Pergamon

European Journal of Cancer Vol. 33, No. 9, pp. 1393–1399, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00103-2

Original Paper

Neurological Monitoring of Neurotoxicity Induced by Paclitaxel/Cisplatin Chemotherapy

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To evaluate the neurotoxicity of paclitaxel/cisplatin chemotherapy, we studied neurological and electrophysiological functions in 14 patients who had been treated with 1–7 courses of paclitaxel/cisplatin. The cumulative paclitaxel and cisplatin doses ranged from 175 to 1225 mg/m^2 and 100–700 mg/m^2, respectively. Neurological examinations as well as motor nerve conduction studies of the peroneal nerve were performed and summarised by means of a peripheral neuropathy score. Neurotoxicity with onset usually after the second treatment cycle occurred in 13 patients. 12 patients complained about sensory symptoms, 13 patients had impaired vibration sense and 8 patients developed additional muscle weakness, predominantly of the legs. Dysfunction of peroneal motor nerve conduction occurred in 13 patients. Reduction of amplitudes as well as slowing of conduction velocities were seen in 13 patients and prolonged distal latencies in 10 patients. The peripheral neuropathy score was elevated in 13 patients. Neurological symptoms, impairment of both vibration sense and tendon reflexes, and the peripheral neuropathy score increased with the cumulative doses of paclitaxel/cisplatin. Serial analysis among selected patients also revealed an increase in neurotoxicity with increasing cumulative drug doses. These data indicate the development of neurotoxicity in most patients treated with paclitaxel/cisplatin and also suggest that early signs of neurotoxicity can be detected by clinical examination with emphasis on symptoms as well as vibration sense and can be well documented by electrophysiological investigations. © **1997 Elsevier Science Ltd.**

Key words: paclitaxel, cisplatin, chemotherapy, neurotoxicity, peripheral neuropathy, monitoring

Eur J Cancer, Vol. 33, No. 9, pp. 1393–1399, 1997

INTRODUCTION

PACLITAXEL IS a novel anticancer drug with clinical activity against a variety of solid tumours [1–3]. Paclitaxel inhibits tubulin depolymerisation, thereby resulting in stable and dysfunctional microtubules [2, 3]. At high doses of paclitaxel (either alone or in combination with cisplatin), neurotoxicity has become the principal dose-limiting side-effect, since neutropenia can be ameliorated by the co-administration of haematopoietic growth factors [4–6]. Predominantly sensory neuropathy has been reported when high single or high cumulative paclitaxel doses alone [1, 4, 7, 8] or in combination with cisplatin [6, 9] have been administered.

Many paclitaxel-based combination chemotherapies are currently being evaluated. The combination with cisplatin is amongst the most promising regimens. Paclitaxel and cisplatin have resulted in improved survival in patients with ovarian carcinomas compared to previous standard chemotherapy [10], and have also shown good activity in advanced non-small-cell lung cancer [11]. Because both drugs are neurotoxic, the broad clinical use of paclitaxel and cisplatin might be limited by the development of clinically significant neurotoxicity. To evaluate this further, we determined the cumulative dose-dependent neurotoxicity of

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Received 16 Oct. 1996; revised 30 Jan. 1997; accepted 25 Feb. 1997.

Table 1. Peripheral neuropathy (PNP) score (modified after Chaudhry and associates, 1994) [9]

	0	1	2	3
Sensory symptoms	None	Numbness/paraesthesia in the feet	Numbness/paraesthesia in feet and fingers	Functionally disabling numbness/paraesthesia
Vibration	Normal 8/8 (tuning fork)	<6/8	<4/8	None
Strength	Normal	Weak toe extension	Weak toe extension and finger abduction	Diffuse generalised weakness
Tendon reflexes	Normal	AJ reduced or absent	AJ absent; others reduced	All reflexes absent
Peroneal MCV (m/sec)	50–42	41–31	<31	
Peroneal distal latency (msec)	3.7–4.8	4.9–6.0	>6.0	
Peroneal amplitude (mV)	10.0–4.0	3.9–2.0	<2.0	

Peripheral neuropathy score: 1–6, mild neuropathy; 7–12, moderate neuropathy; 13–18, severe neuropathy.
AJ, ankle jerk; MCV, motor conduction velocity.

paclitaxel/cisplatin both clinically and electrophysiologically. For this purpose, we also used a neurological and electrophysiological score (Table 1) modified according to the one initially described by Chaudhry and associates [9].

PATIENTS AND METHODS

Patients

14 patients with histologically documented solid tumours were studied. Age, sex and pre-existing risk factors are shown in Table 2. 13 previously untreated patients with non-small-cell lung cancer (patient nos. 1–13) were treated within a phase II trial [11] with paclitaxel (175 mg/m^2 over 3 h on day 1) followed by cisplatin (50 mg/m^2 daily on days 1 and 2). In addition, 1 pretreated (carboplatin, etoposide) female with ovarian cancer (patient no. 14) received similar treatment. Treatment was repeated every 3 weeks.

Neurological examination

A standardised medical history, which included previous or recent sensorimotor symptoms as well as risk factors, and neurological examinations were performed by one investigator in all patients. 7 patients were serially examined and all patients were examined at the end of treatment after having received various cumulative paclitaxel/cisplatin doses. 2 patients were re-examined 8 months after the end of treatment to assess long-term neurotoxicity. The neurological examination evaluated sensory symptoms (pain, tingling, numbness) as well as vibration sense (measured by using a standard tuning fork placed over bony prominences of the great toe, lateral malleolus, patella, hip, index finger and olecranon), strength (toe extensors, foot extensors and flexors, knee extensors, hip flexors, finger abductors, arm extensors and flexors) and deep tendon reflexes. The results of the neurological examinations were categorised into four groups (Table 1).

Electrophysiological studies

Concurrent with clinical neurological examinations, motor nerve conduction studies of the peroneal nerve were performed. Motor nerve potentials were chosen because they are usually easier to obtain than sensory potentials and do not require averaging techniques. Distal latencies (msec), conduction velocities (m/sec) and amplitudes (mV) were measured according to international standard methods. Surface electrodes stimulated the nerve above and under the head of the fibula and just above the ankle. Muscle action potentials in the extensor digitorum brevis were recorded. Results were categorised as indicated in Table 1.

Peripheral neuropathy score

Clinical and electrophysiological findings were summarised by means of a peripheral neuropathy score (PNP score) (Table 1). The score used in our study included peroneal nerve conduction parameters and, therefore, was a modification of the score previously described by Chaudhry and associates [9]. Mild, moderate and severe neuropathy was defined by PNP scores 1–6, 7–12 and >12, respectively.

Linear regression analysis

The association between cumulative drug doses and the degree of neurotoxicity was determined by linear regression analysis.

RESULTS

Evaluation at the end of treatment

Prior to paclitaxel/cisplatin chemotherapy, none of the patients complained about sensorimotor symptoms, but a history of diabetes mellitus was present in 2 patients and chronic alcohol abuse in 1 patient (Table 2). In these 3 patients, electrophysiological data prior to treatment are not available.

The patients received 1–7 (median 4) treatment cycles (Table 2). The cumulative drug doses ranged from 175 to 1225 mg/m^2 (median 700 mg/m^2) paclitaxel and from 100 to 700 mg/m^2 (median 400 mg/m^2) cisplatin. During the course of treatment, neurotoxicity according to a peripheral neuropathy occurred in 13 patients. The degree of neurotoxicity at the end of treatment is summarised for all patients in Table 2.

Complete absence of neurotoxicity was observed in patient no. 1, who had received only one treatment cycle. Twelve patients (86%) complained of sensory symptoms. Predominantly numbness/paraesthesia in a stocking (2 patients) or stocking-and-glove (4 patients) distribution and functionally impairing numbness/paraesthesia (6 patients) were observed. Vibration sense was reduced in 7 patients (50%) and absent in 6 patients (43%).

Six patients (43%) had reduced tendon reflexes and 6 patients (43%) demonstrated generalised areflexia. 8 patients (57%), all of whom had sensory symptoms, developed additional weakness of toe extension and/or finger abduction during the course of treatment. 5 of these 8 patients finally presented with symptoms of diffuse general-

Table 2. Paclitaxel/cisplatin neurotoxicity: clinical and electrophysiological findings

Patient	Age	Sex	Risk factor	Paclitaxel/cisplatin cumulative doses	Symptoms	Vibration	Strength	Reflexes	Peronaeus			PNP score
									MCV	dL	Amp	
1	46	f	–	175/100	0	0	0	0	0	0	0	0
2	48	m	–	175/100	0	1	0	1	1	1	1	5
3	43	m	–	350/200	1	1	0	1	1	1	1	6
4	51	f	–	350/200	2	2	1	2	1	2	2	12
5	49	m	–	175/100	0	0	0	0	0	0	0	0
				350/200	1	1	0	0	1	0	1	4
6	48	f	–	350/200	1	1	0	2	1	2	2	9
				525/300	2	2	1	3	1	2	2	13
7	52	m	Diabetes	175/100	1	1	0	1	1	1	1	6
				350/200	2	2	1	2	2	1	2	12
				525/300	3	3	2	3	2	2	2	16
				700/400	3	3	3	3	2	2	2	18
8	63	m	–	700/400	3	3	3	2	2	2	2	17
9	52	m	–	175/100	0	0	0	0	0	0	0	0
				350/200	1	1	0	0	0	0	1	3
				525/300	1	1	0	0	1	0	1	4
				700/400	2	2	0	1	1	0	1	7
				875/500	2	2	1	2	1	0	1	9
10	63	m	Alcohol	175/100	1	1	0	1	1	0	2	6
				350/200	1	1	0	2	1	1	2	8
				525/300	2	1	1	2	1	1	2	10
				700/400	3	3	2	2	2	2	2	16
				875/500	3	3	3	3	2	2	2	18
11	61	f	–	875/500	3	3	2	2	1	0	2	13
				1050/600	3	3	3	3	1	0	2	15
12	58	m	–	525/300	0	0	0	0	0	0	0	0
				700/400	0	1	0	1	1	1	0	4
				875/500	0	1	0	1	1	1	1	5
				1050/600	1	2	0	2	2	1	1	8
				1225/700	2	3	0	3	2	1	1	12
13	62	m	Diabetes	1225/700	3	3	3	3	2	2	2	18
14	54	f	–	1225/700	3	2	0	2	1	1	2	11

MCV, motor conduction velocity (m/sec); dL, distal latency (msec); Amp, amplitude (mV).

Electrophysiological parameters have been evaluated as described in Patients and Methods. Data are shown at the end of treatment for all patients and additionally during treatment in some patients.

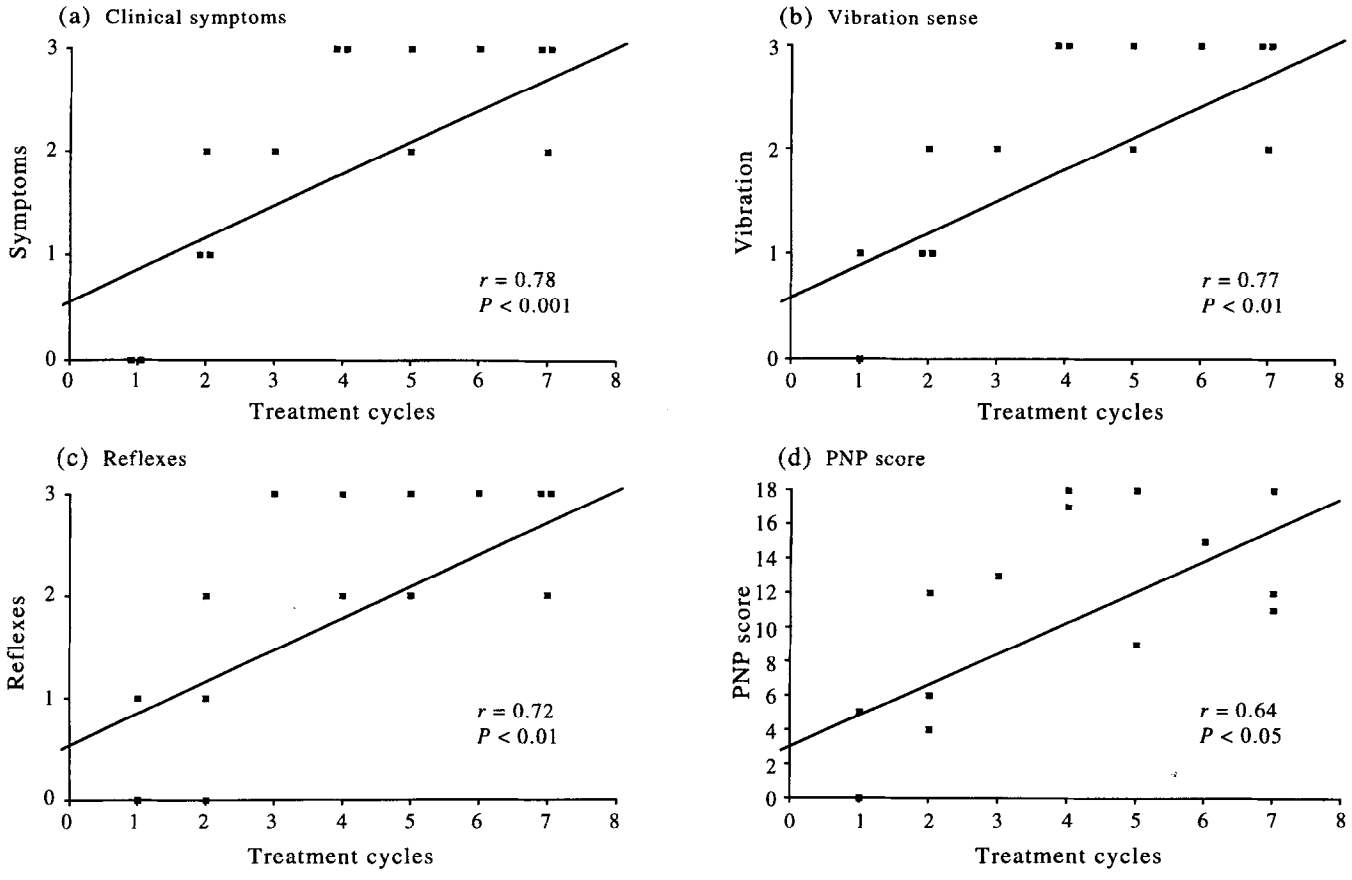

Figure 1. Neurotoxicity dependent on the cumulative doses of paclitaxel/cisplatin. Neurotoxicity was evaluated in 14 patients who had received various numbers of treatment cycles of paclitaxel/cisplatin. Linear regression analysis revealed a correlation between the number of cycles and symptoms, vibration sense, reflexes as well as the PNP score.

ised weakness of upper and predominantly lower extremities. 4 of these 5 patients, including 3 patients with a pre-existing risk, developed a peripheral neuropathy with a PNP score $\geqslant 17$, which resulted in discontinuation of treatment after 4 (2 patients), 5 and 7 cycles, respectively.

In general, the severity of both sensory and motor symptoms was dependent on the cumulative drug doses (Figure 1). Sensory symptoms and reduction of vibration sense were already seen after the second treatment cycle. Severe neurotoxicity (PNP score >12) was first observed after the third treatment cycle (Table 2). Linear regression analysis revealed a good correlation between the cumulative drug doses and clinical symptoms ($r = 0.78$), vibration sense ($r = 0.77$) or reflexes ($r = 0.72$) (Figure 1). No significant correlation was seen in the case of strength.

The electrophysiologic hallmark of axonal neuropathy is a reduction of evoked potential amplitudes, reflecting axonal degeneration. With increasing severity of axonal degeneration, the remaining fast-conducting fibres are lost, electrophysiologically detected by impaired distal latencies and conduction velocities. In our study, motor nerve conduction studies of the peroneal nerve revealed axonal degeneration by reduction of peroneal amplitudes and slowing of nerve conduction velocities in 13 patients (93%) and prolonged distal latencies in 10 patients (71%) (Table 2). Electrophysiological signs of neurotoxicity were absent in the clinically asymptomatic patient after one treatment cycle. Dysfunction in peroneal motor nerve conduction was dependent on the cumulative drug doses (Table 2). A linear correlation between cumulative drug doses and reduction of conduction velocities was observed (data not shown). No significant correlation was seen in the case of distal latencies and amplitudes (data not shown).

The PNP scores obtained from both clinical and electrophysiological findings are shown in Table 2. Neuropathy of grade 1 (mild), 2 (moderate) and 3 (severe) were seen in 3 (21%), 4 (29%) and 6 (43%) patients, respectively. In 1 of these patients (patient no. 10) neurotoxicity was clinically considered to be WHO grade 3 [11]. The score was not elevated in the patient (patient no. 1) who received only one treatment cycle. Linear regression analysis revealed a correlation coefficient of 0.64 ($P < 0.05$) (Figure 1).

Serial evaluations

Longitudinal studies on neurotoxicity are available in selected patients (Figure 2). These studies demonstrated an increase in neurotoxicity (both with regard to clinical symptoms, electrophysiological findings and the PNP scores) with increasing cumulative drug doses. Usually symptoms first appeared after the second treatment cycle. Follow-up examinations of patient nos. 10 and 11 at 8 and 12 months after the end of treatment, respectively, showed no improve-

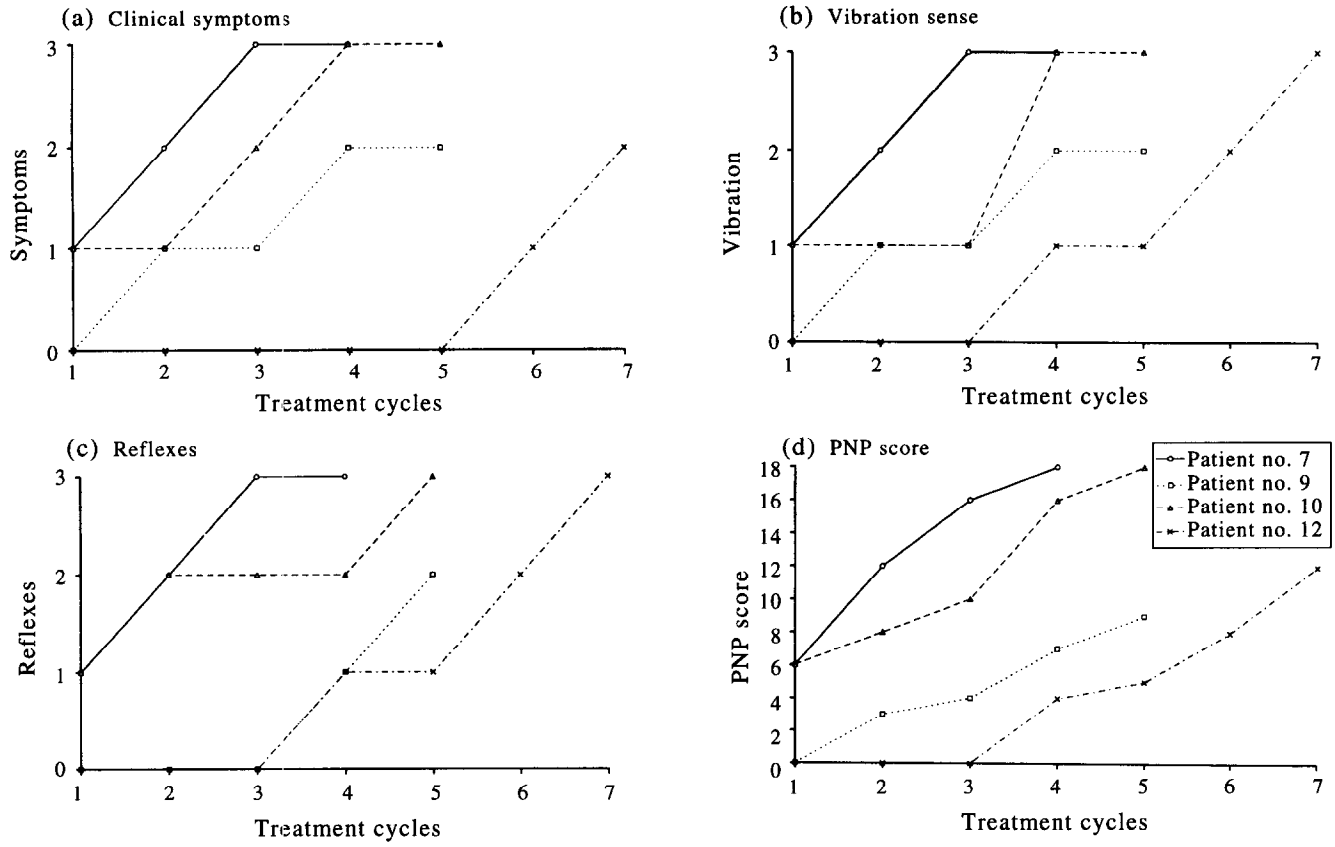

Figure 2. Serial analysis of neurotoxicity. Results of longitudinal evaluation of neurotoxicity are shown for 4 patients. Neurotoxicity increased with increasing numbers of treatment cycles in all 4 patients.

ment, indicating long-lasting and probably irreversible neurotoxicity.

DISCUSSION

In our study, most patients developed peripheral neuropathy which was either mild (PNP score 1–6; 21%), moderate (PNP score 7–12; 29%) or severe (PNP score >12; 43%). All patients with neuropathy complained about sensory symptoms and/or impaired vibration sense, and 8 (57%) experienced additional motor weakness, predominantly of the legs.

Whereas the neurotoxicity of cisplatin is well established as a usually pure sensory neuropathy [12], only a few studies describing the clinical and electrophysiological features of neurotoxicity induced by either paclitaxel monotherapy [7, 8], paclitaxel monotherapy after previous cisplatin administration [1, 8, 13, 14] or paclitaxel/cisplatin combination therapy [9] have been published. Most reports emphasise the development of sensory neuropathies. Sensory symptoms may begin as early as 24–72 h after treatment with high single paclitaxel doses (>200 mg/m^2) [8] but usually appear after multiple cycles at conventional doses, and, as in our study, symptoms progress with each treatment cycle [3, 5]. Single paclitaxel doses of 135–175 mg/m^2 over 3 h have led to frequent but only mild neurotoxicity up to cumulative doses of 1400 mg/m^2 [7]. Paclitaxel doses of 200–275 mg/m^2 over 6, 8 or 24 h have not produced severe neurotoxicity up to cumulative doses of 1250 mg/m^2 [8]. Paclitaxel monotherapy of 110–250 mg/m^2 over 24 h after previous cisplatin therapy have caused only mild neurotoxicity with no WHO grade 3 or 4 toxicity [1]. However, dose-limiting neurotoxicity has occurred with high-dose (300 mg/m^2 over 24 h every 3 weeks) paclitaxel combined with G-CSF [4].

In comparison to paclitaxel monotherapy, the combination paclitaxel/cisplatin appears to result in enhanced neurotoxicity both with regard to frequency and intensity. A correlation between the degree of neurotoxicity and cumulative drug doses was obvious (Figure 1). Our high frequency of neurotoxicity confirms the findings by Chaudhry and associates who reported a 95% incidence of neurotoxicity in a phase I trial with paclitaxel (135–350 mg/m^2 over 24 h), cisplatin (75–100 mg/m^2) and G-CSF [9]. Consistent with this high frequency of neurotoxicity, the clinical evaluation of 20 non-small-cell lung cancer patients treated with this protocol resulted in WHO grade 1–2 and 3–4 neurotoxicities in 65% and 5% of the patients, respectively [11]. Moreover, our study demonstrated moderate to severe neurotoxicity occurring at cumulative doses of 525 mg/m^2 paclitaxel and 300 mg/m^2 cisplatin. However, in the ovarian cancer study with 135 mg/m^2 paclitaxel over 24 h followed by 75 mg/m^2 cisplatin, the incidence of neurotoxicity was low (9% WHO grade 2 and 4% WHO grade 3), despite cumulative doses of 810 mg/mg^2 paclitaxel and 450 mg/m^2 cisplatin [10]. These differences in the frequency and degree of neurotoxicity might be due to differences in doses and/or

schedules (e.g. 3 h versus 24 h). In a randomised trial of paclitaxel monotherapy in relapsed ovarian cancer patients [15], the paclitaxel dose of 175 mg/m^2 was significantly more neurotoxic than the paclitaxel dose of 135 mg/m^2, but the higher dose was slightly more active. In the same trial, neurotoxicity was somewhat less frequent in the 24 h group (40%) than in the 3 h group (49%), but this difference was not statistically significant. Thus, future studies will have to determine whether the development of neurotoxicity can be prevented by altered doses and/or scheduling of the drugs.

Motor neuropathy of paclitaxel therapy is not well documented. This is probably due to the fact that only mild motor weakness, especially mild weakness of the toe extensor muscles, has been observed [3, 5], and these alterations rarely affect motor functions. Previous motor nerve conduction studies have demonstrated only reduced peroneal evoked amplitudes in patients treated with paclitaxel/cisplatin [9]. In contrast, our electrophysiological data with reduced peroneal evoked amplitudes, prolonged distal latencies and slowing of motor nerve conduction velocities suggest that motor nerve involvement is more severe than reported in previous studies of paclitaxel monotherapy [1, 7, 8, 13, 14] as well as paclitaxel/cisplatin combination therapy [9].

The results of our study have several clinical implications. Firstly, baseline evaluations should be performed in order to detect various risk factors and/or pre-existing neuropathies. Because, in our study, all 3 patients with the most severe neuropathy (PNP score 18) had a pre-existing risk (diabetes mellitus, chronic alcohol abuse) without clinical symptoms at the time of study inclusion, patients at risk of neuropathies should be excluded from paclitaxel/cisplatin chemotherapy in the future. Secondly, future prophylactic applications of either cytoprotectors, such as amifostine [16], or nerve growth factors might potentially prevent the emergence of neurotoxicity. Thirdly, sequential neurological examinations might allow early neurotoxic symptoms to be detected and thus help to predict the optimal duration of treatment. These examinations should preferentially include evaluation of symptoms, vibration sense and tendon reflexes. According to our results, additional electrophysiological evaluations do not result in earlier detection of neurotoxicity compared to the clinical examination alone. However, electrophysiological examinations are required for an objective demonstration of the impairment of peripheral nerve functions. A PNP score might allow a more detailed assessment of neurotoxicity compared to the WHO toxicity scale. As seen in our study, clinical evaluation of neurotoxicity by oncologists might underestimate the degree of neurotoxicity as WHO grade 3 neurotoxicity was seen in 1 patient but a PNP score >13 was present in 6 patients. Fourthly, careful neurological and electrophysiological measurements may also allow the topography and degree of paclitaxel/cisplatin neurotoxicity to be defined. This may be of crucial importance with regard to future trials with nerve growth factors for the prevention or reversal of toxic neuropathies [17–19]. Due to their heterogeneity, growth factors will be administered depending on the specific clinical presentation of neurotoxicity and might result in enhanced recovery from neurotoxicity [20]. Finally, neurological examination is strongly recommended for all patients who are to undergo subsequent treatment with neurotoxic drugs after paclitaxel treatment, because these patients are at high risk of developing severe neurotoxicity as has recently been demonstrated for breast cancer patients treated with vinorelbine after paclitaxel exposure [21] and for patients treated with vinorelbine/paclitaxel after previous paclitaxel-containing chemotherapy protocols [22].

In conclusion, paclitaxel/cisplatin results in neurotoxicity in most patients. However, regular clinical neurological examinations before and during treatment with emphasis on neurological symptoms and vibration sense should be helpful for the prevention or early detection of neurotoxicity, and might thus further enhance the clinical acceptance of this otherwise promising treatment protocol.

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