia [13].

In phase I clinical trials on docetaxel, mild neurotoxicity was present sporadically but most patients received low doses and a limited number of courses [19-21]. New et al. reported on a phase I/II trial of 186 patients treated with a wide range of cumulative doses (50 mg/m^2 - 720 mg/m^2) and dose levels (10 mg/m^2 - 115 mg/m^2) [22]. Twenty-one of their patients (11%) developed a mild to moderate sensory neuropathy affecting mainly large fibre function. In 10 patients there was motor involvement. In four phase II trials in patients with non-small-cell lung carcinoma, small-cell lung carcinoma and melanoma treated with docetaxel at a dose of 100 mg/m^2 every three weeks, a usually mild sensory neuropathy developed after three or four cycles in 37%-44% [9-12]. In one of these trials, a severe neuropathy developed in four out of 29 patients, possibly related to alcohol abuse in three of them [11].

Docetaxel induced neuropathy resembles the sensory neuropathy secondary to paclitaxel [13,18]. In our series, signs and symptoms included paresthesias, numbness, loss of sensory qualities and tendon reflexes in both upper and lower extremities. Some patients had pain in hands and feet and two patients developed Lhermitte's sign , which is common with cisplatin neuropathy [23,24], but not observed previously with either paclitaxel or docetaxel. The neuropathic signs and symptoms correlated strongly with the cumulative dose of docetaxel. Within the cumulative dose-range used in our study, the neuropathy was mild in most patients. We found no apparent relation with prior treatment with cisplatin.

We did not establish a significant relation between the VPT and the severity of docetaxel-induced neuropathy. Although the VPT-values were higher with high cumulative doses, the poor association with clinical signs and symptoms indicated that the VPT is not a good indicator of docetaxel-

neuropathy. Several reports demonstrated that the VPT is a reliable indicator of cisplatin-neuropathy [15-17]. This method has also been used with paclitaxel induced neuropathy [18]. In docetaxel-neuropathy small fibre function might be most compromised, suggested by the relative high number of patients with associated pain, unusual in cisplatin neuropathy which affects mainly thick myelinated fibres.

We conclude that docetaxel induces a frequent dose-dependent predominantly sensory neuropathy. The neuropathy is mild in most patients. At higher cumulative dose levels, patients may develop a severe and disabling neuropathy.

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Chapter 5

Clinical characteristics of neuropathy induced by docetaxel

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Abstract

Docetaxel, a semi-synthetic taxane with promising clinical antitumor activity, may cause a usually mild sensory neuropathy. We report six patients who developed a more severe neuropathy following the treatment with docetaxel. The neurological signs and symptoms and the clinical course of this new type of chemotherapy-induced neuropathy are discussed in detail.

The clinical picture is nearly always dominated by a sensory neuropathy, but in more severe cases motor weakness may occur. In some patients Lhermitte's sign develops. Signs and symptoms are usually reversible after discontinuation of docetaxel administration. However, after the cessation of the treatment symptoms may first worsen before improvement occurs. This neuropathy is likely to be related to the effect of docetaxel on microtubule functions in dorsal root ganglion cells, axons and Schwann cells.

Introduction

Docetaxel (Taxotere®; Rhône-Poulenc Rorer) is a new semi-synthetic analogue of paclitaxel (Taxol®). These taxanes represent a unique class of chemotherapeutic agents which exert their action by inhibiting tubulin depolymerization and promoting microtubule assembly, thereby stabilizing microtubules. In Phase I and II clinical trials docetaxel has demonstrated interesting clinical activity in ovarian cancer [1,2], breast cancer [3-7], melanoma [8], non-small-cell lung cancer [9,10] and small-cell lung cancer [11]. In most studies neutropenia is the dose-limiting toxicity. Other side-effects include hypersensitivity reactions, a fluid retention syndrome, gastrointestinal toxicity and skin toxicity.

A usually mild and predominantly sensory axonal neuropathy is reported in phase I and phase II studies. However, occasionally a more severe neuropathy develops, causing painful paraesthesias and weakness. To our knowledge, no attempts have been made to describe docetaxel induced neuropathy in detail. We describe six patients with a moderate or severe docetaxel-induced neuropathy. All patients received docetaxel at a dose of 100 mg/m^2 given as an 1-hour infusion which was repeated every three weeks, without corticosteroid pre-medication. They were all treated within clinical trials and, as a part of this, were undergoing neurological examinations at baseline and on regular intervals during and after the treatment. Based on these observations we will discuss the characteristics of docetaxel neuropathy. Patient's characteristics, signs and symptoms, electrophysiological findings and the course of the neuropathy are summarized in table 5.1.

Case reports

Patient A is a 71-year-old man who developed para-aortal lymphnode metastases from urothelial bladder cancer. The baseline neurological examination performed before the start of chemotherapy was normal, except for the absence of ankle jerks. There was no history of alcohol abuse or diabetes mellitus. He received nine cycles of docetaxel. After three cycles he reported numbness and a heavy feeling in his feet. His nails were painful due to onycholysis. At examination he showed loss of vibratory perception at his feet and loss of knee jerks. After six cycles he noted light paraesthesias and numbness in his hands, and clumsiness. He showed some unsteadiness of gait and loss of joint position sense in his toes. His muscle strength was normal. Despite complete remission of the tumor, the chemotherapy with docetaxel was discontinued after nine cycles because of progressive sensory disturbances of his feet and unsteadiness of gait. At examination a mild drop of both feet was noted. He also had fluid retention causing severe edema in his legs.

In the first months after the last cycle he gradually developed painful paraesthesias in his hands and legs. He was unable to walk. On examination he showed a paraparesis of both legs, a proximal muscle strength MRC grade 3 and distal grade 4, a mild paresis of handmuscles and total areflexia. Hypaesthesia was found below the knees and to mid-palm. Vibratory perception was absent in his hands and legs. Nerve conduction studies and an EMG revealed a severe and mainly axonal neuropathy with abundant denervation potentials, with a slight decrease of the nerve conduction velocities. An abdominal CT-scan showed complete regression of para-aortal metastatic lymphnodes, an MRI-scan of the thoracic and lumbar spine was normal. No other cause for the neuropathy than the chemotherapy with docetaxel was found.

Table 5.1
Signs and symptoms, EMG and course of docetaxel induced neuropathy in six patients

age-/sex	cumulative dose	1st symptom	other signs and symptoms	EMG	course
A 71/M	900 mg/m^2	numbness feet (300 mg/m^2)	pain, paraesthesias, severe weakness, total areflexia, loss vibratory + joint position sense, hypaesthesia	fibrillations ++ N Med: dl 4.0ms, MNCV 39m/s, N Per: MUAP absent (distal stim.) N Tib: dl 4.6ms, MNCV 37m/s	progression after stop treatment complete recovery
B 60/F	700 mg/m^2	paraesthesias hands (700 mg/m^2)	numbness, loss dexterity, loss ankle + knee jerks, loss vibratory + joint position sense, Romberg's sign	not done	incomplete recovery
C 69/M	700 mg/m^2	paraesthesias hands + feet (400 mg/m^2)	numbness, Lhermitte, paresis, areflexia, hypaesthesia, loss vibratory sense	fibrillations + N Med, N Sur: SNAP absent N Per: dl 5.0ms, MNCV 32m/s H-reflex M soleus: absent	unknown
D 47/M	600 mg/m^2	paraesthesias hands + feet (200 mg/m^2)	pain, numbness, loss ankle jerks, loss dexterity, uncertainty walking, loss vibratory + joint position sense	not done	progression after stop treatment
E 31/F	100 mg/m^2	numbness hands + feet (100 mg/m^2)	hypaesthesia, areflexia, Romberg's sign	SNCV: N Med 45m/s, N Uln 40m/s, N Sur 33m/s	symptoms after 1 cycle some improvement after stop treatment
F 40/F	500 mg/m^2	Lhermitte (100 mg/m^2)	paraesthesias, loss ankle + knee jerks	not done	improvement after stop treatment

dl = distal latency, MNCV = motor nerve conduction velocity, SNAP = sensory nerve actio potential, MUAP = motor unit action potential,
N Med = Median nerve, N Uln = Ulnar nerve, N Sur = Sural nerve, N Per = Peroneal nerve, N Tib = Tibial nerve

The signs and symptoms gradually improved spontaneously. Five months after the last cycle the pain had disappeared and he was able to walk unassistedly. The EMG at that time showed no denervation potentials anymore, but a persistent mild slowing of the nerve conduction velocities. He recovered almost completely, being able to walk and bicycle for several hours 10 months after the last cycle.

Patient B, a 60-year-old woman, developed liver-metastases from ovarian cancer. She had been treated with chemotherapy containing cisplatin one year before. The baseline neurological examination before the docetaxel treatment showed no signs or symptoms of a neuropathy. She received seven cycles of docetaxel. After four cycles she reported painful and discolouring nails, without signs or symptoms of neuropathy. The chemotherapy was discontinued after the seventh cycle because of progressive cancer. At that time the patient reported mild paraesthesias in her hands, and at examination a loss of ankle jerks was found. The paraesthesias subsequently progressed, and the patient complained of numbness in hands and feet with loss of dexterity. At examination four months after the last cycle she showed loss of vibratory perception and joint position sense at her feet, a positive Romberg's sign and loss of knee jerks. The muscle strength was normal. At further follow-up these signs and symptoms improved. Nine months after the last cycle the patient reported normal dexterity, but still complained about paraesthesias. She died one year after the last cycle from progressive disease.

Patient C, a 69-year-old man, had initially been treated for bladder cancer with local radiotherapy. He subsequently developed multiple bone metastases and local progression with infiltration into the left lumbosacral plexus. At the neurological examination there was a mild paresis MRC grade 4 of the left

foot dorso-flexors, absence of the left ankle jerk and hypaesthesia at the lateral foot. He then received seven cycles of docetaxel. After four cycles he reported mild paraesthesias in his hands, and at examination loss of vibratory perception at his toes and loss of tendon reflexes at his legs were found. Despite a partial tumor response, the chemotherapy was discontinued after the seventh cycle because of progressive neuropathic symptoms, consisting of numbness and severe paraesthesias in hands and feet, tingling in hands and feet with flexion of the neck and difficulty in walking. At examination three weeks after the last cycle a paralysis of left foot dorso-flexors and MRC grade 3 weakness of foot flexors, complete areflexia and hypaesthesia of hands and legs below the knees were found. The EMG and nerve conduction studies revealed a severe mainly sensory neuropathy and a lesion of the left ischiadic nerve. Progression of the tumor was diagnosed three months later, thereafter the patient was lost to the follow-up.

Patient D, a 47-year-old man with Recklinghausen's disease type 1, initially underwent a resection of a malignant pleural schwannoma. One year later he received two cycles of ifosfamide and adriamycine because of a local relapse with cutaneous metastases, without response. Therefore, the treatment was changed and he received six cycles of docetaxel.

Before the start of the therapy with docetaxel he had no signs or symptoms of neuropathy. After two cycles he experienced temporary paraesthesias in hands and feet. After four cycles, ankle jerks were lost and there was a mild impairment of the joint position sense of the toes. Mild paraesthesias in hands and feet recurred after the sixth cycle. The docetaxel was stopped because of progressive disease, but the neuropathic symptoms continued to progress gradually. He complained of painful paraesthesias, numbness, loss of dexterity and uncertainty in walking. The examination two

months after the last cycle revealed impairment of the vibratory perception and joint position sense at the feet, normal strength and loss of knee and ankle reflexes. Four months after the last cycle he died.

Patient E, a 31-year-old woman, developed liver-metastases from breast cancer. Because of progressive disease during chemotherapy with cyclofosfamide and adriamycine the treatment was changed to docetaxel after six cycles. Three days after the first cycle she noted numbness in her hands and legs. Examination revealed hypaesthesia below the knees and in her hands, generalised areflexia, positive Romberg's sign and normal muscle strength. Blood examination showed mild elevated liver enzymes and mild anaemia, but no other abnormalities. Examination of CSF was unremarkable. Nerve conduction studies showed only a slowing of the sensory nerve conduction velocities. Because of toxicity the treatment was discontinued. She reported some improvement in the neuropathic symptoms after this period. She died shortly afterwards.

Patient F was a 40-year-old woman with metastatic breast cancer. After first- and second line chemotherapy and hormonal therapy, the treatment with docetaxel was started because of progressive disease. She received five cycles. At base-line examination there were no neuropathic signs or symptoms. Shortly after the first cycle she noted painful tingling in hands and feet triggered by neck flexion. A cervical MRI showed two small metastases in the sixth and seventh vertebral body, without epidural compression. The serum vitamin B12 value was normal. Besides this Lhermitte's sign she had no other neurological symptoms, but she developed mild paraesthesias in her fingers and feet during the next three cycles. At examination a loss of knee and ankle jerks was found. Because of toxicity

(onycholysis, anorexia, fatigue, polyneuropathy) the treatment was discontinued after five cycles. Lhermitte's sign persisted up to two months after the cessation of the chemotherapy, but thereafter gradually disappeared.

Discussion

We present six cases of neuropathy induced by chemotherapy with docetaxel, a new semi-synthetic taxane. The currently most extensively studied taxane, paclitaxel, causes a predominantly sensory, both axonal and demyelinating neuropathy which is related to both single dose and cumulative dose of the drug [12,13]. Its pathophysiologic mechanism is presumably related to the promotion of microtubule aggregation in neurons, axons and Schwann cells [12]. In phase I and II clinical trials on docetaxel, a mild dose-dependent neurotoxicity affecting mainly sensory functions has been observed [8-11,14-18]. In a phase II study on docetaxel conducted in our institution 20 out of 41 evaluable patients treated with cumulative doses ranging 150-1100 mg/m^2 developed a usually mild neuropathy [17]. However, following the treatment with a cumulative dose above 600 mg/m^2, we observed in four out of 15 patients a moderate or severe neuropathy interfering with function [17]. These four patients are presented in this paper (A,B,C and D) together with a patient who had Lhermitte's sign (F) and a patient who participated in another trial on docetaxel (E).

The clinical picture in our patients was dominated by sensory signs and symptoms. Symptoms usually started with paraesthesias and numbness in hands and feet, sometimes interfering with dexterity and steadiness of gait. At this stage the symptoms were usually easily differentiated from symptoms caused by edema and skin or nail disorders. Loss of tendon reflexes and vibratory perception were an early sign. Loss of joint position sense and

sensory ataxia developed with further progression of the neuropathy. Often the paraesthesias were painful, suggesting involvement of small fibre.

In patient A the severe sensory neuropathy was accompanied by loss of strength leading to asevere disability. New et al. found evidence of motor weakness in half of the patients with docetaxel neuropathy [18]. In patient C the muscle weakness was associated with a lesion of the ischiadic nerve superimposed on a sensory neuropathy. Although he had involvement of the sciatic nerve at an earlier stage of his disease, at the time he developed motor weakness there was no evidence of tumor recurrence. The sciatic nerve may have been more vulnerable to neuropathy. However, this must be stated with some restraint, as tumor progression was diagnosed five months later.

Two patients developed Lhermitte's sign during the treatment with docetaxel. Lhermitte's sign is common with cisplatin neuropathy [19,20] and may represent involvement of either the dorsal root ganglia or posterior columns [19]. It has not been reported previously with either paclitaxel or docetaxel. Neither of these patients had been treated with cisplatin, and no other cause for Lhermitte's sign was found.

The course of docetaxel-induced neuropathy was notable. Signs and symptoms appeared during chemotherapy after two to four cycles and progressed gradually with new cycles. In most patients the main factor appeared to be the cumulative dose of docetaxel. Patient E, however, showed a moderate neuropathy after only one cycle, suggesting an individual susceptibility. In most patients treated with docetaxel neuropathy symptoms improve 6-8 weeks after treatment discontinuation [18]. In contrast, in three of our patients (A, B and D) the neuropathy progressed for several months after the cessation of the treatment. This phenomenon, or "coasting", is also present following the treatment with cisplatin and may be related to pathological changes in axonal transport [21-25]. In most patients with sufficient

follow-up neuropathic signs and symptoms were at least partly reversible. Despite a severe weakness, recovery was almost complete in patient A.

Although paclitaxel and docetaxel neuropathy is mainly a sensory axonal neuropathy, the electrophysiologic data in our patients and those of others suggest that in more severe cases of docetaxel neuropathy a mixed axonal-demyelinating neuropathy may develop [18]. The precise mechanism of this neuropathy is unknown, but based on the resemblance with paclitaxel in its mechanism of action it might be caused by the effects of docetaxel on microtubules. The predominance of sensory features with onset simultaneously in hands and feet in many of our patients suggests that this neuropathy may not be a dying back, length dependent neuropathy, but a neuronopathy primarily affecting the dorsal root ganglion [26].

In conclusion, neuropathy is not a predominant side-effect of docetaxel [17,18]. However, especially following the treatment with a high cumulative dose, some patients may develop a severe and disabling neuropathy. Further study for risk factors of docetaxel neuropathy is of high clinical relevance, in view of the continuously accumulating evidence that docetaxel holds promise as an effective antineoplastic agent

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Chapter 6

Lhermitte's sign following chemotherapy with docetaxel

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Neurology in press

Abstract

Specific causes for Lhermitte's sign (LS) in cancer patients are spinal cord compression, radiation therapy to the spinal cord and cisplatin chemotherapy. We observed a transient LS in 5 out of 87 patients treated with more than two cycles of 100mg/m^2 docetaxel (Taxotere). LS developed either concurrent or after the onset of docetaxel induced sensory neuropathy, and disappeared after the discontinuation or dose reduction of chemotherapy.

Introduction

Although more properly designated a symptom than a sign, Lhermitte's sign (LS) is an electric shock-like sensation which shoots down the back and into the limbs when the neck is flexed. LS may be seen in a variety of disorders of the spinal cord, such as demyelinating disease, vitamine B12 deficiency, spinal cord compression and spinal cord tumors. In cancer patients, it may also develop following radiotherapy of the spinal cord and after chemotherapy with cisplatin [1]. We describe five patients who developed LS during the treatment with docetaxel (Taxotere), a new cytotoxic agent.

Patients and methods

All patients participated in phase II trials on docetaxel chemotherapy. They received docetaxel in three-weekly cycles: patient A with 50 mg/m2 on day 1 and day 8 of each cycle, Patients B-E with 100 mg/m2 docetaxel on day 1 as a one-hour infusion. As a part of these studies all patients were evaluated prospectively for neurotoxicity with baseline and follow-up neuroexams, including specific questioning for the presence of LS. In each of the presently described patients the neurological baseline investigations were normal.

Results

Patient A, a 40-year-old woman was treated for recurrent metastatic breast cancer with docetaxel. Shortly after the first cycle of docetaxel she had transient paresthesias in her feet; she also noticed that neck flexion triggered a painful tingling in her hands and feet. No other neurological symptoms were present. The MRI of the cervical spine showed two small bone metastases without spinal cord compression. Serum vitamin B12 was normal. Following further treatment she developed persistent paresthesias in her fingers and feet. After four cycles, loss of tendon reflexes was found. Following the next cycle the treatment was discontinued because of toxicity. LS and

paresthesias persisted up to two months after the cessation of the chemotherapy, and disappeared thereafter. Shortly afterwards, progressive disease was diagnosed and she was lost to the follow-up.

Patient B, a 47-year-old woman was treated with docetaxel for recurrent metastatic breast cancer. After two cycles she developed paresthesias in fingers and toes. Physical examination showed the absence of tendon reflexes and loss of vibration sense. Symptoms progressed during the next cycles. After five cycles she had numbness of fingers and toes, paresthesias in the entire feet, slight proximal weakness, and Romberg's sign was positive. Now, flexion of the neck provoked paresthesias in the entire legs. Nerve conduction velocity (NCV) studies showed a sensori-motor axonal polyneuropathy. Because of toxicity the treatment was discontinued. In the next months the paresthesias and LS disappeared although some numbness of the fingers persisted.

Patient C, a 51-year-old woman with metastasized breast cancer was treated with docetaxel as a second line chemotherapy. Following the third cycle she developed some paresthesias in her feet. Following the fifth cycle, paresthesias in her feet had worsened and she developed numbness in her feet and paresthesias in her hands. At examination, loss of vibration and position sense at her feet was found. Following the next cycle, she noticed that anteflexion of her neck greatly increased the paresthesias in her feet. NCV studies showed an axonal mixed sensorimotor neuropathy. Because of toxicity the treatment was discontinued. Eight weeks later, both sensory complaints and LS were improving. Shortly afterwards, she died from progression of cancer.

Patient D, a 36-year-old woman was treated with docetaxel for bone metastasis of breast cancer. Following the third cycle, she developed transient paresthesias and numbness of her feet. She also noticed that flexion of the neck provoked the paresthesias in her feet. The MRI of the cervical spine showed bone metastasis without cord compression, the CSF was normal. Vitamin B12 and folic acid were also normal. Following the fourth cycle, reflexes were absent but no significant sensory abnormalities were found. Following each cycle numbness and paresthesias increased, but improved in the days before the next cycle. NCV studies following the sixth cycle showed an axonal sensory neuropathy. The neurological examination was unchanged. Following the eighth cycle, the dosage of docetaxel was reduced to 75mg/m2 per cycle because of leukopenia. With this dosage, the symptoms of neuropathy and LS disappeared, and no further episodes of leukopenia occurred.

Patient E, a 69-year-old man, with bladder cancer had developed multiple bone metastases and local progression with infiltration into the left lumbosacral plexus. He received seven cycles of docetaxel. After four cycles he reported mild paraesthesias in his hands, and at examination loss of vibratory perception at his toes and loss of tendon reflexes at his legs were found. After the seventh cycle progressive neuropathic symptoms, consisting of numbness and severe paraesthesias in hands and feet, and difficulty in walking, developed. He had noticed tingling in hands and feet with flexion of the neck. Despite a partial tumor response, the chemotherapy was discontinued. The EMG and nerve conduction studies revealed a severe mainly sensory neuropathy. Progression of the tumor was diagnosed three months later, thereafter the patient was lost to the follow-up.

Discussion

We descibe five patients who developed LS during the treatment with docetaxel. LS has also been described in cisplatin and in pyridoxine induced neuropathy [1,2]. Similar to these drugs docetaxel may induce a predominantly sensory axonal neuropathy causing paresthesias and numbness in a stocking-and-glove-fashion [3,4]. Four of the presently reported patients developed a mild or moderate sensory neuropathy within three cycles of treatment. This suggests they may have been more vulnerable to neurotoxic effects of docetaxel than the average patient. Two patients developed LS at the same time as the neuropathy, the other three became aware of this phenomenon following an additional three cycles. As all patients had a docetaxel induced sensory neuropathy, as a discontination of treatment or dose reduction of docetaxel led to improvement of both neuropathy and LS, and no other cause for LS was found, we presume the LS in these patients was caused by the docetaxel chemotherapy.

We believe LS may not be rare in patients treated with docetaxel. Patients A and E were already mentioned in an earlier study on docetaxel induced neuropathy in 41 patients [4]. The other three patients in this report are from a group of 46 patients who were evaluated for the development of neuropathy and who had been treated with more than two cycles of docetaxel. Thus, we observed LS in five out of 87 patients treated with more than two cycles of docetaxel.

LS is usually considered a symptom of spinal cord involvement, for which reason LS in cisplatin neuropathy has been considered as evidence of a toxic effect of cisplatin on the spinal cord [5,6]. However, the different clinical presentation of LS in spinal cord lesions due to, for instance, spinal cord compression as compared to in cisplatin or docetaxel induced LS, suggests a different mechanism in both phenomena. In spinal cord lesions, patients

usually report electric shock-like sensations along the spine and legs provoked by neck flexion. In cisplatin or docetaxel induced LS neck flexion usually provokes paresthesias in feet or legs, and in some cisplatin treated patients paresthesias or electric shock sensations can also be elicited by Lasegue's manoeuvre [1].

Cisplatin primarily affects the dorsal root ganglia; in experimental pyridoxin neuropathy, a low dose of pyrodixin causes an axonal sensory neuropathy, whereas higher doses cause necrosis of the dorsal root ganglia with Wallerian degeneration of both peripheral and central sensory neurons (in the spinal cord) [5,7]. Neurofysiological studies have demonstrated that LS reflects an abnormal mechanosensitivity of damaged sensory axons in either the spinal cord, or the dorsal roots or the dorsal ganglia [8,9]. On flexing the neck, the spinal canal lengthens which causes stretching of the spinal cord and the intrathecal nerve roots. Thus, it is likely that LS in toxic sensory neuropathies is due to the stretching of degenerated, abnormally mechano-sensitive axons in roots and dorsal columns following a lesion of the sensory neuron in the dorsal ganglion. This would imply involvement of the sensory cell body in patients with docetaxel induced LS. In paclitaxel induced neuropathy, both a distal dying back axonopathy and a neuronopathy have been postulated as the primary pathological process. This may also depend on the dosage of paclitaxel, similar to in experimental pyridoxin neuropathy, and on the susceptibility of an individual patient [3,10]. As docetaxel and paclitaxel neuropathy have a great similarity, these assumptions will also hold for docetaxel neuropathy.

In conclusion, docetaxel chemotherapy may cause LS, but if LS develops in cancer patients one should always consider the possibility of spinal cord compression.

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Chapter 7

Effect of corticosteroid co-medication on incidence and severity of neurotoxicity induced by docetaxel

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submitted

Abstract.

Docetaxel is a new antimicrotubule agent that induces a predominantly sensory neuropathy that is mild in most patients. This prospective study was performed to determine if corticosteroid co-medication reduces the incidence and severity of Docetaxel-induced neuropathy.

Two groups of patients treated with Docetaxel in subsequent cohorts were prospectively analyzed for neurotoxicity. Group A consisted of 38 patients with a variety of solid tumors, who were treated in studies before corticosteroid co-medication was recommended, while 49 female patients in group B with metastatic breast cancer were treated after co-medication with corticosteroids was introduced as a routine. Neuropathy was evaluated by a clinical sum-score for symptoms and signs and by measurement of the Vibration Perception Threshold (VPT). The severity of the neuropathy was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC).

In 42% of the patients of group A and in 65% of the patients of group B a mainly mild neuropathy was documented. There was no statistically significant difference in neurotoxicity between group A and B. The cumulative dose of Docetaxel showed a significant correlation with the post-treatment scores of the VPT, sensory sum-score, grade of paresthesias, and grade of neurosensory- and neuromotor toxicity.

We conclude that corticosteroid co-medication does not reduce the development of Docetaxel-related neuropathy.

Introduction

Docetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France) is a new semi-synthetic taxoid that is prepared from 10-deacetyl baccatin III, a non-cytotoxic precursor extracted from the needles of the European Yew, Taxus Baccata. Like Paclitaxel (Taxol), Docetaxel acts as an antimicrotubule agent that enhances polymerization of the tubulin into stable microtubules and inhibits microtubule depolymerization. This leads to a disruption of the equilibrium within the microtubule system and ultimately to cell death [1-4].

In phase I studies on the single agent Docetaxel the major dose limiting toxicity (DLT) was neutropenia which appeared to be short-lasting, dose-dependent, schedule-independent and non-cumulative [5-10]. Based on these phase I studies the recommended single agent dose and schedule for Docetaxel was 100 mg/m^2 given as a one hour infusion every 3 weeks. Phase II studies on Docetaxel showed activity in breast cancer [11-15], non-small cell lung cancer [16-18], head and neck cancer [19], gastric cancer [20], melanoma [21], soft tissue sarcoma [22], and pancreatic cancer [23]. The most important side effect was an early short-lasting neutropenia which in 20% of the patients was complicated by an infection [1]. Other side effects included alopecia, nausea, vomiting, diarrhea, mucositis, asthenia, infrequent hypersensitivity reactions, skin reactions, nail changes, fluid retention and a mild sensory neuropathy [1,24-26].

We prospectively assessed neurotoxicity in 41 patients treated with Docetaxel as first or second line chemotherapy. Docetaxel induced a predominantly sensory neuropathy in 20 out of 41 patients that was mild in most patients. However, at cumulative doses above 600 mg/m^2, 3 out of 15 patients developed a moderate neuropathy and 1 out of 15 patients a severe one [24]. Most of these patients did not receive corticosteroid co-medication. In the present study we prospectively assessed neurotoxicity in patients with

metastatic breast cancer who were treated in a multicentre study of Docetaxel, and who routinely received corticosteroid co-medication during five days. The results of this prospective study were compared with those of the previous study [24], with the aim to determine if corticosteroid co-medication reduces and/or delays Docetaxel-induced neurotoxicity.

Patients and methods

In two groups of patients with metastatic or locally advanced cancer neurotoxicity was assessed prospectively. Group A included patients with metastatic or locally advanced cancer who participated in one of four different multicentre phase II trials on the activity of Docetaxel as first or second line chemotherapy as described before [24]. The patients with breast cancer who were randomized to receive prophylactic corticosteroids were excluded from the analyses. Group B consisted of patients with histologically or cytologically proven breast cancer who had not responded to conventional chemotherapy and participated in a compassionate use programme. Eligibility criteria for all studies were: 1) age $\geq$ 18 years; 2) WHO performance status 0-2; 3) adequate hematological (granulocytes $\geq$ 2.0 x 10^9/l), renal (serum creatinine $\leq$ 1.5 x upper normal limit) and hepatic function (total serum bilirubin $\leq$ 1.25 x upper normal limit); 4) no clinical signs of symptomatic peripheral neuropathy grade 2 or more according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) [27]. All patients had given informed consent.

Docetaxel was supplied by Rhône-Poulenc Rorer (Antony, France) and administered as a one hour infusion at a dose of 100 mg/m^2 every 3 weeks. In six patients of group A the dose per cycle was divided and given on days 1 and 8 every 3 weeks [28]. In group B all patients received co-medication consisting of 8 mg of Dexamethasone orally 13 hours, 7 hours, and 1 hour

before Docetaxel infusion, followed by Dexamethasone 8 mg orally twice a day during 96 hours after Docetaxel administration. In group A no corticosteroids were given because these patients were treated in studies before corticosteroid co-medication was recommended. No other neurotoxic drugs were used during the study or follow-up period.

The severity of the neuropathy was evaluated by a questionnaire for neurological symptoms, by standardized neurological examination and by measurements of the Vibration Perception Threshold (VPT) before the start of the treatment, after every two cycles, at 2 weeks after the last dose of Docetaxel, and every 3 months thereafter. The questionnaire established separately absence (0) or presence (1) of paresthesias, numbness, loss of dexterity and unsteadiness of gait. On sensory examination, position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tendon-reflexes of the legs were each scored as normal (0) or abnormal (1). A sum-score for these signs and symptoms was calculated (minimum 0, maximum 11). The severity of paresthesias was graded on a 5-point scale (0, no; 1, temporary; 2 continuous & light; 3, severe; 4, unbearable). Sensory loss was defined as an abnormal test on either position sense, vibration sense or pin-prick sense. Patients were asked whether they experienced Lhermitte's sign or pain. The distal muscle strength in the lower extremities was tested. Motor signs were defined as the presence of objective weakness. The severity of the neuropathy was scored according to the NCI Common Toxicity Criteria (CTC) [27] for sensory neuropathy (0, no symptoms or signs; 1, mild paresthesias, loss of deep tendon reflexes; 2, moderate paresthesias, objective sensory loss; 3, severe paresthesias, sensory loss interfering with function). The VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type IV (Somedic AB, Stockholm, Sweden) and recorded in micrometers of skin displacement.

This Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The mean value of three measurements of the VPT determined with the method of limits was considered the actual VPT [29]. The VPT has been shown to be a reliable technique to monitor Cisplatin neuropathy and shows a good correlation with the sum-score of neuropathic signs and symptoms as observed previously [30-32]. It has been used to quantify paclitaxel-induced neuropathy [33].

For the assessment of neurotoxicity, the post-treatment evaluation on day 90 was chosen as the primary endpoint, since a relation was suggested between Docetaxel-induced toxicity and the cumulative dose. Cycles of Docetaxel given after the last neurological evaluation, which occurred in 27 patients, were not counted in the analysis and excluded from the calculation of the cumulative dose.

Primary endpoints for the analysis were the VPT, the sensory sum-score, the grade of paresthesias, the CTC neurosensory grade and the CTC neuromotor grade. Because of the skewed distribution of the VPT the natural logarithm was used for statistical analysis. The post-treatment grade of patients with pre-existing paresthesias, CTC neurosensory or CTC neuromotor with grade ≥ 1, was considered 0 if it had not increased at post-treatment evaluation. Analysis of co-variance was applied to test for a difference between the two treatment groups in post-treatment sensory sum-score and log VPT while adjusting for pre-treatment values, age and the cumulative dose of Docetaxel (log transformed). Ordinal logistic regression analysis, according to the proportional odds model [34], was applied to compare the two groups with respect to the post-treatment grade of paresthesias, neurosensory and neuromotor, adjusted for age and cumulative

dose of Docetaxel. The p-values reported in the results section for the comparison of groups A and B are all based on these adjusted analyses.

Results

A total of 87 patients were evaluable for neurotoxicity. Patient characteristics are given in table 7.1. The two groups we studied differed in several ways; group A consisted of patients with various tumor types of whom nine patients had received Cisplatin as prior antitumor therapy, whereas all patients of group B were females with metastatic breast cancer of whom most were pretreated with non-neurotoxic chemotherapy. The patients with breast cancer in group A did not receive corticosteroid co-medication. In both groups there was 1 patient with diabetes mellitus and 2 patients of group A reported alcohol abuse.

Table 7.2 represents the number of cycles and the cumulative dose of Docetaxel administered to both groups. All patients started treatment at a dose of 100 mg/m^2 every three weeks, but in some patients dose reductions were required because of various adverse effects. In the six breast cancer patients of group A the dose per cycle was divided and given on day 1 and 8 every three weeks. The cumulative dose of Docetaxel was < 300 mg/m^2 in 15 patients of group A and in 10 patients of group B, 300-600 mg/m^2 in 9 patients of group A and in 15 patients of group B, and > 600 mg/m^2 in 14 and 24 patients of group A and B respectively.

Table 7.1

Patient characteristics

	Group A	Group B
number of patients	38	49
age median years	52	50
(range)	(28-73)	(31-73)
sex male/female	15/23	-/49
WHO performance stati		
0	16	13
1	19	33
2	3	3
prior treatment		
cisplatin	9	1
vincristine	-	-
other chemotherapy	15	45
tumor type		
breast	6	49
ovarian	10	-
sarcoma	7	-
bladder	7	-
head and neck	5	-
melanoma	2	-
colorectal	1	-

Table 7.2

Number of cycles and cumulative dose of Docetaxel

	Group A	Group B
number of cycles		
median	4	6
(range)	(2-11)	(1-20)
cumulative dose (mg/m^2)		
median	363	575
(range)	(100-1100)	(100-1700)

Before the start of the treatment four patients in group A and three patients in group B showed a mild sensory neuropathy. The four patients in group A had been pretreated with Cisplatin. In table 7.3 the increase in the sensory sum-score, VPT, paresthesias and grade of neurosensory and neuromotor toxicity are shown at the post-treatment evaluation in relation to the treatment group. According to CTC criteria 16 patients of group A (42%) and 32 patients of group B (65%) developed a sensory neuropathy. There was no statistically significant difference between groups A and B in the post-treatment scores of the VPT ($p = 0.87$), sensory sum-score ($p = 0.83$), paresthesias ($p = 0.62$), and CTC neuromotor ($p = 0.53$). In group B somewhat higher CTC neurosensory grades were found compared to group A ($p = 0.04$).

Table 7.3
Increase in neurotoxicity in relation to treatment group

	Group A		Group B	
number of assessable patients	38		49	
sensory sum-score increase mean ±SD	2.5 ±2.7		2.7 ±2.2	
VPT ratio post/pre treatment mean ±SD	1.2 ±0.7		1.5 ±0.9	
	N	%	N	%
Paraesthesias				
no increase	18	47	28	57
grade 1	9	24	6	12
grade 2	9	24	6	12
grade 3	1	3	7	14
grade 4	1	3	2	4
CTC neurosensory				
no increase	22	58	17	35
grade 1	14	37	21	43
grade 2	2	5	9	18
grade 3	0	0	2	4
CTC neuromotor				
no increase	34	89	42	86
grade 1	3	8	4	8
grade 2	0	0	3	6
grade 3	1	3	0	0

Table 7.4

Increase in neurotoxicity in relation to cumulative dose of Docetaxel

	< 300 mg/m²		300-600 mg/m²		> 600 mg/m²	
group	A	B	A	B	A	B
number of patients	15	10	9	15	14	24
sensory sum-score Increase[1]	1.2 ±1.1	0.6 ±1.1	2.2 ±2.2	3.3 ±2.4	4.0 ±3.4	3.1 ±1.9
VPT ratio[2]	1.3 ±0.9	1.1 ±0.6	1.0 ±0.2	1.3 ±0.7	1.3 ±0.8	1.8 ±1.3
paraesthesias						
No increase	9	8	4	6	5	14
Grade 1	5	1	2	3	2	2
Grade 2	1	0	3	3	5	3
Grade 3	0	1	0	1	1	5
Grade 4	0	0	0	2	1	0
CTC neurosensory[3]						
No increase	13	10	5	2	4	5
Grade 1	2	0	4	8	8	13
Grade 2	0	0	0	5	2	4
Grade 3	0	0	0	0	0	2
CTC neuromotor[3]						
No increase	15	9	9	13	10	20
Grade 1	0	1	0	1	3	2
Grade 2	0	0	0	1	0	2
Grade 3	0	0	0	0	1	0

[1] *Difference between post-treatment and pre-treatment score. Values are means ±SD.*
[2] *Ratio of post-treatment and pre-treatment score. Values are means ±SD.*
[3] *Incidence at post-treatment evaluation; in case of pre-existing graded toxicities, only higher grades are counted.*

Table 7.4 represents the mean increase in the sensory sum-score, the mean VPT ratio, the increase in the severity of paresthesias, the CTC-neurosensory grade and the CTC-neuromotor grade at the post-treatment evaluation classified by the cumulative dose. At a cumulative dose of Docetaxel < 600 mg/m² six out of 24 patients in group A showed a mild

sensory neuropathy, while in group B eight out of 25 patients developed a mild sensory neuropathy and five out of 25 patients developed a moderate one. At a cumulative dose $\geq$ 600 mg/m^2 10 out of 14 patients in group A developed a sensory neuropathy that was mild in eight patients and moderate in two patients. In group B 19 out of 24 patients who had received a cumulative dose $\geq$ 600 mg/m^2 developed a sensory neuropathy that was mild in 13 patients, moderate in four patients and severe in two patients. Neuromotor toxicity was reported in four patients of group A and in seven patients of group B. Neurotoxicity was a reason to stop the Docetaxel treatment in three patients (8%) of group A and in six patients (12%) of group B.

The cumulative dose of Docetaxel showed a positive association with all post-treatment scores when adjusted for the pretreatment score, age and treatment group: VPT ($p = 0.02$), sensory sum-score ($p < 0.001$), grade of paresthesias ($p = 0.11$), CTC neurosensory ($p < 0.001$), and CTC neuromotor ($p = 0.09$)

Discussion

Docetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, France) is a new antimicrotubule agent that has shown activity in a variety of solid tumors [11-23]. It induces a frequent dose-dependent, predominantly sensory neuropathy that is mild in most patients [24-26]. New et al [25] reported a sensorimotor neuropathy in 11% of 186 patients that were treated with Docetaxel at a wide range of cumulative doses (50-720 mg/m^2) and dose levels (10-115 mg/m^2). Hilkens et al [24] documented a sensory neuropathy in 20 (49%) out of 41 patients that was mild in most patients, but at cumulative doses of Docetaxel higher than 600 mg/m^2 3 patients developed a moderate neuropathy and 1 patient a severe one. The clinical characteristics of severe peripheral

neuropathy were described in detail [35]. Disabling and painful paresthesias, loss of tendon reflexes, loss of dexterity and steadiness of gait and proximal weakness dominated the clinical picture in these patients. In some patients Lhermitte's sign was observed [35,36]. Freilich et al [37] reported a motor neuropathy due to the treatment with Docetaxel in 7 out of 60 patients (12%). The motor weakness was predominantly proximal; it seemed idiosyncratic as it occurred at any stage of treatment and had a variable course. The motor neuropathy appeared to be reversible upon the cessation of the Docetaxel therapy.

The present study was performed to determine if corticosteroid co-medication reduces the incidence and/or severity of Docetaxel-related neuropathy. In the early studies on Docetaxel, corticosteroid co-medication was not given routinely. However, in a phase II study of the EORTC Breast Cancer Study Group in which patients treated with Docetaxel were randomized between prophylactic oral antihistamine with or without methylprednisolone, corticosteroids appeared to decrease the severity of Docetaxel-related fluid retention [28]. Furthermore, the application of corticosteroid co-medication markedly reduced the incidence of hypersensitivity reactions induced by Docetaxel [38]. Considering these observations it was recommended to administer corticosteroid co-medication routinely in later studies on Docetaxel.

Hilkens et al performed a prospective study in which patients treated with Docetaxel were assessed for neurotoxicity [24]. Most of these patients did not receive corticosteroid co-medication, except for some patients with breast cancer who participated in a phase II study in which patients were randomized to receive pre-medication with or without methylprednisolone [28]. In the present analysis we deleted the patients who were randomized to receive corticosteroid co-medication (group A) and compared the results of

this group with the results of a study that prospectively assessed patients for neurotoxicity who were treated with Docetaxel and received corticosteroid co-medication (group B). The two groups differed in several ways; the patients in group A had a variety of tumor types and 9 out of 38 patients were pre-treated with Cisplatin. The patients in group B, however, were all females with metastatic breast cancer who were pre-treated with non-neurotoxic chemotherapy.

There was no statistically significant difference in the post-treatment scores of the VPT ($p = 0.87$), sensory sum-score ($p = 0.83$), paresthesias ($p = 0.62$), and CTC neuromotor ($p = 0.53$) when adjusted for the pretreatment score, age, treatment group and the cumulative dose of Docetaxel. In group B somewhat higher CTC neurosensory grades were reported compared to group A ($p = 0.04$). This could be explained by the fact that the median number of cycles administered and the cumulative dose of Docetaxel were higher in group B than in group A. The cumulative dose of Docetaxel was strongly associated with all post-treatment neurotoxicity scores.

We conclude that corticosteroid co-medication does not reduce the incidence or severity of Docetaxel-related neuropathy. Nevertheless there is a role for corticosteroids since they do reduce the incidence of hypersensitivity reactions and Docetaxel-related fluid retention

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Chapter 8

Peripheral neurotoxicity induced by combination chemotherapy with docetaxel and cisplatin

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Abstract

Docetaxel, a new semi-synthetic taxoid that has demonstrated promising activity as an anti-neoplastic agent, was administered in combination with cisplatin to 63 patients in a dose-escalating study. As both drugs were known to be potentially neurotoxic, peripheral neurotoxicity was prospectively assessed in detail. Neuropathy was evaluated by clinical sum-score for signs and symptoms and by measurement of the Vibration Perception Threshold (VPT). The severity of the neuropathy was graded according to the National Cancer Institute's 'Common Toxicity Criteria'.

The docetaxel-cisplatin combination chemotherapy induced a predominantly sensory neuropathy in 29 (53%) out of 55 evaluable patients. At cumulative doses of both cisplatin and docetaxel above 200 mg/m^2, 26 (74%) out of 35 patients developed a neuropathy which was mild in 15, moderate in 10 and severe in one patient. Significant correlations were present between both the cumulative dose of docetaxel and cisplatin and the post-treatment sum-score of the neuropathy ($p < 0.01$) as well as the post-treatment VPT ($p < 0.01$). The neurotoxic effects of this combination were more severe than of either cisplatin or docetaxel as a single agent at comparable doses.

Introduction

Docetaxel (Taxotere®) is a new semi-synthetic taxoid that has demonstrated substantial clinical activity against a wide variety of solid tumors [1-7]. Docetaxel inhibits tubulin depolymerization and promotes microtubule assembly, resulting in dysfunctional microtubules [1].

In view of their partly non-overlapping side-effects and their activities in a wide range of tumor types, developing combination chemotherapy regimens including both taxoids and platins is of major interest [8-10]. An important dose-dependent side-effect of cisplatin is the development of peripheral neuropathy, mainly affecting thick-fiber mediated sensory qualities [11-15]. Neuropathy has also been reported as a dose-dependent side-effect of the treatment with paclitaxel (Taxol®) [16,17]. As expected, trials on the combination chemotherapy of cisplatin and paclitaxel found a high incidence of peripheral neuropathy [8-10].

Peripheral neurotoxicity has been reported as a frequent, but usually mild side-effect of docetaxel in several phase I and phase II studies [2-7,18-21]. The neurotoxic effects of docetaxel in a combination chemotherapy with cisplatin are unknown. In our institution a phase I trial on the combination of docetaxel and cisplatin in metastatic or locally advanced solid tumors was conducted [22]. To study the neurotoxicity of this combination chemotherapy we prospectively evaluated all patients participating in this trial by detailed neurological examinations.

Patients and methods

All participating patients had a metastatic or locally advanced solid tumor for which no other appropriate anti-tumor therapy was available. Other inclusion criteria were age 18-75 years, WHO performance status 0-2, no prior treatment with platinum derivates or taxoids, normal organ functions,

a life expectancy of 3 months or more and written informed consent. Patients with a symptomatic peripheral neuropathy grade 1 or more according to the "National Cancer Institute (NCI) criteria" (Table 8.1) and patients with brain or leptomeningeal metastases were excluded.

The chemotherapy was administered in 3-weekly regimens. Docetaxel, supplied by Rhône-Poulenc Rorer, was given as a 1-hour infusion. Cisplatin was dissolved in 3% saline and administered as a 3-hour infusion with 24 hours of hyperhydration. In most patients docetaxel was given 3 hours prior to cisplatin. In some patients the sequence was reversed and docetaxel was given 18 hours following the cisplatin administration. Scheduled dose-escalation included cisplatin doses of 50, 75 and 100 mg/m^2 and docetaxel doses of 55, 70, 85 and 100 mg/m^2. No other neurotoxic drugs were applied during the trial or follow-up period.

Table 8.1
Severity of paresthesias and 'Common Toxicity Criteria' of the NCI

PARESTHESIAS	CTC-NEUROSENSORY
0 = no	0 = no symptoms or signs
1 = temporary	1 = mild paresthesias, loss of
2 = continuous & light	deep tendon reflexes
3 = severe	2 = moderate paresthesias,
4 = unbearable	objective sensory loss
	3 = severe paresthesias, sensory
	loss interfering with function

The severity of the neuropathy was assessed by a questionnaire for neurological symptoms, by standardized neurological examination and by measurements of the Vibration Perception Threshold (VPT) before the start of the treatment, after each cycle, at 2 weeks after the last dose of docetaxel and every 3 months thereafter. The questionnaire established separately absence (0) or presence (1) of paresthesias, numbness, loss of dexterity and unsteadiness of gait. On sensory examination position sense, vibration sense, pin-prick sensation, Romberg's sign, Romberg's sign with heel-to-toe stand and tendon-reflexes of the legs were each scored as normal (0) or abnormal (1). A sum-score for these signs and symptoms was calculated (minimum 0, maximum 11). The severity of the paresthesias was graded on a 5-point scale (Table 8.1). Sensory loss was defined as an abnormal test on either position sense, or vibration sense or pin-prick sense. Patients were asked whether they experienced Lhermitte's sign or pain. The distal muscle strength in the lower extremities was tested. Motor signs were defined as the presence of objective weakness. The severity of the neuropathy was scored according to the NCI Common Toxicity Criteria (CTC) for sensory neuropathy (Table 8.1). The VPT was measured at the dorsum of the second metacarpal bone of the left hand with a Vibrameter type IV (Somedic AB, Stockholm, Sweden) and recorded in micrometers (μm) of skin displacement. This Vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations of vibratory amplitude. The method of limits was used to obtain the mean VPT and this was repeated three times [23]. The VPT has been shown to be a reliable technique to monitor cisplatin neuropathy and shows a good correlation with the sum-score of neuropathic signs and symptoms as observed previously [24-26]. It has been applied to quantify paclitaxel-induced neuropathy [17].

In some patients electrophysiological studies were done before and after the treatment. The distal latency and nerve conduction velocity (NCV) of the ulnar (sensory and motor), peroneal (motor) and sural nerve, the compound motor action potential (CMAP) of the ulnar and peroneal nerve and the sensory nerve action potential (SNAP) of the ulnar and sural nerve were determined. A 50% decrease in CMAP and SNAP amplitude and a 15% decrease of NCV were considered abnormal.

The first post-treatment evaluation was used as a primary endpoint for the assessment of neurotoxicity. Cycles of docetaxel and cisplatin given after the last neurological evaluation, which occurred in eight patients, were not counted in the analysis and excluded from the calculation of the cumulative dose.

A subdivision was made into three groups according to the cumulative dose of cisplatin and docetaxel. The mean increase in the sum-score and the ratio of VPT post-treatment with respect to the VPT pre-treatment (VPT post/pre ratio) within groups were calculated. A comparison of the severity of neuropathy in relation to cumulative dose was made with two other prospective trials performed in our institution in the same period [15,21]. In these trials cisplatin and docetaxel were studied as single chemotherapeutic agents and identical methods for the measurement of neuropathy were applied as described here.

The incidence of neurological signs and symptoms at the first evaluation after the last cycle was determined. Patients with pre-existing signs or symptoms were not included in these calculations. Graded paresthesias pre-treatment were included only if there was an increase in the grade of paresthesias post-treatment. The change in the sensory sum-score and the VPT post/pre ratio were calculated for each patient. Spearman rank-correlations were calculated to describe the strength of the association

between cumulative doses of cisplatin and docetaxel and the increase in the sensory sum-score and the VPT post/pre ratio. Because of the skewed distribution of the VPT the geometric mean was used to determine the mean of the VPT post/pre ratio. For the sensory sum-score the arithmetic mean was calculated.

Results

Sixty-three patients were entered into the trial. Eight of these 63 patients were excluded from the assessment of neurotoxicity because a pre-treatment evaluation was lacking. Patient characteristics, tumor-type and previous chemotherapy of 55 patients evaluable for the present analysis are shown in table 8.2. Twenty-seven patients had previously been treated with non-neurotoxic chemotherapy. One patient had been treated with vincristine. None of the patients had received a prior treatment with cisplatin. Five patients had diabetes mellitus and 5 patients reported alcohol abuse.

Twenty patients received 1-2 cycles, 6 patients 3-4 cycles, 28 patients 5-6 cycles and 1 patient 8 cycles before their last evaluation. Per cycle the mean dose of cisplatin was 74 mg/m^2 (range 50 -100 mg/m^2) and of docetaxel 82 mg/m^2 (range 38-100). The mean cumulative dose given of cisplatin was 297 mg/m^2 (range 75-600 mg/m^2) and of docetaxel 326 mg/m^2 (range 75-600 mg/m^2). The mean duration of the follow-up after the last cycle was 96 days (range 7-315 days)

Table 8.2
Patient characteristics and tumor type

number of evaluable patients		55
sex	male/female	26/29
age	mean (yrs)	53
	(range)	(21-74)
tumor type		
	colorectal	23
	ACUP[1]	14
	breast	5
	head and neck	3
	sarcoma	2
	melanoma	2
	NSCLC[2]	2
	miscellaneous	4
prior therapy		
	cisplatin	-
	vincristine	1
	other chemotherapy	27

[1]) *Adenocarcinoma of unknown primary*
[2]) *Non-small cell lung carcinoma*

Table 8.3 shows the incidence of neuropathic signs and symptoms at the first post-treatment evaluation. Paresthesias were seen in 24 patients (44%): in both hands and feet (n=18) or in the feet only (n=6). Three patients suffered from pain in either hands or feet, which was felt to be secondary to the neuropathy.

Table 8.3
Neuropathic signs and symptoms at first post-treatment evaluation

	N	(%)
paresthesias	24/55	(44)
grade 1	8[1]	
grade 2	9[2]	
grade 3	5[3]	
grade 4	2	
pain	3/54[4]	(6)
numbness	17/53	(32)
loss of dexterity	14/53	(26)
unsteadiness of gait	9/53	(17)
Lhermitte's sign	7/54	(13)
sensory loss	19/46	(41)
motor signs	9/54	(17)
Romberg's sign	2/51	(4)
loss of knee jerks	23/55	(42)
loss of ankle jerks	29/45	(64)

[1]) *Excluding one patient with pre-existing paresthesias grade 1*
[2]) *Including one patient with pre-existing paresthesias grade 1*
[3]) *Including one patient with pre-existing paresthesias grade 2*
[4]) *Patients with these signs or symptoms at the pre-treatment evaluation or with missing data were excluded*

Table 8.4
Severity of neuropathy in relation to cumulative dose of docetaxel and cisplatin

Cisplatin Docetaxel	< 200 mg/m^2 < 200 mg/m^2 N = 20	200-400 mg/m^2 > 200 mg/m^2 N = 16	>400 mg/m^2 >200 mg/m^2 N = 19
sensory sum-score increase[1] mean (±SD)	1.1 ±1.2	4.3 ±2.4	3.5 ±2.9
VPT post/pre ratio[2] mean (±SD)	1.2 ±0.7	1.9 ±0.9	4.3 ±4.0
paresthesias[3]			
grade 1	1(1)[4]	2(2)	5(3)
grade 2	1(1)	5(4)	3(7)
grade 3	-	2(3)	3(3)
grade 4	-	2(2)	-(1)
CTC neurosensory[3]			
grade 1	3(2)	7(7)	8(10)
grade 2	-(1)	5(4)	5(3)
grade 3	-	-(1)	1(3)

[1]) *difference between the first post-treatment and the pre-treatment score.*
[2]) *difference between the first post-treatment and the pre-treatment score, divided by the pre-treatment score (post/pre ratio).*
[3]) *incidence at the first post-treatment evaluation.*
[4]) *= numbers when maximum scores post-treatment are considered.*

Table 8.4 shows the mean increase in the sensory sum-score, the mean VPT post/pre ratio, the severity of paresthesias and the CTC-neurosensory-grade at the first post-treatment evaluation classified by a cumulative dose of docetaxel and cisplatin. According to the CTC criteria, 29 patients developed a sensory neuropathy. In the group with a cumulative dose of both cisplatin and docetaxel below 200 mg/m^2 three out of 20 patients showed a mild sensory neuropathy (grade 1). Out of 16 patients treated with a cumulative dose of docetaxel above 200 mg/m^2 and of cisplatin between 200 and 400 mg/m^2, 12 patients developed a sensory neuropathy which was mild in seven patients (grade 1) and moderate in five patients (grade 2). In the group with a cumulative dose of cisplatin above 400 mg/m^2 and docetaxel above 200 mg/m^2, 14 out of 19 patients developed a sensory neuropathy, grade 1 in eight, grade 2 in five, and grade 3 in one patient. In four patients the treatment had to be discontinued because of neurotoxicity.

Twenty-three patients had two or more post-treatment evaluations. Two of these patients developed a mild neuropathy (grade 1) during the follow-up. In four patients the neuropathy further deteriorated during follow-up: one patient developed a moderate neuropathy (grade 2) and three patients a severe (grade 3) one.

In 43 patients the sequence of the administration was docetaxel prior to cisplatin and in 12 patients vice versa. There was no difference in the severity of neurotoxicity as measured with the sensory sum-scores between these two different regimens.

We found a clear correlation between the increase in the VPT and the increase in the sum-score ($R_s = 0.34$, $p = 0.02$) following treatment. The cumulative dose of both docetaxel and cisplatin showed a statistically significant correlation with the increase in the sum-score ($R_s = 0.44$ and 0.39 respectively, $p < 0.01$) and the change in the VPT ($R_s = 0.68$ and 0.65

respectively, $p < 0.001$). Figure 8.1 shows the VPT post/pre ratio in relation to the cumulative dose of docetaxel and cisplatin. Figure 8.2 shows the relation of the cumulative doses of these drugs and the change in the sensory sum-score.

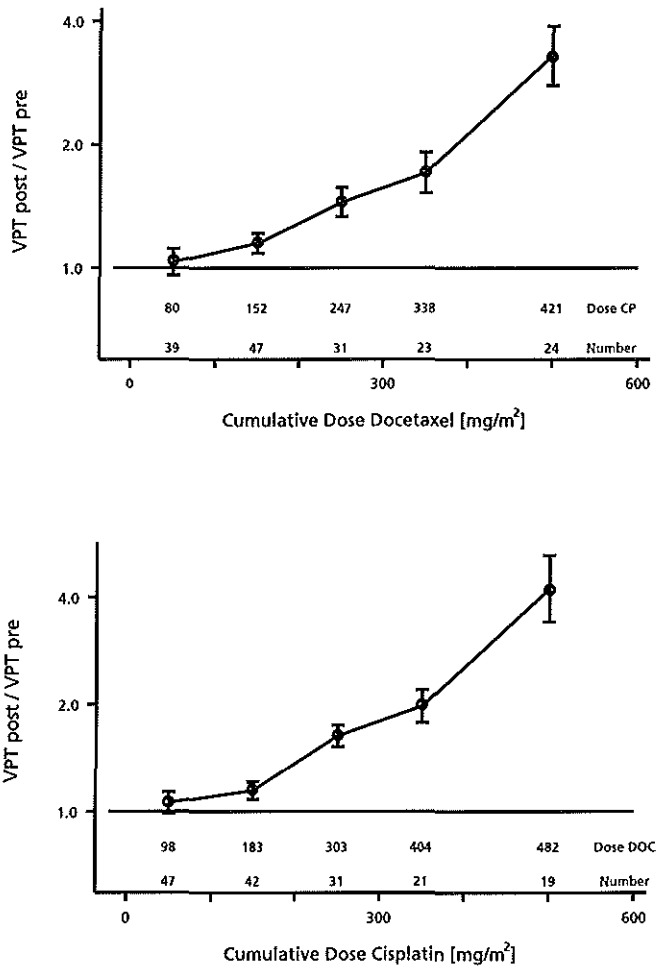

Figure 8.1

The mean change (± SE) in vibration perception threshold (VPT) post-treatment in relation to the cumulative dose of docetaxel and cisplatin (mg/m²). The figures above the horizontal axis indicate the number of patients evaluated and the mean dose of cisplatin (CP) and docetaxel (DOC) in each dose subgroup.

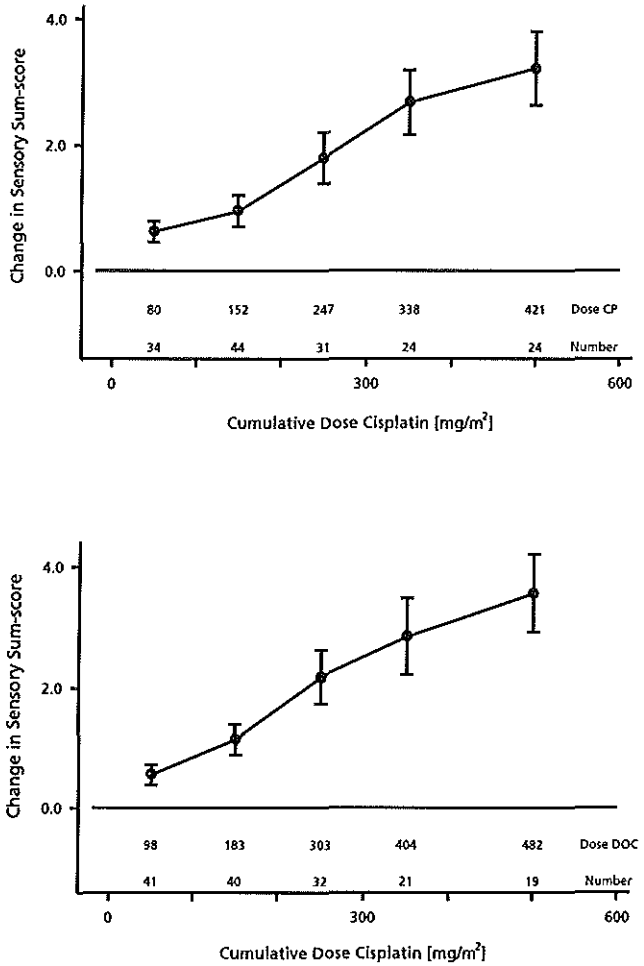

Figure 8.2

The mean change (± SE) in sensory sum-score post-treatment in relation to the cumulative dose of docetaxel and cisplatin (mg/m²). The figures above the horizontal axis indicate the number of patients evaluated and the mean dose of cisplatin (CP) and docetaxel (DOC) in each dose subgroup.

Electrophysiological studies before and after the treatment were done in 26 patients. It showed a decrease in SNAP amplitudes in 15 patients, a decrease in CMAP amplitudes in one patient and a decrease in both SNAP and CMAP amplitudes in four patients. The NCV studies were unchanged in six patients most of whom had been treated with low cumulative doses of

both cisplatin and docetaxel. The cumulative dose in the four patients with both motor and sensory involvement was similar to the cumulative dose in patients with only sensory involvement.

Table 8.5 shows a comparison of the severity of the neuropathy in relation to the cumulative dose of docetaxel between patients in the combination chemotherapy trial and patients treated with docetaxel only in another prospective trial conducted in our institution[21]. At low cumulative doses of docetaxel (and consequently also low doses of cisplatin in the combination chemotherapy trial) there is a low incidence of neuropathy in both trials. When patients with cumulative doses of docetaxel above 300 mg/m^2 are considered, a higher incidence and a more severe neuropathy is found in patients treated with the combination chemotherapy in comparison with the patients treated with docetaxel only. Figure 8.3 compares the relative change in VPT and the change in sensory sum-score in relation to the cumulative dose of cisplatin between patients from this trial and patients treated with cisplatin only [15]. It shows a more severe neuropathy in the patients treated with the combination chemotherapy regimen, especially at higher cumulative doses of cisplatin.

Table 8.5
Comparison of the severity of the neuropathy between patients treated with only docetaxel [21] and patients treated with a docetaxel-cisplatin combination chemotherapy, in relation to the cumulative dose of docetaxel

	Docetaxel <300 mg/m^2		Docetaxel 300-600 mg/m^2	
	without Cisplatin	with Cisplatin	without Cisplatin	with Cisplatin
N	14	24	12	31
cum.dose cisplatin mean (±SD)	-	157 ±65	-	406 ±110
sensory sum-score increase[1] mean (±SD)	1.5 ±1.2	1.5 ±1.7	2.9 ±2.5	3.9 ±2.7
VPT post/pre ratio[2] mean (±SD)	1.4 ±0.9	1.2 ±0.7	1.1 ±0.4	3.3 ±2.7
paresthesias[3]			(50%)	(65%)
grade 1	5	1	3	7
grade 2	1	1	3	8
grade 3	-	1	-	4
grade 4	-	1	-	1
CTC neurosensory[3]			(58%)	(77%)
grade 1	2	3	7	15
grade 2	-	2	-	8
grade 3	-	-	-	1

[1]) *difference between the first post-treatment and the pre-treatment score.*
[2]) *difference between the first post-treatment and the pre-treatment score, divided by the pre-treatment score (pre/post ratio)*
[3]) *incidence at the first post-treatment evaluation*

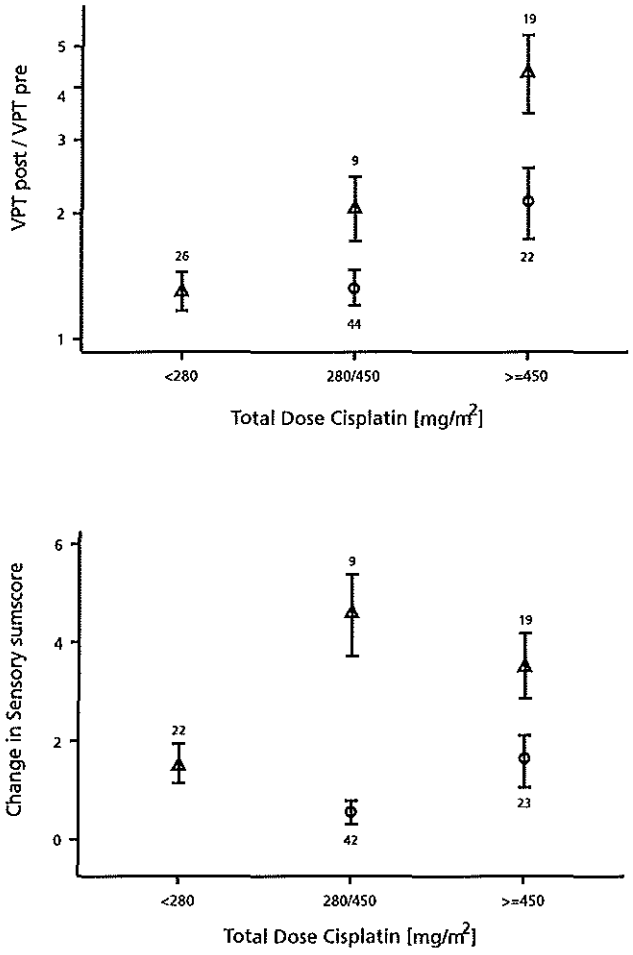

Figure 8.3

The mean change (± SE) in vibration perception threshold (VPT) and sensory sum-score post-treatment in relation to the cumulative dose of cisplatin (mg/m^2). Triangles indicate patients treated with the docetaxel-cisplatin combination chemotherapy and circles indicate patients treated with only cisplatin [15]. The figures indicate the number of patients evaluated.

Discussion

In recent years docetaxel appeared to be one of the most active new anti-neoplastic agents. Peripheral neuropathy is one of the potentially dose-limiting side-effects. In several phase II trials on docetaxel a mild to moderate mainly sensory neuropathy was observed [2-7,20,21,27]. In a study of 41 patients treated with the single agent docetaxel (100 mg/m^2 every three weeks; cumulative doses of 200-1100 mg/m^2) 49% of the patients developed a usually mild neuropathy [21]. The neuropathy appeared to be dose-dependent and caused a severe and disabling neuropathy in some patients at higher dose levels. Severe motor involvement occurred in two of these patients.

In trials on a combination chemotherapy of cisplatin with another taxoid, paclitaxel, a high incidence of neuropathy was found. In a phase I study of paclitaxel (110-200 mg/m^2 per cycle) and cisplatin (50-75 mg/m^2 per cycle) in 44 patients (median no. of cycles 3; range 1-12), 27% developed a mild to moderate neuropathy [10]. The incidence of neuropathy was disproportionately higher than expected with either paclitaxel or cisplatin at comparable single and cumulative doses. In a study of 32 patients treated with higher doses of paclitaxel (135-350 mg/m^2 per cycle) and cisplatin (75-100 mg/m^2 per cycle) 75% developed a neuropathy [8]. It was suggested that the neuropathy was mainly due to paclitaxel. The severity of the neuropathy was related to both the cumulative and single dose of paclitaxel and the presence of a pre-existing medical disorder associated with neuropathy (diabetes,alcoholism). The neuropathy was of an axonal nature with predominantly sensory signs although electrophysiological studies established involvement of motor nerves as well [9].

To date there are no results of studies on docetaxel-cisplatin combination chemotherapy regimens. In the present study we observed that 53% of the patients treated with docetaxel and cisplatin, in a wide range of cumulative

doses, developed a mainly sensory neuropathy. When only patients with cumulative doses of docetaxel and cisplatin above 200 mg/m^2 were considered, 71% developed a neuropathy. At higher dose levels some patients showed a moderate or severe neuropathy. Nine of these patients had motor signs. In five out of 26 patients in whom neurophysiological studies were performed motor involvement was found. Neuropathy was the dose limiting side-effect in four patients.

We were able to compare the results of this trial with two other trials performed in our institution in which patients were treated with either docetaxel or cisplatin as single a agent [15,21]. As expected the combination of these two neurotoxic agents tends to induce a more severe neuropathy than either of the two drugs alone. However, since these single and combination chemotherapy schedules were not studied in a comparative trial, this should be interpreted with caution. As the cumulative dose of cisplatin and the cumulative dose of docetaxel were closely related in our study, we could not detect which drug accounted for most of the neuropathy. A synergistic effect of the two drugs cannot be excluded.

The value of the VPT as a sensitive indicator of neuropathy in this study is not unequivocal. Several reports have demonstrated that the VPT is a reliable measure of cisplatin neuropathy [24-26]. In a previous study we did not establish a significant relation between the VPT and the severity of docetaxel-induced neuropathy, possibly because small fibre functions are compromised in this neuropathy [21]. The change in the VPT in this study can probably be accounted for by cisplatin, that mainly affects large myelinated fibres.

In a phase I study on a paclitaxel-cisplatin combination chemotherapy it was suggested that the sequence of cisplatin administration before paclitaxel may be related to more profound neutropenia [10]. We were unable to detect

differences in the severity of neurotoxicity in relation to the sequence of administration of cisplatin and docetaxel. Since only 12 patients received cisplatin prior to docetaxel no firm conclusions can be drawn.

In conclusion: the combination chemotherapy of docetaxel and cisplatin induces a dose-dependent sensory neuropathy. At a higher dose range neuropathy is encountered in a relatively high proportion of patients. With cumulative doses of both cisplatin and docetaxel between 200 and 600 mg/m^2 one-third of the patients developed a moderate or severe neuropathy. The severity of the neuropathy is higher than with the use of either cisplatin or docetaxel as a single agent at comparable doses. Further study on the possible attenuating effects of neuroprotective agents such as WR-2721 (amifostine) [28-30], glutathion [31,32] and nerve growth factor [33,34] is warranted.

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Chapter 9

Validation of methods for assessment of chemotherapy-induced neuropathy

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Abstract

Peripheral neuropathy is frequently observed in patients treated with the chemotherapeutic agents cisplatin, vincristine or taxoids. Several clinical scales for the grading of chemotherapy-induced peripheral neuropathy have been developed, but none of these scales have been validated or standardized.

We report on our experience with a neurotoxicity assessment protocol in a group of 298 cancer patients who participated in prospective trials in which the potential neurotoxicity of several chemotherapeutical agents was investigated, and in a control group of 55 healthy subjects. This protocol includes the standard assessment of neurological signs and symptoms including an 11-point sum-score, quantitative measurement of the vibration perception threshold (VPT) and grading according to the "common toxicity criteria" (CTC). We determined the following biometric properties of these tests: 1)the relation between VPT, age and sex 2)the intra-patient variability of signs and symptoms 3)the correlation between the different parts of the neurotoxicity assessment protocol.

The normal values for the VPT and the relation to age were similar as found in previous studies, and the intra-subject variability was acceptably low (coefficient of variation 25%). The VPT was related to values of the sum-score ($r = 0.54$; $p < 0.001$) and the CTC grade ($r = 0.56$; $p < 0.001$). We found only a small variability for most sum-score items of intra-patient measurement (0.5-10.5%). Some items of the sum-score become abnormal at an early stage (e.g. paraesthesias, sRomberg, ATR), other items at a later one (e.g. Romberg's sign, pin-prick and position sense). There was a significant variation in the outcome of the sum-score as compared to the CTC score.

We conclude that our protocol appears to be a feasible method for the assessment of chemotherapy-induced neuropathy in large groups of patients.

For individual patients the utility of a grading scale depends on whether this scale would indicate the degree of disability, handicap and quality of life. Further prospective study, therefore, is necessary to better define a standardized and validated neurotoxicity assessment protocol that can be used in clinical trials as well as in individual patients.

Introduction

The assessment of chemotherapy-induced toxicity is an important part in the evaluation of treatment regimens in cancer. A number of scales and protocols have been developed to improve the reporting of toxic effects[1-3]. Peripheral neuropathy is frequently observed in patients treated with the commonly used anti-neoplastic agents cisplatin, vincristine or taxoids. The clinical severity may range from the presence of paraesthesias and some loss of sensory function to disabling symptoms including neuropathic pain, sensory ataxia, motor weakness or autonomic dysfunction[4]. An accurate diagnosis and grading of the severity of the chemotherapy-induced neuropathy are crucial for a proper assessment of the neurotoxicity of these and future drugs.

In most studies grading scales based on the information from the clinical history and the neurological examination have been used (Table 9.1)[1-3,5-8]. In addition methods of quantitative sensory testing (QST) have been applied as an objective measure for the severity of the neuropathy[9-13]. Some authors advocate the use of a calculated neurotoxicity sum-score based on changes in symptoms, signs, QST and nerve conduction studies[14-17]. None of these scales have been validated nor have they been studied on their association with the degree of disability, handicap or quality of life.

In our institution a large number of clinical trials on chemotherapeutic drugs are carried out on ongoing basis, testing new agents or schedules. In

some of these trials, an extensive assessment of neurotoxicity using a standardized protocol has been applied on patients participating in studies with potentially neurotoxic drugs. Here, we report on the analysis of the results from 1050 test-procedures in 353 subjects in order to determine the biometric properties of each of the elements of our neuropathy assessment protocol.

Table 9.1

Grading scales for symptoms and signs used for the assessment of severity of chemotherapy-induced sensory neuropathy

	grade 1	grade 2	grade 3	grade 4
Common toxicity criteria (NCI)	mild paresthesias, loss of DTR	mild or moderate objective sensory loss, moderate paresthesias	severe objective sensory loss or paresthesias that interfere with function	
WHO criteria[2]	paresthesias and/or decreased DTR	severe paresthesias	intolerable paresthesias	
Northern California Oncology group[3]	mild pain or paresthesias	moderate pain, paresthesias	severe pain, paresthesias	
Grunberg[4]	numbness or tingling fingers or toes	numbness or tingling in hands or feet	clumsiness fine movements	difficulty ambulation
Castellanos[7]	paresthesias and/or decreased DTR	mild objective sensory abnormalities and/or absent DTR	severe paresthesias with moderate objective sensory abnormalities	complete loss of sensation
Ajani[1]	paresthesias, decreased DTR	mild objective abnormality, absence of DTR, mild to moderate functional abnormality	severe paresthesias, moderate objective abnormality, severe functional abnormality	complete sensory loss, loss of function
Eastern Cooperative Oncology group[5]	mild paresthesias, decreased DTR	severe paresthesias, absent DTR	disabling sensory loss, severe pain	
LoMonaco[6]	acro-paraesthesias, dysaesthesia or sensation of swollen hands	paraesthesias in hands or feet, reduced or absent vibratory sensation and DTR, subjective clumsiness of fine movements or gait	sensory complaints referred to as troublesome or painful or extended proximally, absent vibratory sensation and DTR, objective clumsiness of fine movements,Romberg+	Sensory complaints troublesome or unbearable, absent vibratory sensation and DTR, distal hypaestesias, ataxia, fine movements possible under visual control

DTR = distal tendon reflexes

Methods

In the Daniel den Hoed Cancer Centre in The Netherlands, a standardized protocol has been developed for the assessment of peripheral neurotoxicity in patients participating in prospective trials on the efficacy of

chemotherapeutic agents in cancer. The requirements for neurotoxicity assessment include time-efficiency and reliability with as little of inconvenience for the patient as possible, in order to facilitate frequent and repetitive testing on an out-patient basis. The focus of the test battery is aimed at the scoring of the sensory signs and symptoms, since many of the initial trials included cisplatin, which induces a purely sensory neuropathy. This protocol has been in use for several years now.

The neurotoxicity test battery includes a questionnaire for neurological symptoms, a standardized neurological examination for sensory and motor signs and the measurement of the vibration perception threshold (VPT). Patients are tested before initiation of the therapy and at regular intervals during and after the period of administering chemotherapy.

Assessment of neuropathic signs and symptoms

The questionnaire establishes the presence of paresthesias or numbness in hands or feet, loss of dexterity and unsteadiness of gait. The absence of each symptom is scored 0, its presence is scored 1. The severity of the paresthesias is graded on a 5-point scale (0 = no, 1 = temporary, 2 = continuous & light, 3 = severe, 4 = unbearable). Patients are asked whether they experience Lhermitte's sign or pain. On standardized neurological examination of the sensory system position sense, vibration sense, pin-prick sensation at the great toe, Romberg's sign, Romberg's sign with heel-to-toe stand (sensitized Romberg = sRomberg) and knee- and ankle-tendon-reflexes of both legs are each scored as either normal(0) or abnormal(1). The muscle strength in the lower extremities is tested by standing on the heels and the two-step test (testing the ability of stepping two steps for both legs separately). A sum-score for the severity of the neuropathy is calculated by counting the scores for normal(0) and abnormal(1) signs and symptoms (minimum 0, maximum 11). In a later stage we add the scoring of the

severity of neuropathy according to the NCI Common Toxicity Criteria (CTC) for sensory neuropathy (Table 9.1).

Vibration perception threshold

The VPT is measured at the dorsum of the second metacarpal bone of the left hand. Patients are sitting in a quiet room with their left hand resting on a table. We use a Vibrameter Type III and later Type IV (Somedic AB, Stockholm, Sweden), a hand-held instrument that applies a vibration stimulus with a frequency of 100 Hz by means of a rod with a diameter of 13mm. The rod is positioned at the middle of the second metacarpal bone. Adjustment of application pressure can be visually controlled during measurement. By means of a transducer in the stimulator, the vibration amplitude is measured directly at the stimulation site, which eliminates the variable damping effect of underlying tissues, and is presented in the actual displacement of the skin in micrometers (μm) on a calibrated digital display. Patients are first familiarized with the vibratory sensation of the Vibrameter. We use the method of limits as described by Goldberg and Lindblom[18]: increasing the stimulus strength from zero to the point where the vibratory sensation is first perceived, and then decreasing the stimulus strength from a slightly supramaximal level to the point where the sensation disappears; the average of these two values is taken as the actual VPT. We perform three measurements on each assessment and the mean of these measurements is being considered to represent the VPT. We perform measurements only on one hand as Elderson reported no difference in the VPT measurement of either hands or feet in patients with cisplatin neuropathy[9].

Subjects

Measurements according to the test-protocol were performed for 55 healthy control subjects and 298 patients. In order to study the intra-subject variability 51 of the 55 controls (25 males, 30 females; median age 41 yrs, range 19-70 yrs) were measured on two separate occasions with a median interval of 91 days (range 8-612 days). All measurements in control subjects were done by one of two investigators(PH,VvR).

The 298 patients (180 males, 118 females; median age 53, range 21-76 yrs) were enrolled in a total of seven trials in the period 1990-1995, which studied the neuropathic effects of cisplatin, docetaxel (Taxotere®) or the combination of these drugs. All patients with at least two neurological assessments were included in this study. Most patients (n=269) had undergone one pre-treatment evaluation, while 29 patients had had no pre-treatment evaluation. The 944 patient evaluations were carried out by seven different investigators.

Analysis

The following biometric properties of the tests were studied.

1. The relation between the VPT, age and sex, restricted to the scores of the control subjects and to the pre-treatment scores of the patients and the intra-subject variability of the VPT.
2. The intra-patient variability of all signs and symptoms scored in the period from the
   pre-treatment till the end of the treatment and in the period thereafter.
3. The correlation between the different measurements.

Ad 1.

Because of the skewed distribution of the VPT, the natural logarithm was used for statistical analysis. The means and standard deviation of VPT are reported in original units, but are derived from the mean and standard deviation of log(VPT) by back transformation. The relation between the logarithm of the VPT with age and sex was determined by linear regression analysis. The VPT values of the control subjects with two measurements counted half in this analysis. Repeated VPT measurements in the control subjects were used to estimate the intra-subject variability in the VPT assessment. Under the assumption that the size of the measurement errors is proportional to the true value of the VPT, the intra-subject variability in the VPT is best expressed by the coefficient of variation (CV). The CV was derived by the following formula: $CV = \sqrt{(\sum_i (l_{1i} - l_{2i})^2 / 2.N)}$ where l_1 and l_2 are the natural logarithm of the first and second assessment of the VPT, and $\sum_i$ indicates summation over the N=51 control subjects with two VPT measurements.

Ad 2.

In the analysis of dichotomous signs and symptoms, scored as normal or abnormal, the question arises how to express the intra-patient variability of these scores. The score of a subject at a certain time depends on a 'true' underlying condition of the subject at that time, but is also dependent on supposedly random day-to-day fluctuations and on measurement errors. In the assessment of the neurotoxic effect of chemotherapeutic agents, one is mainly interested in the change of the true underlying condition i.e. the peripheral nerve function and not in random day-to-day fluctuations. When the true underlying condition does not change, as may be assumed for control subjects, the intra-patient variability of a score can be expressed by the fraction of paired observations with different scores. However, especially

for patients under or after treatment the true condition may not be constant over time. A change of a sign-symptom score from normal to abnormal may be compatible with an effect of the treatment. In the period after the treatment abnormalities that have appeared during the treatment may resolve over time.

The following measures for intra-patient variability were calculated for each sign or symptom. For the control subjects the percentage of patients with a different score on the two different occasions was used. For the patients the sequence of measurements of each sign and symptom was divided in two periods. Period A was defined as the period from pre-treatment until the first abnormal score post-treatment. Period B was defined as the period after period A. Note that period B starts with an abnormal score. If there are no observations or no abnormal scores post-treatment, period B is empty. For both periods only the data of patients with at least two measurements of signs or symptoms in that period were used. The data of all pairs of subsequent measurements of all patients were pooled for each period and frequencies N_{ij} were calculated. N_{ij}, with i and j equal to 0 or 1, stands for the number of pairs of scores (i,j), 0 for normal and 1 for abnormal. From the N_{ij} the following measures of fluctuation were calculated: $F_{01}=N_{01}/(N_{01}+N_{00}+N_{11}+N_{10})$ and $F_{10}=N_{10}/(N_{10}+N_{11}+N_{00}+N_{01})$. F_{01} measures how often a normal score changes into an abnormal score, while F_{10} measures how often an abnormal score changes into a normal score. F_{10} is a relevant measure for fluctuations in period A, in which one would not expect improvements, while F_{01} is a relevant measure for period B. These measures serve primarily as a method to compare the signs and symptoms with one another and cannot be interpreted in an absolute sense.

Ad 3.

The correlation between the different signs or symptoms scores and VPT was studied by calculating for each item the proportion of remaining items with abnormal scores and the mean VPT, separately for observations scoring either normal or abnormal.

In addition to this analysis of the biometric properties of the test-protocol, we studied the relationship between the CTC grading system for sensory neuropathy with the sum-score and VPT.

Results

Measurements on control subjects.

* Vibration perception threshold

With a linear regression analysis of log(VPT) on age, the following models are fitted for male and female control subjects.

$^{10}\log(VPT) = -0.66\ (\pm 0.09) + 0.010\ (\pm 0.002) * age$ (males)

$^{10}\log(VPT) = -0.61\ (\pm 0.05) + 0.007\ (\pm 0.001) * age$ (females)

Within brackets the standard errors of the estimates are shown. The difference in the regression lines between male and female patients is statistically significant (P=0.0008). These models explain 36 percent of the variance in the log(VPT) between subjects as due to the variation in age, both in males and females.

The coefficient of variation of the VPT is calculated from the repeated measurements of the control subjects and estimated to be 25%. Standardized VPT values, adjusted for age and sex, are calculated as the ratio of the observed VPT and the expected VPT as derived from the fitted regression

model. The variation between subjects in the VPT is found to be 37% (47% for males and 28% for females).

* Signs and symptoms

Most of the signs and symptoms are scored normal for healthy control subjects on both occasions. Exceptions are paraesthesias (7% abnormal), numbness(1%), vibration sense (12%), Romberg(1%), sRomberg (16%) and ankle tendon reflex (4%) (Table 2). Different scores on the two occasions are observed for numbness (1/51), vibration sense (3/51) and sRomberg (6/51).

Measurements on patients

With the exception of sRomberg, ankle tendon reflexes (ATR) and vibration perception sense, before treatment abnormal signs and symptoms were rare though slightly more frequent than in controls (Table 9.2). The VPT pre-treatment for male patients is similar to the values in controls. For female patients, however, the pre-treatment values of the VPT are higher than those for controls and show a larger variation. During and post-treatment the percentage abnormalities of all items and VPT increased. At that time paraesthesias, sRomberg and ATR are the most frequent abnormalities.

Table 9.2

Percentage of abnormal scored items in 55 healty subjects and in 298 cancer patients with 270 measurements at pre-treatment evaluation and 664 measurements in these patients during treatment or post-treatment.

	controls	pre-treatment	during- or post treatment
number of subjects	55	269	298
number of observations	106	270	664
	% abnormal	% abnormal	% abnormal
paraesthesias	7	5	38
numbness	1	3	26
loss dexterity	0	2	17
unsteadiness gait	0	2	13
position sense	0	3	11
vibration sense	12	12	31
pin-prick sense	0	3	7
Romberg	1	3	8
sRomberg	16	42	57
knee tendon reflex	0	2	28
ankle tendon reflex	4	18	53
% of abnormal items mean (±SD)	4% (±7)	8% (±10)	25% (±23)
VPT (mean ±SD)	0.53 ±0.25	0.76 ±0.44	1.28 ±1.01
standardized (% ±SD)[1]			
males	100 ±45	96 ±49	168 ±121
females	100 ±28	134 ±80	210 ±155

[1] *Standardized VPT score defined as the ratio of VPT and the expected value on the basis of age and sex.*
sRomberg = Romberg's sign on heel-to-toe-stand
VPT = Vibration Perception Threshold

The numbers of pairs of subsequent scores and measures of fluctuation F_{01} and F_{10} (see methods) for every sign and symptom in the periods A (during) and B (post treatment) are shown in Table 9.3. In period A, we observed high values of N_{00} and low values of F_{01}, which implies that scores often remain normal during treatment. A change from normal to abnormal was observed

most frequently for paraesthesias, sRomberg and ATR. Most of the signs and symptoms show little fluctuation (F_{10}) once they have become abnormal (0.5-4.2%) with the exception of the sRomberg which shows the highest fluctuation in this period (10.5%). In period B, i.e. from the first abnormal score post-treatment, the frequency of changes from abnormal to normal (F_{10}) scores are high. Abnormal ATR, knee tendon reflexes (KTR), paraesthesias and sRomberg usually remain abnormal. Once a sign or symptom has become normal post-treatment, they remain normal in the majority of the cases, which is reflected in low values of F_{01} (1.8-7.1%).

Table 9.4 shows the association between the items of the sum-score. It shows that if one item is normal other items are often normal, too. A normal score on paraesthesias, sRomberg and ATR are the best predictors for a normal score on other items with respectively only 10%, 7% and 8% of the other signs or symptoms being abnormal. A normal ATR and sRomberg are associated with the lowest mean VPT. An abnormal score on one item often goes together with abnormal scores on other items and an increased VPT. Abnormal scores for loss of dexterity, unsteadiness of gait, position sense, abnormal pin-prick sense and Romberg are the best predictors for an abnormal score on other items. Patients with an abnormal pin-prick sense show the highest VPT. An abnormal sRomberg is least predictive for abnormalities on other items (on average only 32%) and has the lowest average VPT.

Table 9.3
The numbers of pairs of subsequent scores and measures of fluctuation during treatment (period A).

	N_{00}	N_{01}	N_{11}	N_{10}	F_{01} (%)	F_{10} (%)
paraesthesias	246	35	34	10	0.8	3.1
numbness	306	28	26	9	7.6	2.4
loss dexterity	360	25	16	4	6.2	1.0
unsteadiness gait	392	15	6	11	3.5	2.6
position sense	382	9	3	6	2.3	1.5
vibration sense	261	30	25	14	9.1	4.2
pin-prick sense	422	4	1	2	0.9	0.5
Romberg	414	4	2	4	0.9	0.9
sRomberg	143	38	57	28	14.3	10.5
knee tendon reflex	278	28	18	4	8.5	1.2
ankle tendon reflex	164	42	63	9	15.1	3.2

The numbers of pairs of subsequent scores and measures of fluctuation post-treatment (period B).

	N_{00}	N_{01}	N_{11}	N_{10}	F_{01} (%)	F_{10} (%)
paraesthesias	10	2	80	19	1.8	17.1
numbness	11	4	43	22	5.0	27.5
loss dexterity	10	1	24	18	1.9	34.0
unsteadiness gait	7	2	25	12	4.3	26.1
position sense	15	4	16	21	7.1	37.5
vibration sense	17	6	50	37	5.5	33.6
pin-prick sense	10	2	12	19	4.7	44.2
Romberg	14	1	12	16	2.3	37.2
sRomberg	7	7	118	30	4.3	18.5
knee tendon reflex	5	2	40	11	3.4	19.0
ankle tendon reflex	2	3	70	9	3.6	10.7

N_{ij} = number pairs of subsequent measurements with i and j equal to 0 or 1 (0 for normal and 1 for abnormal)
$F_{01} = N_{01}/(N_{01}+N_{00}+N_{11}+N_{10})$
$F_{10} = N_{10}/(N_{10}+N_{11}+N_{00}+N_{01})$.
sRomberg = Romberg's sign with heel-to-toe-stand

Table 9.4
Relation of a normal and abnormal score of one single item with the percentage of other abnormal items of the sum-score and vibration perception threshold (VPT) in 1050 measurements.

		% abnormal other items mean (±SD)	VPT mean (±SD)
paraesthesias	normal 74%	10 (±13)	0.86 (±0.59)
	abnormal 26%	43 (±22)	1.60 (±1.37)
numbness	normal 82%	12 (±14)	0.90 (±0.63)
	abnormal 18%	52 (±21)	1.75 (±1.62)
loss dexterity	normal 89%	14 (±15)	0.93 (±0.66)
	abnormal 11%	59 (±21)	1.97 (±2.04)
unsteadiness gait	normal 91%	15 (±17)	0.95 (±0.70)
	abnormal 9%	57 (±24)	1.88 (±1.90)
position sense	normal 92%	16 (±18)	0.95 (±0.69)
	abnormal 8%	54 (±25)	2.21 (±2.12)
vibration sense	normal 76%	12 (±15)	0.85 (±0.55)
	abnormal 24%	41 (±24)	1.76 (±1.61)
pin-prick sense	normal 95%	17 (±19)	0.96 (±0.68)
	abnormal 5%	57 (±27)	2.93 (±3.33)
Romberg	normal 94%	17 (±19)	0.97 (±0.72)
	abnormal 6%	50 (±27)	2.04 (±2.04)
sRomberg	normal 51%	07 (±13)	0.80 (±0.53)
	abnormal 49%	32 (±22)	1.29 (±1.07)
knee tendon reflex	normal 81%	12 (±14)	0.89 (±0.61)
	abnormal 19%	54 (±20)	1.87 (±1.63)
ankle tendon reflex	normal 62%	08 (±11)	0.80 (±0.51)
	abnormal 38%	40 (±22)	1.52 (±1.26)

sRomberg = Romberg's sign with heel-to-toe-stand

Table 9.5 shows the percentage of each item that scored abnormal in relation to the severity of the neuropathy as expressed by the percentage of abnormal items in the sum-score. It shows to what extent one single item contributes to the sum-score. For example paraesthesias, vibration sense, sRomberg and ATR greatly contribute to an abnormal sum-score at a low severity of neuropathy (9-25% of abnormalities in the sum-score). With high severity of neuropathy (75%-100% of abnormalities in the sum-score), the

items pin-prick sense and Romberg are still scored as normal in a high percentage of patients.

Table 9.5
The percentage of each item scored abnormal in relation to the severity of neuropathy as expressed by the percentage of abnormal items in the sum-score.

	abnormal items 9-25% (n=371)	abnormal items 25-50% (n=222)	abnormal items 50-75% (n=83)	abnormal item 75-100% (n=25)
paraesthesias	17 %	55 %	85 %	96 %
numbness	5 %	33 %	83 %	96 %
loss dexterity	2 %	15 %	66 %	92 %
unsteadiness gait	3 %	13 %	43 %	88 %
position sense	2 %	15 %	30 %	77 %
vibration sense	18 %	49 %	66 %	100 %
pin-prick sense	2 %	8 %	20 %	65 %
Romberg	4 %	10 %	19 %	60 %
sRomberg	64 %	80 %	87 %	100 %
knee tendon reflex	1 %	35 %	78 %	100 %
ankle tendon reflex	27 %	78 %	94 %	100 %

sRomberg = Romberg's sign on heel-to-toe-stand

Table 9.6 shows the relation of the CTC grading system for sensory neuropathy with the sum-score and the VPT. These findings only relate to a subgroup of patients, since the CTC score was introduced at a later time in the protocol and was used in docetaxel and cisplatin-docetaxel combination trials only. Higher CTC-grades are associated with higher percentages of abnormal items and higher mean VPT. There is, however, for all CTC-grades a substantial variation in the percentage of abnormal items of the sum-score.

Table 9.6
The common toxicity criteria (CTC) for sensory neuropathy in relation to the percentage of abnormal items in the sum-score and to the vibration perception threshold (VPT).

CTC-sensory	Grade 0	grade 1	grade 2	grade 3
N observations	437	149	34	11
% abnormal items				
0 %	225	0	0	0
0-25 %	169	27	0	0
25-50 %	43	79	6	2
50-75 %	0	41	20	1
75-100%	0	2	8	8
mean ±SD	8% ±10	40% ±17	66% ±16	81% ±20
VPT (mean ±SD)	0.76 ±0.43	1.31 ±0.82	2.61 ±2.49	7.76 ±10.64

Discussion

Chemotherapy-induced peripheral neurotoxicity may influence the quality of life of patients with cancer and interfere with an optimal treatment. A reliable assessment of neuropathy is thus important for research purposes as well as for clinical practice. Ideally, results from clinical studies should indicate at what single or cumulative doses significant neuropathy will emerge. For individual patients, neuropathy assessment tools should give a reliable indication of a severe and disabling neuropathy early enough for a re-adjustment of the treatment. Several scales have been developed to grade chemotherapy-induced neuropathy, but so far no attemps have been made to standardize these[1-3,5-8,14].

In the assessment of diabetic neuropathy, progress on nerve testing has been made by achieving consensus on standardized measurements for clinical, morphological, biochemical, electrodiagnostic and quantitative sensory testing[19]. For assessment of signs and symptoms, Dyck introduced different scales by using items from the history for sensory, motor and

autonomic nervous system dysfunction[20,21] and items from the conventional neurological examination including scores for cranial nerve, motor and sensory deficits[20]. These clinical scales have been validated showing a high reproducibility[22] and a significant association with electrodiagnostic testing, VPT and cold detection thresholds[23,24] as well as with pathological findings in nerve biopsies[25]. Such a widely accepted approach on chemotherapy-induced neuropathy is lacking.

The assessment of neurotoxicity has been studied by grading scales for clinical signs and symptoms, nerve conduction studies (NCS) and methods of quantitative sensory testing (QST). Most of the clinical scales use a combination of subjective information from the history together with more or less objective findings from the neurological examination mainly focusing on sensory signs and symptoms (Table 9.1).

Conventional NCS have been conducted extensively in cisplatin neuropathy. Marked reductions in sensory nerve action potentials (SNAP) and mild slowing of sensory nerve conductions velocity (SNCV) is observed once the neuropathy is clinically manifest[8,26-29]. In paclitaxel neuropathy a reduction of SNAP and compound muscle action potentials (CMAP) amplitudes have been observed[17]. NCS do not seem to be more accurate than clinical testing[27] and the development of clinical symptoms precedes any significant change in NCS[8,15].

A quantitative measurement of the VPT has found to be a reliable technique to monitor cisplatin neuropathy. It shows a satifactory correlation with the occurrence of signs and symptoms of sensory dysfunction[9-12]. In docetaxel-induced neuropathy the VPT was poorly associated with the severity of the neuropathy[13].

In our neurotoxicity assessment protocol we use a combination of clinical scoring and VPT measurement. In the sum-score, we abstract information from the history and neurological examination and score several items as normal or abnormal. This method has been used before but without validation[10]. In addition, we use the CTC grading system for sensory neuropathy.

This protocol has now been applied in several prospective trials representing large numbers of patients treated with different neurotoxic agents. In this report, we present the validation of our method by analysing and correlating the biometric findings. The value of this analysis is somewhat limited because of the explorative nature and the lack of a golden standard for "severity of neuropathy".

For the validation of the clinical scale, we determined the percentage of inconsistent scores for each item. We found a low intra-subject variability in normal subjects, except for Romberg's sign in heel-to-toe stand (sRomberg)(11.8%). During and post-treatment, we observed a low level of fluctuation in the scoring of most items (0.5-4.2%; sRomberg 10.5%) suggesting a high consistency. This was partly due to the fact that most items remained normal during treatment.

We found a low percentage of abnormalities for most items of the clinical scale in normal subjects and in cancer patients at the time of the pre-treatment evaluation. Exceptions were sRomberg, the vibration perception sense of the great toe, and the achilles tendon reflex. The higher frequency of abnormalities of some items in cancer patients in comparison to normal subjects may be partly due to a higher median age in this group, but may also reflect "subclinical" neuropathy induced by previous chemotherapy or cancer-related neuropathy[30,31]. As expected during chemotherapy the number of abnormal items and the sum-score increases. Some items become

abnormal early in the development of a neuropathy (e.g. paraesthesias, sRomberg, ATR), other items at a later stage (e.g. Romberg's sign, pin-prick and position sense). None of these items alone would indicate the development of a neuropathy. A normal sRomberg, however, is probably a sensitive test for ruling out the presence of a sensory neuropathy. On the other hand, although a positive sRomberg represents a sensitive marker for the presence of a sensory neuropathy, it also represents a highly a-specific finding.

Our clinical scale was clearly related to the CTC score, but there was considerable variation in the outcome of the sum-score. Application of our sum-score has the advantage over the four graded CTC-scale that it is based on more signs and symptoms of neuropathy and would thus provide more information on different aspects of neuropathy. Possibly it is also a better indicator of the severity of neuropathy, but that has yet to be determined.

In the control group we found normal values for the VPT at the hands and a clear correlation between age and the VPT comparable to others[18,32]. Intra-subject variability was small. The coefficient of variation of the VPT was acceptably low. In patients the pretreatment VPT was higher in females and this finding may reflect previous chemotherapy with cisplatin in some of these women. During and after chemotherapy, the VPT was related to values of the sum-score and the CTC grade. In an earlier report we have already established a strong correlation between the VPT and sum-score in cisplatin neuropathy[33]. In docetaxel neuropathy, however, we did not find such a relationship[13], which questions the use of this tool in taxoid neurotoxicity monitoring.

We conclude that our neurotoxicity test-protocol represents a feasible method for the assessment of chemotherapy-induced sensory neuropathy on a large scale. The limitations of the present analysis preserves us from making firm statements concerning the validity of our assessment method. The low intra-subject variability of scoring most test-items and the close relation between the sum-score and the VPT in cisplatin neuropathy, however, suggest that our method is a reliable tool in the assessment of sensory nerve dysfunction in clinical trials.

Further study on the assessment of chemotherapy-induced neuropathy is warranted. In addition to the VPT, which primarily is a measure of large myelinated fibre function, other QST methods may be explored to detect dysfunction of smaller efferent fibres. For the assessment of clinically relevant neuropathy in individual patients, grading scales of only signs and symptoms are insufficient. The utility of any clinical grading scale depends on how this scale relates to the degree of disability, handicap and quality of life. This should be subjected to further research.

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10 Summary and conclusions

Potential causes of neuropathy associated with cancer include the impingement by tumor on a nerve or root, metastases to a nerve, leptomeningeal metastases, radiation injury, paraneoplastic neuropathies, metabolic disturbances, nutritional deficits and the toxic effects of drugs.

Peripheral neuropathy induced by anti-neoplastic agents are among the many troublesome side-effects encountered in the treatment of cancer. Clinical severity may range from some loss of the sensory function and paraesthesias to neuropathic pain, severe sensory ataxia or motor weakness and may lead to serious disability. The involvement of autonomic nerve fibres may cause ileus, orthostatic hypotension, impotence or incontinence and may also affect the quality of life.

Preventing or modifying the neurotoxic side-effects of chemotherapeutic agents may thus reduce a potential handicap and disability. The therapeutic efficacy may improve as protection of the nerve function may obviate a discontinuation of cancer therapy. Better understanding of dosing-schedules may prevent or ameliorate neurotoxicity of chemoactive agents. A modification of these schedules constitutes one way to prevent nerve damage. Preclinical studies on the effects of neuroprotective agents in chemotherapy-induced neuropathy have revealed promising results. The utilization of these drugs, however, is still experimental.

In the Daniel den Hoed Cancer Centre many clinical trials on chemotherapeutic drugs are performed, testing new schedules or new drugs. This setting provides the opportunity for standardized and ongoing assessment of neurotoxicity in relatively large groups of patients participating in studies testing potentially neurotoxic drugs. A neurotoxicity

test-protocol was developed that could be performed quickly and on an out-patient basis. This test-protocol has been in use since 1990. In this thesis, the clinical characteristics and time-course of neurotoxicity induced by a number of chemotherapeutical drugs and their assessment with a new test-protocol are investigated.

In *chapter 1* an overview of the relevant literature on chemotherapy-induced peripheral neuropathy is presented. Many chemotherapeutic agents have occasionally been reported to be neurotoxic, but for only a few of these drugs peripheral neuropathy is a clinical significant side-effect. The use of high-dose regimens or combination chemotherapy of more than one neurotoxic agent has made better insight into the neurotoxic effects of these drugs essential. The neurotoxicity of vincristine and cisplatin has been extensively investigated and is reviewed here. Emphasis is laid on new and promising chemotherapeutic agents in which neuropathy is a prominent side-effect, i.e. paclitaxel (Taxol®), docetaxel (Taxotere®) and suramin. The degree of neurotoxicity in all these agents is determined by the dose per cycle, the cumulative dose or the dose-intensity. Attemps to prevent the neurotoxic side-effects of cisplatin by modifying dosing-schedules are addressed. The relatively scarce data on the preclinical and clinical use of neuroprotective agents are discussed.

Chapter 2 describes a study on neurotoxicity assessment in 66 patients with solid cancer treated with an intensive weekly regimen of cisplatin (cumulative dose: mean 430 mg/m^2, range 280-510). A mild to moderate neuropathy was found in 71% of the patients and a severe neuropathy in 9%. The severity of the neuropathy was strongly related to the cumulative dose of cisplatin. Cisplatin-neuropathy progressed after cessation of therapy for a

period of approximately three months ("coasting") in many patients. This phenomenon makes it difficult to timely stop or re-adjust the schedule in the individual patient. The long-term follow-up in this study (12 months) may explain the high frequency of neuropathy as compared to observations of other investigators.

The anti-tumor effects of cisplatin are enhanced by intensive dosing schedules at the cost of more side-effects. In *chapter 3* the effect of dose-intensity of cisplatin on neurotoxicity is discussed. The literature on this issue contains conflicting data. A high dose-intensity has been associated with both an increase and decrease of neurotoxicity. The patient group from the previous chapter is compared with two groups treated with cisplatin using different dosing-schedules of lower dose-intensity. The analysis demonstrates that the severity of the neuropathy expressed as the maximum post-treatment vibration perception threshold (VPT) was not related to dose-intensity but only to cumulative dose. A stronger dose-intensity of cisplatin administration within a dose range of 70-100 mg/m^2 per cycle and a cumulative dose range of 280-675 mg/m^2 does not seem to play a major role in the development of neuropathy. The efficacy of cisplatin may thus be improved by the use of more intensive dosing schedules without a simultaneous risk on increased neurotoxicity.

In *chapter 4* the assessment of peripheral neurotoxicity in 41 patients treated with docetaxel is described. Docetaxel is a semi-synthetic analogue of paclitaxel and effective in a variety of solid tumors. Peripheral neuropathy is one of the potentially dose-limiting side-effects. The cumulative dose these patients received varied considerably (150-1100 mg/m^2). A predominantly sensory neuropathy developed in 20 patients, mainly of mild character. The

severity of the neuropathy appeared to be dependent on the cumulative dose. At cumulative doses above 600 mg/m^2, 3 out of 15 patients developed a moderate neuropathy and 1 out of 15 patients a severe one. Two of these patients showed motor involvement. We conclude that neuropathy is not a predominant side-effect of docetaxel. However, following treatment with a high cumulative dose, some patients may develop a severe, disabling and dose-limiting neuropathy. A quantitative measurement of VPT was not or weakly associated with the severity of this type of neuropathy.

In *chapter 5* the clinical characteristics and electrodiagnostic findings of docetaxel-induced peripheral neuropathy are described by presenting case-reports of five patients who developed a marked neuropathy. Sensory signs and symptoms predominate, although in one patient a severe weakness developed. We observed progression of the neuropathy after cessation of the treatment in three patients. Regression of signs and symptoms occured in two patients that could be followed for at least six months. One patient developed a prominent sensory neuropathy after only one cycle, suggesting individual susceptibility for neurotoxic effects of docetaxel.

In *chapter 6* five patients are presented who developed Lhermitte's sign following the treatment with docetaxel, a phenomenon also seen in cisplatin neuropathy. Its mechanism may reflect an abnormal mechano-sensitivity of sensory axons at the level of either the roots or dorsal columns following dorsal root ganglion damage. This observation supports the hypothesis that docetaxel-neuropathy also affects the dorsal root ganglion.

Chapter 7 involves a study that was performed to determine the effects of corticosteroid co-medication on the development of docetaxel-induced

neuropathy. Co-medication of corticosteroids is intended to reduce docetaxel-induced fluid-retention and hypersensitivity reactions. The patient group described in *chapter 4* was treated with docetaxel without corticosteroid co-medication, since this was not recommended at that time. They were compared with a docetaxel-treated group of 49 patients with breast cancer who received corticosteroid co-medication routinely. There was no statistically significant difference in neurotoxicity between these groups, suggesting that corticosteriods do not reduce the development of docetaxel-induced neuropathy.

Chapter 8 describes the neurotoxicity assessment in 63 patients participating in a phase I dose-finding trial on a combination chemotherapy of docetaxel and cisplatin. Neuropathy developed in 29 out of 55 evaluable patients (53%). We compared the results with two other trials in which patients received either cisplatin or docetaxel as single agents, presented in *chapters 2* and *4*. The combination of these agents induces a more severe neuropathy than either of the two drugs. We were unable to demonstrate whether the drugs have a synergestic neurotoxic effect or which drug mainly contributes to the severity of the neuropathy.

A reliable assessment of the severity of chemotherapy-induced peripheral neurotoxicity is relevant for the evaluation of treatment protocols. In *chapter 9* the neurotoxicity test-protocol that has been developed in the Daniel den Hoed Clinic is described. It includes a standard assessment of signs and symptoms, the calculation of an 11-point-sum-score, quantitative measurements of the vibration perception threshold and grading according to the "common toxicity criteria" (CTC). This protocol can be performed quickly on an out-patient basis with a minimum of inconvenience for the

patient. The validation of this protocol by analysing 944 neurotoxicity assessments before, during or after chemotherapy in 298 patients that participated in trials on cisplatin and docetaxel and in 55 healthy control subjects is discussed. The VPT was statistically significant related to values of the sum-score and CTC grade, We found low intra-subject variability for the VPT and for most items of the sum-score. This protocol appears to be a feasible method for the assessment of chemotherapy-induced neuropathy and may serve as a basis for further development of a reliable grading-scale.

Currently, no effective therapeutic options are available once a patient develops a chemotherapy-induced neuropathy. The prevention of neurotoxicity by modifying dosing-schedules or the administration of neuroprotective agents would have great clinical significance. A better understanding of the clinical factors involved in the development of chemotherapy-induced neuropathy and the pathophysiological mechanisms is needed to find effective means to prevent or treat a dose-limiting neurotoxicity. Clinical trials should include a follow-up period long enough to observe the progression of the neurotoxicity after cessation of chemotherapy. Consensus on the assessment and grading of neurotoxicity would facilitate further study. The availability of a neurotoxicity-protocol as described in this thesis and the definition of clinical characteristics and time-course as determined by us are useful to acquire these goals in the near future

11 Samenvatting en conclusies

Een perifere neuropathie bij patiënten met kanker kan veroorzaakt worden door compressie van een tumor op een zenuw of zenuwwortel, metastasering naar een zenuw, leptomeningeale metastasering, bestralingseffecten, paraneoplastische fenomenen, metabole afwijkingen, voedingsdeficiënties en de toxische effecten van medicamenten.

Een door chemotherapie veroorzaakte polyneuropathie is één van de vele hinderlijke bijwerkingen van oncologische behandelingen. De ernst hiervan varieert sterk. Sommige patiënten ervaren paraesthesiëen of hebben lichte sensibele uitval als enig verschijnsel. Anderen worden ernstig gehandicapt door het optreden van neuropathische pijn, sensibele ataxie of spierzwakte. De kwaliteit van leven kan verder verslechteren door functiestoornissen van het autonome zenuwstelsel leidend tot orthostatische hypotensie, impotentie, incontinentie of ileus.

Een vermindering van de neurotoxische effecten van cytostatica zou naast een afname van bijwerkingen ook gunstig voor de therapeutische effectiviteit kunnen zijn: een adequate anti-tumorbehandeling hoeft niet voortijdig te worden gestaakt en er kunnen hogere doseringen worden gebruikt. Het doseringsschema van de chemotherapie kan van invloed zijn op het ontstaan van neurotoxiciteit. Kennis van de factoren die hierbij van belang zijn, kan bijdragen tot aanpassingen van deze schema's om zenuwschade zoveel mogelijk te beperken. Er zijn veelbelovende publikaties verschenen van pré-klinische studies over de effecten van neuroprotectieve stoffen op chemotherapie-geïnduceerde polyneuropathie. De ontwikkeling van deze agentia verkeert echter nog in een experimentele fase.

In de Daniel den Hoed kliniek worden jaarlijks vele klinische studies verricht naar de effectiviteit van nieuwe toedieningsschema's van bestaande chemotherapeutica of van nieuwe cytostatica. Dit bood ons de mogelijkheid om gestandaardiseerde metingen van neurotoxiciteit te doen in relatief grote groepen patiënten die met potentieel neurotoxische stoffen werden behandeld. Hiertoe werd een neurotoxiciteit testprotocol ontwikkeld dat poliklinisch in korte tijd kan worden uitgevoerd en een minimale belasting geeft voor de patiënt. Dit testprotocol is in gebruik sinds 1990. In dit proefschrift worden de klinische kenmerken van een aantal door chemotherapie veroorzaakte polyneuropathieën beschreven. Daarnaast wordt ons testprotocol voor het vaststellen van neurotoxiciteit onderzocht (*hoofdstuk 9*).

In *hoofdstuk 1* wordt een overzicht gegeven van de relevante literatuur op het gebied van chemotherapie-geïnduceerde polyneuropathie. Bij veel chemotherapeutica is het voorkomen van neurotoxiciteit beschreven, maar slechts bij enkele van deze agentia wordt een polyneuropathie als een klinisch significante bijwerking beschouwd. Het toenemend gebruik van chemotherapie met hoge doses of combinaties van neurotoxische cytostatica heeft een beter inzicht in de schadelijke effecten van deze medicamenten op perifere zenuwen noodzakelijk gemaakt. De neurotoxiciteit van vincristine en cisplatin is in het verleden uitgebreid onderzocht en wordt hier besproken. De nadruk in dit hoofdstuk wordt echter gelegd op nieuwe, veelbelovende cytostatica die polyneuropathie als een belangrijke bijwerking hebben, met name paclitaxel (Taxol®), docetaxel (Taxotere®) and suramine. De ernst van de neurotoxiciteit van deze middelen wordt bepaald door de dosis per kuur, de cumulatieve dosis of de dosis-intensiteit. Pogingen de neurotoxische bijwerkingen van cisplatin te voorkómen door het

doseringsschema aan te passen worden besproken. De thans bekende gegevens over het gebruik van neuroprotectiva worden uiteengezet.

Hoofdstuk 2 beschrijft het optreden van neurotoxiciteit bij 66 patiënten met een solide maligniteit die werden behandeld met cisplatin in een intensief doseringsschema (cumulatieve dosis: gemiddeld 430 mg/m^2, bereik 280-510 mg/m^2). Een lichte tot matig ernstige polyneuropathie ontwikkelde zich bij 71% van de patiënten en een ernstige polyneuropathie bij 9%. De ernst van de polyneuropathie was sterk gerelateerd aan de cumulatieve dosis cisplatin. Bij veel patiënten verergerde de cisplatin-polyneuropathie gedurende de eerste drie maanden ná het staken van de therapie. Dit fenomeen maakt beslissingen over het tijdig stoppen of aanpassen van de dosis in de individuele patiënt moeilijk. In vergelijking met andere auteurs wordt een hoge frequentie van polyneuropathie in deze studie gevonden, hetgeen kan worden verklaard door de langdurige follow-up periode (12 maanden).

Door het gebruik van meer intensieve doseringsschema's worden de anti-tumor effecten van cisplatin versterkt ten koste van het optreden van meer bijwerkingen. In *hoofdstuk* 3 wordt het effect van dosis-intensiteit van cisplatin op neurotoxiciteit besproken. De literatuur op dit gebied is niet eenduidig. Zowel een toe- als afname van neurotoxiciteit door gebruik van een hoge dosis-intensiteit is beschreven. De patiëntengroep van *hoofdstuk* 2 wordt vergeleken met twee patiëntengroepen die behandeld werden met doseringsschema's met een lagere dosis-intensiteit. De ernst van de polyneuropathie uitgedrukt als de maximale vibratie-perceptie-drempel (VPT) na de therapie bleek alleen gerelateerd aan de cumulatieve dosis en niet aan de dosis-intensiteit. Binnen het dosisbereik van deze studie (per

kuur: 70-100 mg/m^2, cumulatief: 280-675 mg/m^2) lijkt de dosis-intensiteit van cisplatin geen belangrijke rol te spelen in het optreden van een polyneuropathie. Het gebruik van meer intensieve doseringsschema's ter verhoging van de effectiviteit van cisplatin gaat niet gepaard met een verhoogd risico op polyneuropathie.

In *hoofdstuk 4* wordt de neurotoxiciteit van het perifere zenuwstelsel beschreven bij 41 patiënten die werden behandeld met docetaxel. Docetaxel is een semi-synthetisch analogon van paclitaxel, waarbij gebruik wordt gemaakt van een stof die geëxtraheerd wordt uit de naalden van de Europese Taxus Baccata. Docetaxel is effectief gebleken tegen verschillende solide tumoren. Een polyneuropathie is één van de potentiële dosisbeperkende bijwerkingen. De bereikte cumulatieve dosis varieerde aanzienlijk tussen patiënten (150-1100 mg/m^2). Er ontwikkelde zich een voornamelijk sensibele polyneuropathie in 20 patiënten. De ernst van de polyneuropathie bleek afhankelijk te zijn van de cumulatieve dosis. Van de 15 patiënten die een cumulatieve dosis hoger dan 600 mg/m^2 ontvingen, waren er drie met een matig ernstige en één met een ernstige polyneuropathie. Bij twee van deze patiënten waren er tevens motorische verschijnselen. Polyneuropathie is niet een prominente bijwerking van docetaxel in lage dosering. Bij het gebruik van een hoge cumulatieve dosis kunnen sommige patiënten echter een ernstige, invaliderende en dosisbeperkende polyneuropathie ontwikkelen. Kwantitatieve metingen van de VPT waren slechts zwak geassocieerd met de ernst van polyneuropathie. De VPT is geen geschikte kwantitatieve sensibele test voor monitoring van deze vorm van polyneuropathie.

In *hoofdstuk 5* worden de klinische kenmerken en electromyografische bevindingen van docetaxel-geïnduceerde polyneuropathie beschreven aan de hand van vijf ziektegeschiedenissen. Er werden met name sensibele symptomen gevonden, echter bij één patiënt ontstond een ernstige spierzwakte. Na het staken van de therapie werd bij drie patiënten een progressie van de polyneuropathie geconstateerd. Bij de twee patiënten die tenminste zes maanden konden worden vervolgd, trad er een verbetering op. Eén patiënt ontwikkelde een forse sensibele polyneuropathie na slechts één kuur, hetgeen een individuele gevoeligheid voor de neurotoxische effecten van docetaxel doet vermoeden.

In *hoofdstuk 6* worden vijf patiënten gepresenteerd die het teken van Lhermitte ontwikkelden na chemotherapie met docetaxel. Dit fenomeen is ook bij cisplatin-neuropathie beschreven. Als mechanisme wordt een abnormale mechanische gevoeligheid verondersteld van sensibele axonen van wortels of achterhoornen na schade aan het dorsale sensibele ganglion.

Hoofdstuk 7 omvat een prospectieve studie naar de effecten van corticosteroïden op incidentie en ernst van docetaxel-geïnduceerde polyneuropathie. Co-medicatie met corticosteroïden wordt momenteel gebruikt tegen het optreden van door docetaxel veroorzaakte vochtretentie en overgevoeligheidsreacties. De patiëntengroep van *hoofdstuk 4* ontving geen corticosteroïden tijdens chemotherapie met docetaxel, omdat het nut daarvan destijds nog niet onderkend was. Deze groep patiënten werd vergeleken met een groep van 49 patiënten met borstkanker die naast docetaxel routinematig corticosteroïden ontvingen. Er was geen statistisch significant verschil in neurotoxiciteit aantoonbaar tussen beide groepen. De

ontwikkeling van docetaxel-geïnduceerde neuropathie wordt niet beïnvloed door co-medicatie met corticosteroïden.

Hoofdstuk 8 beschrijft een prospectieve studie naar de neurotoxiciteit veroorzaakt door combinatie chemotherapie met docetaxel en cisplatin. In 29 van de 55 evalueerbare patiënten (53%) werd een voornamelijk sensibele polyneuropathie geconstateerd. Bij een cumulatieve dosis boven de 200 mg/m^2 van zowel cisplatin als docetaxel ontwikkelden 26 van de 35 patiënten (74%) een neuropathie. Deze was licht bij 15 patiënten, matig ernstig bij 10 patiënten en ernstig bij 1 patiënt. Deze bevindingen werden vergeleken met twee andere trials waarbij patiënten werden behandeld met cisplatin of docetaxel als enkelvoudige chemotherapie, beschreven in respectievelijk *hoofdstuk 2* en *hoofdstuk 4*. Combinatie-chemotherapie induceert een ernstiger polyneuropathie dan cisplatin of docetaxel in vergelijkbare doseringen alleen. Het kon niet worden aangetoond of de middelen een synergetisch effect hebben wat hun neurotoxische werking betreft en welke van de twee middelen het meest bijdraagt aan de neurotoxiciteit.

Betrouwbare metingen van de ernst van chemotherapie-geïnduceerde polyneuropathie zijn van belang voor de evaluatie van behandelingsprotocollen. In *hoofdstuk 9* komt het neurotoxiciteit testprotocol aan de orde dat wordt gebruikt in de Daniel den Hoed kliniek. Dit protocol bevat een gestandaardiseerde anamnese en neurologisch onderzoek resulterend in een som-score van 11 punten, kwantitatieve metingen van de vibratie perceptie drempel (VPT) en gradering d.m.v. de "common toxicity critera" (CTC). Ter validatie van het protocol werden de 944 neurotoxiciteit metingen vóór, tijdens en na chemotherapie in 298

patiënten die participeerden in onderzoeken met cisplatin of docetaxel en de metingen in 55 gezonde vrijwilligers geanalyseerd. De VPT bleek statistisch significant geassocieerd met de som-score en de CTC-gradering. Een lage intra-subject variabiliteit voor VPT en voor de meeste items van de som-score kon worden aangetoond. Dit protocol lijkt een bruikbare methode voor het vaststellen van chemotherapie-geïnduceerde polyneuropathie en kan dienen als een basis voor de verdere ontwikkeling van een graderingsschaal.

Momenteel bestaan er geen therapeutische opties wanneer een patiënt een chemotherapie geïnduceerde polyneuropathie ontwikkelt. Het voorkómen van neurotoxiciteit door modificatie van het doseringsschema of het gebruik van neuroprotectieve stoffen zou grote klinische consequenties hebben. Kennis van klinische factoren en pathofysiologische mechanismen die betrokken zijn bij het ontstaan van een chemotherapie-geïnduceerde polyneuropathie is van belang om methoden te ontwikkelen die tot preventie of behandeling van neurotoxiciteit kunnen leiden. Bij klinisch onderzoek dient de follow-up periode lang genoeg te zijn om progressie van de polyneuropathie na het staken van de chemotherapie aan te tonen. Consensus over het vaststellen van neurotoxiciteit en gradering van de ernst ervan is van belang voor de voortgang van verder onderzoek op dit gebied. De beschikbaarheid van klinische kenmerken en het neurotoxiciteit-protocol zoals beschreven in dit proefschrift kunnen hieraan een bijdrage leveren.

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13 Curriculum vitae

Pieter Hilkens was born in Velsen on the 10th of Februari, 1961. From 1973 to 1979 he attended the "Erasmus College" in Zoetermeer. He studied medicine at the University of Leiden from 1979 to 1987. During this period he worked for five years at the cornea-transplantation project of Eurotransplant. From November 1983 to June 1984 he was a research-assistant in anaesthesiology at the University of Utah, Salt Lake City, USA. After receiving his medical degree in 1987 he was a resident in neurology at the "Elisabeth Gasthuis" in Haarlem and the "Westeinde Ziekenhuis" in The Hague. In 1989, he began his formal training in neurology at the "Westeinde Ziekenhuis" (Head: Dr. J.Th.J. Tans). From July 1993 to June 1994 he continued his training at the department of neuro-oncology of the "Daniel den Hoed Kliniek" in Rotterdam (Head: Dr. Ch.J. Vecht). In this period the research that resulted in this thesis was started. He was a resident in clinical neurophysiology at the "Westeinde Ziekenhuis" (Head: Dr. A.W. de Weerd) from July 1994 to July 1995. Since August 1995 the author has been working as a neurologist at "Rijnstate Ziekenhuis", in Arnhem.

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