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Neurotoxicity is not Enhanced by Increased Dose Intensities of Cisplatin Administration

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It is uncertain whether intensive dosing schedules of cisplatin, intended to attain a higher anti-tumour efficacy, alter the 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 neuropathy was determined by measurement of the vibration perception threshold (VPT) before treatment and during follow-up for 2–12 months after the last cycle. 66 patients were treated with an intensive weekly regimen of doses varying from 70 to 85 mg/m^2 in 1 day (trial A), 21 patients with a 3-weekly combination chemotherapy containing cisplatin 75 mg/m^2 in 1 day (trial B) and 20 patients with a 3-weekly regimen containing cisplatin 20 mg/m^2 for 5 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 pretreatment VPT ($P < 0.001$) and with the cumulative dose of cisplatin ($P < 0.001$). Following 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 treatment with more intensive dosing schedules, employing equal cumulative doses of cisplatin, does not result in a concomitant increase in neurotoxicity within a cumulative dose range of 280–675 mg/m^2.

Key words: neuropathy, cisplatin, vibration perception threshold
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INTRODUCTION

CISPLATIN IS a cytotoxic agent effective against a wide spectrum of solid tumours. *In vitro* studies on human cancer cell lines and a number of clinical trials have suggested a dose–response relationship to cisplatin [1–3]. Administration of more intensive dosing schedules of cisplatin have become feasible, because potentially severe side-effects, such as 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 characterised by paresthesias, numbness, loss of tendon reflexes and a decrease in mainly thick-fibre-mediated sensory qualities such 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 3 months after cessation of therapy ("coasting"), with subsequent but incomplete recovery thereafter [8–10]. It is presently uncertain if the severity of 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. 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 in the trials, WHO performance status had to be 0–2 and life expectancy more than 3 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 participated in a phase II study on the effect of weekly cisplatin on locally advanced or metastatic solid tumours. Cisplatin was dissolved in 3% NaCl and administered in a 3-h infusion with standard pre- and posthydration. Adminis-

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tration took place in a weekly regimen in doses varying from 70 to 85 mg/m^2 in six intended cycles. In some patients, 1 week off therapy was allowed after the third cycle. In most patients, cisplatin was combined with etoposide at 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 1–21 every 4 weeks for a maximum of four cycles. Trial B consisted of patients with ovarian cancer who were treated with cisplatin in a 3-weekly schedule of 75 mg/m^2 in 1 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 with a schedule of 20 mg/m^2 cisplatin on 5 consecutive days every 3 weeks for four intended cycles. They were cotreated with etoposide 120 mg/m^2 for 3 days every 3 weeks and bleomycin 30 mg weekly or ifosfamide 1.2 g/m^2 for 5 days 3-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 placebo during chemotherapy were used for comparison in this study. 9 patients from trial B received Org 2766 during the follow-up period, starting 1 month after the last cycle of cisplatin. In trials B and C, cisplatin was dissolved in NaCl 0.9% and administered in a 4-h infusion with standard pre- and posthydration. None of the patients in trials A, B or 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 VPT were performed before the start of 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 VPT before the start of treatment and during follow-up until at least 2 months after cessation of cisplatin treatment, in order to be eligible for the assessment of neurotoxicity. 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 micrometres (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 pretreatment VPT with age, and regression analysis was used for comparison of several prognostic factors with maximum post-treatment VPT. Analysis of covariance was used to study the association of dose intensity and maximum post-treatment VPT, taking into account both total cumulative dose and pretreatment VPT.

RESULTS

66 patients were treated in a weekly schedule (trial A), 21 patients in a 3-weekly schedule (trial B) and 20 patients in a 3-weekly schedule with administration divided over 5 consecutive days (trial C). Patients' characteristics and tumour types in these three groups are shown in Table 1. The average age in group C was lower because of the tumour type (mainly younger males with testicular cancer).

Table 1. Patients' characteristics and tumour types in trials A, B and C

	Trial A	Trial B	Trial C
Number of patients	66	21	20
Male/female	51/15	0/21	20/0
Age (years)			
Mean years	55	58	29
Range	34–71	28–73	18–41
Tumour 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 2 shows dosing schedule, cumulative dose and dose intensity of cisplatin and pre- and post-treatment VPT in trials A, B and C. There is a difference in values for mean pretreatment 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 pretreatment 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 prescheduled interruption of chemotherapy or for reasons of toxicity.

The variation in cumulative dose within each trial is due to 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 cessation of chemotherapy. The

Table 2. Dosing schedule, cumulative dose and dose intensity of cisplatin and pre- and post-treatment VPT in trials A, B and C

	Trial A	Trial B	Trial C
Dosing schedule			
mg/m^2	70–85	75	5 × 20
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 ± S.D.	0.8 ± 0.5	0.6 ± 0.3	0.3 ± 0.1
Maximum post-treatment VPT			
Mean ± S.D.	2.4 ± 1.9	3.6 ± 3.7	1.3 ± 1.7

maximum post-treatment VPT of these patients was not apparently different from the other patients. The variation in cumulative dose and dose intensity, both between and within the trials, was exploited to analyse the association of the maximum post-treatment VPT with cumulative dose, dose intensity, age and pretreatment VPT. Age ($P < 0.001$) or similarly pretreatment VPT ($P < 0.001$), and cumulative dose ($P < 0.001$) were strongly associated with 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 cumulative dose.

Figure 1 shows the relation of maximum post-treatment VPT, adjusted for pretreatment 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 trial C did not affect this line. Regression lines for each of the trials separately (not shown for clarity) were close to, and not statistically significant from, the line shown.

This implies that, in this study population, the level of neurotoxicity, as measured by the maximum post-treatment VPT, depends primarily on the pretreatment 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.

DISCUSSION

The observation that co-administration of hypertonic saline and vigorous hydration can minimise cisplatin-induced nephrotoxicity has led to the use of higher doses and more intensive dosing schedules of cisplatin, aiming at better tumour control [2, 3, 17, 17]. 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 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 of at least 2, but in the majority of cases 3–6 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 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 5 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 5-day continuous infusion has been observed [25]. Other studies reported that a schedule with administration of 100 mg/m^2 cisplatin on days 1 and 8 was less toxic than when the same total dose was given over 5 days (five × 40 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 and associates 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 with patients treated with conventional dosing schedules (50 mg/m^2 every 4 weeks), suggesting that higher dose intensities of cisplatin give rise to increased neurotoxicity [11]. In contrast, Cavaletti and associates found a lower incidence of neuropathy in patients treated with 50 mg/m^2 cisplatin given every week in nine cycles than patients with 75 mg/m^2 cisplatin every 3 weeks in six cycles [12].

To determine the influence of dose intensity on the severity of neuropathy, we compared patients from three trials treated with dosing schedules differing by the dose intensity of cisplatin administered. Compared to patients in trials A and B, the value for mean pretreatment VPT was lower in patients from trial C because they were younger. The difference in pretreatment VPT between trials A and B may reflect a higher incidence of pre-existing neuropathy in patients in trial A, who all had advanced disease. The cause of this cancer-associated neuropathy is uncertain, but is probably related to aspecific factors, such as cachexia, malnutrition and tumour progression [28, 29]. Following correction for pretreatment VPT and cumulative dose of cisplatin, no significant difference in post-treatment neuropathy was observed between patients in these three groups, suggesting that

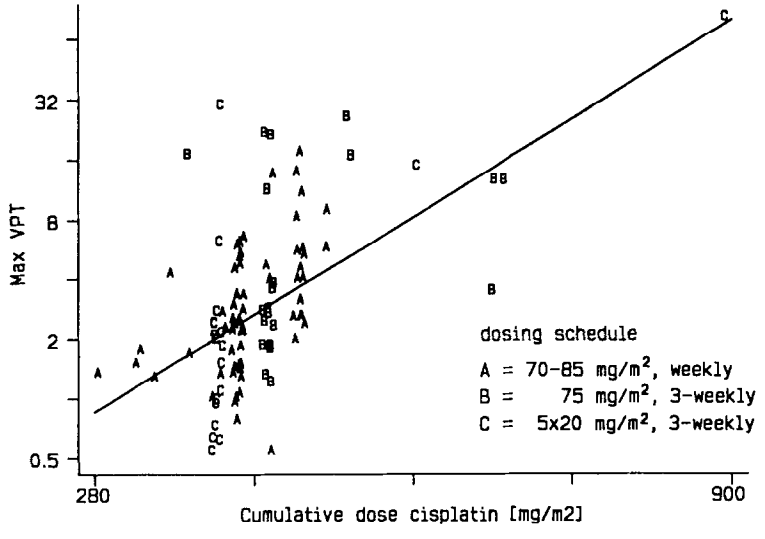

Figure 1. Maximum post-treatment VPT versus cumulative dose of cisplatin adjusted for pretreatment VPT. A, B and C indicate three trials with different dosing schedules. A = 70–85 mg/m^2 weekly; B = 75 mg/m^2 3-weekly; C = five × 20 mg/m^2 3-weekly.

dose intensity is not a factor of major importance for the development of neuropathy. It is well known that VPT increases with age [16], and we confirmed this in our study. The patients in trial C had a lower mean post-treatment VPT, but they also had much lower pretreatment VPT values, because they were younger. We found a strong, significant correlation between pretreatment VPT and post-treatment VPT values, indicating that the change in VPT may be a better measure for neuropathy than its absolute value.

One reason for the discrepancies between studies on the influence of dosing schedule [11, 12] may be the length of observation after cessation of cisplatin cycles. As the neuropathy commonly continues to deteriorate up to approximately 3 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 is not associated with an increased risk of 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 the vehicle for cisplatin administration, while patients from trials B and C received 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 cessation of cisplatin treatment in 9 patients from trial B influenced the results, since we did not find a difference in post-treatment VPT between patients either with or without Org 2766. Another point of consideration is that the dose range in this study population is limited, and that the numbers of patients treated in trials B and C are rather small. The fact that the regression lines of maximum post-treatment VPT versus 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 adminstration. These results suggest that the anti-tumour 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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