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Neurotoxic Side-effects of Cisplatin

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INTRODUCTION

IN THE last decade an increasing number of papers has been published on the neurotoxicity of anticancer agents. With the improvement of supportive care the administration of higher cumulative dosages is now a reality and as a conseqeunce neurotoxic side effects are encountered more frequently. In this review iatrogenic neurotoxiciy in cancer patients is discussed, with emphasis on cisplatin induced neurotoxicity.

A wide variety of neurological signs and symptoms can be diagnosed in patients treated for cancer [1]. In the differential diagnosis, neurological symptoms due to treatment, the neurological symptoms directly related to the tumour and metastases must be taken into consideration. For instance, a peripheral neuropathy may be related to treatment but can also occur as a paraneoplastic phenomenon. In these cases the peripheral neuropathy is already present before treatment is instituted. The duration of this type of neuropathy may vary between 2 and 11 months before the presence of a malignant tumour is confirmed. Treatment of the malignancy can improve the neurological symptoms. Weissman *et al.* reported on a 61-year-old man who was found to have small cell lung cancer following a one year history of a progressive peripheral sensorimotor neuropathy [2]. The neuropathy initially improved following chemotherapy, but subsequently progressed to the point of respiratory failure. Treatment with plasma exchange, additional chemotherapy, and radiotherapy resulted in a sustained complete tumour remission and neurological recovery. This example illustrates the importance to recognise a sensorimotor neuropathy as related to the tumour and not related to the antineoplastic treatment.

NEUROTOXICITY DUE TO CISPLATIN

A number of severe side-effects accompany the use of cisplatin. Short-term phenomena like nausea and vomiting are seen in nearly all treated patients. More threatening are the effects of cisplatin that appear at higher cumulative doses. A loss of hearing, first affecting the higher frequency ranges, can lead to clinical deafness, especially after regimens with high single doses of cisplatin. Renal toxicity causing a marked reduction in the glomerular filtration rate can be reduced by forced hydration, diuretics and a slow rate of infusion of the drug. The use of more aggressive single-dose treatment has put emphasis on cisplatin induced neurotoxicity, now regarded as the major dose-limiting side-effect. Neurological toxicity occurring in patients treated with cisplatin is limited in most cases to peripheral

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neuropathy and ototoxicity. Less frequent signs of neurotoxicity described in the literature include Lhermitte's sign, retrobulbar neuritis, encephalitic symptoms and an autonomic neuropathy.

Lhermitte's sign is an electric-like paraesthesia precipitated by cervical spine flexion and has recently been described as a self-limiting complication in cisplatin-treated patients. The development of Lhermitte's sign accompanied by cervical motor neuropathy, dorsal column myelopathy, and sensory neuropathy in a patient treated with cisplatin and etoposide for small cell lung cancer was recently reported by List *et al.* [3]. They described persistence of the neurologic deficit, suggesting that potentially irreversible spinal cord toxicity may complicate treatment with cisplatin in combination with etoposide.

A less well known neurologic complication is that in patients receiving cisplatin cerebral herniation can occur. Walker *et al.* [4] described five patients with intracranial mass lesions who experienced cerebral herniation and coma following intravenous cisplatin therapy. Although the pathogenesis of the acute cerebral swelling is unknown, it is most likely multifactorial. Possible contributing factors include pre-existing cerebral edema, acute hypo-osmolality with fluid shifts into an already swollen brain, seizures and possible direct neurotoxicity of cisplatin.

Cisplatin neuropathy is the most common encountered side effect. The neuropathy is characterised by numbness, tingling sensations, loss of vibratory sensation and diminished proprioception. Spinal ataxia resulting in disability may ensue. The motor system does not seem to be affected at all [5, 6]. The first symptoms are those of a bilateral sensory neuropathy with numbness and tingling, often in a stocking and glove distribution. As the neuropathy continues position sense becomes progressively impaired. In severe cases this may lead to wheelchair dependence because of a severe sensory ataxia. These symptoms are often accompanied by uncomfortable and painful paraesthesias. Muscle strength remains essentially the same.

Monitoring of cisplatin neuropathy

Even before the clinical symptoms become apparent, examination reveals an increase in vibration perception threshold. Quantitative measurement of vibration perception thresholds in patients treated with cisplatin is a relatively simple, accurate and reliable technique to monitor cisplatin neuropathy. Measurement is only required at the hand. Elderson *et al.* [3] used this method in 20 ovarian cancer patients treated with cisplatin-based chemotherapy. Following the administration of cisplatin (300 mg/m^2 and more) the vibration perception threshold was shown to be significantly elevated in all patients, despite the absence of clinical symptoms and signs in a number of patients. The changes seen in hands and in feet were comparable. There was no significant difference between the left and the right hand side [7]. Lipton confirmed the usefulness of the vibration threshold to monitor cisplatin neuropathy. He used vibration threshold (VT) determinations to assess the function of the sensory system in 171 patients with cancer and 58 healthy subjects. Significant differences in VT indicated dysfunction of this sensory system in the cancer group. 12% of the cancer patients had elevated VT compared with 1.7% of control subjects. Elevated VT was not associated with risk factors for neuropathy such as diabetes, renal disease or poor nutrition. Although VT elevation was associated with alcoholism and increasing age, these variables accounted for only a small proportion of the variance in VT [8].

Clinical data

It is without doubt that cisplatin induced neuropathy becomes more severe with increasing cumulative doses. The Netherlands Joint Study Group for Ovarian Cancer evaluated the incidence of neuropathy in 395 ovarian cancer patients treated with or without cisplatin in two subsequent studies. In the 292 patients treated with cisplatin, the overall incidence of neurotoxicity in any grade of severity was 47%. Of this, about an equal percentage of the patients suffered from a mild or a moderate degree of neurotoxicity. Severe neurotoxicity, characterised by walking disability was rare (4%). No prognostic factors, that might distinguish categories of patients more or less likely to develop a neuropathy due to cisplatin treatments, could be identified. The median number of courses after which symptoms of a neuropathy develop is 5–6 in the cyclophosphamide/hexamethylmelanine/doxorubicin/cisplatin (CHAP-5) regimen, and 7 in the cyclophosphamide/cisplatin (CP) regimen. This corresponds with a cumulative dose of cisplatin of between 500 and 600 mg/m^2 [9]. In the literature cisplatin neuropathy is seen in frequencies varying from 5% to 100% of the patients. The interpretation of the various figures is difficult. This is due to the use of different treatment regimens and periods of follow-up. Also, the term "neuropathy" is often used, without a clear definition. However, taken as a whole an average 48% of the patients have the neuropathy during any stage of cisplatin treatment [9].

Cisplatin neuropathy is more frequently observed in high-dose treatment regimens. This is due to the larger cumulative doses given to these patients and not to the increased toxicity of the individual injections containing a high dose of cisplatin. High-dose cisplatin therapy, defined as 200 mg/m^2/course, is currently undergoing extensive clinical trials in a variety of solid tumours. The reduction of the incidence and severity of cisplatin-induced nephrotoxicity has led to these clinical trials of higher doses of cisplatin. By maintaining nephrotoxicity to acceptable levels, dose response relationships have shown increased efficacy of cisplatin therapy. However, new dose-limiting toxicities, primarily severe neurotoxicity and myelosuppression, prevented further dosing increases [10].

Hainsworth *et al.* [11] reported recently on 25 newly diagnosed patients with advanced epithelial ovarian cancer treated with an extensive induction chemotherapy regimen using high-dose cisplatin in combination with cyclophosphamide and doxorubicin. 2 intensive induction courses of chemotherapy were administered at 28-day intervals, which consisted of cisplatin 40 mg/m^2 daily for 5 days, cyclophosphamide, and doxorubicin. 4 courses of chemotherapy using cisplatin 60 mg/m^2, doxorubicin and cyclophosphamide followed the high-dose induction therapy. 2 of the first 6 patients died during high-dose induction therapy (1 died of neutropenia and sepsis, 1 of intracerebral haemorrhage). Doxorubicin was subsequently omitted from the induction therapy due to unacceptable myelosuppression; no deaths occurred in the remaining 19 patients, and myelosuppression was manageable. Peripheral neuropathy was the most severe side-effect with this regimen. This complication was unpredictable, developed during the third or fourth month of treatment, and was disabling in 5 patients. Other toxicity included prolonged nausea and vomiting (8 patients), ototoxicity (5 patients), and nephrotoxicity (2 patients) but these did not compromise therapy. All 23 assessable patients had objective response to therapy. Although this regimen was tolerated by most patients, the unpredictable occurrence of disabling neuropathy limits its usefulness [11].

After high dose treatment, the neuropathy may worsen even after cessation of treatment. Grundberg *et al.* [12] noted a high incidence of progressive peripheral neuropathy, which continued for several months after the discontinuation of cisplatin chemotherapy. Of the 6 patients treated, 4 received at least 3 cycles of therapy (median total cisplatin dose, 685 mg/m^2; range 500–725 mg/m^2). All 4 patients developed a progressive peripheral neuropathy, with a worsening of toxicity by 1–3 grades over the 2–3 months after cisplatin discontinuation. 1 patient progressed from grade I (mild paresthesia) to grade IV (inability to walk) over a period of 3 months after the discontinuation of therapy. Stricter rules for early dose de-escalation and discontinuation may be required for very high-dose cisplatin regimens. Delayed progressive neuropathy should be recognised as a possible late complication of this form of therapy.

After the more conventional dose schedules cisplatin neuropathy is irreversible in 30–50% of the patients. Long-term data are available from combination regimens used for patients with testicular cancer. Hansen *et al.* [13] from the Finsen Institute in Copenhagen published the results on 30 patients treated for germ cell cancer with 6 cycles of cisplatin, vinblastine and bleomycin who participated in a follow-up examination of neurotoxicity 49 to 106 months after treatment. Of these, 22 patients (73%) had sensory loss; half of them complained of paraesthesias. The vibration perception threshold was increased in 24 patients (80%). Motor conduction velocity (CV) along the peroneal nerve was normal. The average sural nerve CV was decreased ($P < 0.01$) and the sensory action potential amplitude was reduced ($P < 0.01$). Warm perception threshold was increased in 10 patients (33%). Cortical-evoked potentials after tibial nerve stimulation had increased latencies in 29 patients (97%). The peripheral CV along the tibial nerve was slowed in 19 patients, and the central conduction time from Th12 to cortex was significantly prolonged in 15 patients. The changes in conduction along peripheral and central pathways after tibial nerve stimulation are compatible with a toxic effect on the sensory root ganglia causing a "dying back" axonal degeneration of central and peripheral nerve fibres [13]. Because in this study cisplatin was used in combination with vinblastine (another neurotoxic drug) it is not clear whether cisplatin is fully responsible for the findings of Hansen *et al.*

PATHOGENESIS

Thusfar the pathogenesis of cisplatin neuropathy remains obscure. The fact that cisplatin affects the sensory peripheral nerve fibres points towards an involvement of the dorsal root ganglia. The cell bodies of the sensory nerves are located in the dorsal root ganglia outside the central nervous system. These cells are not protected by the blood–brain barrier. The blood–brain barrier constitutes a very effective defence against cisplatin. If one measures the cisplatin content of several tissues, the same levels of cisplatin concentrations are found in the dorsal root ganglia as in tumour tissue, whereas the cisplatin concentrations in the brain and spinal cord are at least a 10 fold lower [14]. How cisplatin attacks the neurons is unclear. Peyrot *et al.* [15] showed that hydrolysed cisplatin (the active form) inhibits tubulin microtubule polymerisation *in vitro*. Comparing the interaction of cisplatin with accepted microtubule poisons such as colchicine and vinca-alkaloids, he observed a far slower action rate of cisplatin with tubulin than of these other compounds, indicating that the mechanisms of their binding to tubulin must be different. If this interaction with tubulin is the damaging mechanism of neurons *in vivo* as well, cisplatin interferes with the cytoskeleton synthesis and maintenance, and impairs neuronal function in this way. Terheggen *et al.* [16] looked at cisplatin-DNA adducts in dorsal root ganglias and only found these adducts in satelite cells, not in the cell body of the sensory neurons themselves. We recently found evidence for effects of cisplatin on mRNA expression in dorsal root ganglia of sensory neurons in rats in a very early stage of intoxication.

AMELIORATION OF CISPLATIN NEUROTOXICITY

Sulphur containing compounds

Despite the still unknown pathogenesis of cisplatin induced neuropathy, some therapeutic options are available. One of the oldest treatment options is derived from attempts to decrease cisplatin induced nephrotoxicity. It was found that a number of sulphur (thiol-group) containing compounds protect against the nephrotoxic properties of cisplatin without interfering with its antitumour activity. Among the compounds tested in clinical trials are sodium thiosulphate [17], ethiofos [18], diethyldithiocarbamate (DDTC) [19] and glutathion [20]. Some authors reported successful attempts to overcome high-dose cisplatin nephrotoxicity with thiosulphate protection but the non-renal toxicity, especially neurotoxicity remained substantial [21]. Interesting results have been reported using WR-2721.

WR-2721 (S-2-(3-aminopropylamino)-ethylphosphorotiotoic acid, ethiofos) is an aminothiol compound; in the animal model it protects against the nephrotoxicity, neurotoxicity, and haematologic toxicity of cisplatin. Ethiofos has to be dephosphorylated by membrane alkaline phosphatase, becoming a free sulphydryl as it enters the cell. Most malignant cells lack the necessary alkaline phosphatase in their membrane and are therefore not targets for the protective action of ethiofos. Glover *et al.* [22], from the University of Pennsylvania, initiated phase I trials of ethiofos and cisplatin to determine toxicity when ethiofos was given prior to escalating doses of cisplatin. With mannitol diuresis and ethiofos, transient nephrotoxicity occurred in 9 of 30 (30%) patients treated with cisplatin 150 mg/m^2 and in 7% of patients given cisplatin 120 mg/m^2. Bone marrow suppression was mild and infrequent. Mild to moderate peripheral neuropathies occurred in 26% of patient courses following a mean cumulative cisplatin dose of 725 mg/m^2. Antitumour responses were observed in 25 of 53 patient with metastatic head and neck cancer, and in 7 of 13 patients with metastatic breast cancer refractory to conventional chemotherapy. Controlled studies of ethiofos and cisplatin will be performed in the Eastern Cooperative Oncology Group in these disease sites to better define the activity of this regimen and its toxicity [22].

Glutathion (GSH) is a naturally occurring tripeptide (τ-Glu-Cys-Gly) that is used in a great number of redox reactions. Although an increased GSH-turnover rate is shown to be one of the factors responsible for cisplatin resistance in a human small cell lung carcinoma *in vitro* [23], others found no clinical evidence of interference with cisplatin oncolytic activity *in vivo* [24, 25].

Di Re *et al.* [25] from the Istituto Nazionale dei Tumori in Milan used GSH as a chemo-protector in an attempt to improve the therapeutic index of cisplatin. A total of 40 consecutive patients with ovarian carcinoma were treated with cisplatin (40 mg/m^2 daily for 4 consecutive days) and cyclophosphamide (600 mg/m^2 intravenously on day 4). The treatment was repeated every 3–4 weeks for 5 courses unless progression or severe toxicity occurred. Before each cisplatin administration, patients received GSH (1500 mg/m^2) intravenously over 15 min, with

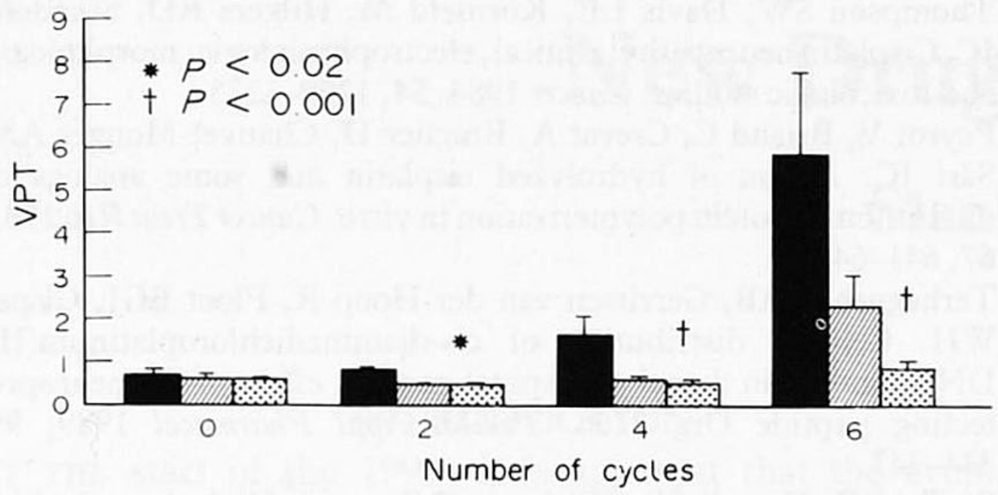

Fig. 1. Vibration perception thresholds (VPT) in μm (S.E.) as measured before chemotherapy and after 2, 4 and 6 treatment cycles. Solid bars = placebo group, hatched = low and dotted = high dose Org 2766.

a standard intravenously hydration (2000 ml fluid) without diuretics. 3 patients were not evaluable for response because they prematurely discontinued their treatment. In all, 23 patients (62%) achieved complete clinical remission (negative second-look laparatomy in 16), with an overall response rate of 86%. A randomised study is mandatory before it can be concluded that these results are improved compared to the more conventional dose schedules. Nausea and vomiting was the most severe acute toxic effect; myelosuppression was acceptable. Renal impairment was effectively prevented by GSH. Unfortunately neurotoxicity (not associated with motor dysfunction) was the most significant cumulative toxicity in patients (24/32) receiving 4–5 courses. These uncontrolled results cannot lead to definite conclusions with regard to the role of glutathion in preventing neurotoxicity. Preclinical testing of GSH in a rat model and further clinical studies using the vibration threshold as a parameter are warranted.

Neuropeptides

Apart from these sulphur-containing compounds, believed to protect against direct interactions between cisplatin and cell compounds (as DNA) another group of drugs have been investigated: neuropeptides. Among the oldest of these compounds is an ACTH(4-9) analogue, Org 2766. In 1980 it was reported that ACTH(1-39) (the complete ACTH-molecule) enhanced peripheral nerve regeneration in adrenalectomised rats [26]. Consecutive structure-activity studies done by Bijlsma *et al.* [27] limited this neurotropic activity to ACTH(1-13) (α-MSH) and its smaller fragments ACTH(1-10), ACTH(4-10) and ACTH(4-9). The last peptide (Org 2766) completely lacks both melantropic and corticotropic activity. In 1987 De Koning *et al.* [28] described a rat model for cisplatin neuropathy, and subsequent reports on the protecting effects of Org 2766 in this rat model followed [29].

Stimulated by these observations a randomised, double-blind, placebo-controlled study was initiated to assess the efficacy of Org 2766, in the prevention of cisplatin neuropathy in women with ovarian cancer. The analogue was given subcutaneously in a dose of 0.25 mg (low dose) or 1 mg (high dose) m^2 of body-surface area before and after treatment with cisplatin and cyclophosphamide (75 and 750 mg m^2 every 3 weeks). The threshold of vibration perception was used as the principal measure of neurotoxicity. After four cycles of chemotherapy, the mean (S.E.) threshold value for vibration perception in the placebo group increased from 0.67 (0.12) to 1.61 (0.43) microns of skin displacement (see Fig. 1). In the high-dose treatment group, there was no increase in the threshold value after four cycles (from 0.54 [0.12] to 0.50 [0.06] micron). After six cycles of chemotherapy, the threshold value was 5.87 (1.97) microns in the placebo group (more than an 8 fold increase from base line), as compared with 0.88 (0.17) micron (less than a 2 fold increase) in the high-dose treatment group. In the high-dose group, fewer neurological signs and symptoms were recorded than in the placebo group. With the lower dose of the analogue, these protective effects were less prominent. No side-effects were seen after treatment with Org 2766. The rates of clinical response to chemotherapy were similar in all groups. These results suggest that Org 2766 can prevent or attenuate cisplatin neuropathy without adversely affecting the cytotoxic effect of the drug [30].

Based on this study, further trials are presently being performed in Europe, the United States, Japan and Australia in patients with both testicular and ovarian cancer.

Other drugs and approaches

Another drug with potential neuroprotective properties is nimodipin. Nimodipin is a calcium-entry blocker of the dihydropyridine type with proven neurotropic activities in several models of experimental nerve damage [31]. This compound was found in the rat to protect against neuropathy as well as Org 2766 [32]. Thus far, no clinical experience with this agent in cisplatin induced neuropathy exists, but it might become an important protective drug in the future, especially since there is evidence that Org 2766 and nimodipin have a synergistic action on peripheral nerve regeneration after a sciatic nerve crush in the rat.

A different approach to prevent cisplatin neurotoxicity was studied by Sebille *et al.* [33]. They used continuous infusion of cisplatin in patients with head and neck cancer. The toxicity of cisplatin on peripheral nerves was studied using electrophysiologic recordings in 52 patients. Induction chemotherapy (cisplatin: 25 mg/m^2/day, days 1–4) was administered by continuous infusion every 3 weeks. Electrophysiological recordings were performed before and after completion of three courses of chemotherapy (cisplatin total dose: 250–300 mg/m^2). The comparison between the recordings showed that 14% of the patients had an increase in the latency of the soleus muscle monosynaptic reflex as studied by the Hoffman reflex and 9% showed a decrease in the conduction velocity of the cutaneous sensory fibers of the median nerve. These results, concluded the authors, indicated a low prevalence of cisplatin-induced neuropathy [33]. Probably their findings are the result of the low cumulative dosage of cisplatin administered in their study. A randomised study comparing this schedule with the conventional approach using the vibration perception threshold to monitor the toxic effects of cisplatin and carefully determining the response rates is mandatory before any definitive conclusions can be drawn.

TREATMENT OF AN EXISTING NEUROPATHY

In patients surviving after cisplatin treatment, the neurotoxic side-effects may compromise the quality of life permanently. For this reason it may be of interest to know whether Org 2766 can induce a repair of an established neuropathy. For this reason Hamers *et al.* [32] performed a "repair" experiment in rats. In this experiment cisplatin was given intraperitoneally in a dose of 1.5 mg/kg, twice weekly for 5 weeks. After a rest period of 10 days Org 2766 10 μg subcutaneously was given every 48 h to a group of 20 rats. A second group of 10 cisplatin treated rats were given saline instead of Org 2766. A third group of 10 healthy untreated rats served as age controls. Longitudinal

measurements of sensory nerve conduction velocity were used as parameter. It was found that the cisplatin induced neuropathy in the Org 2766 treated rats recovered completely, whereas sensory nerve conduction velocity measurements in saline controls remained significantly lower (Student's t test: $P < 0.02$). The results of this experiment lend support to the rationale for the already ongoing studies of Org 2766 in patients with established cisplatin induced polyneuropathy.

CONCLUSION

Cisplatin neuropathy is a severe dose limiting side-effect. Especially in treatment schedules using higher dosages of cisplatin, this side-effect can lead to a disabling neuropathy. For this reason much effort has been made in the last decade to find methods to protect nerves from cisplatin toxicity. So far the use of the neuropeptide Org 2766 has led to promising results in preclinical studies as well as in clinical trials. Confirmation of the results has to be awaited and can be expected in the next year. Nimodipin also warrants further clinical studies and the combination of this agent with Org 2766 may further increase the protective properties of both agents.

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