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Paclitaxel (Taxol) Induces Cumulative Mild Neurotoxicity

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Paclitaxel (Taxol), a new antineoplastic drug, has been reported to be neurotoxic at doses above 200 mg/m² per course. It is uncertain whether neurotoxicity is related to cumulative amounts of paclitaxel. Neuropathy was prospectively assessed in 18 patients with breast cancer, receiving between two and eight courses of 135 or 175 mg/m² of paclitaxel. Vibratory perception thresholds (VPT) and tendon reflex scores were proportionally related to the corresponding cumulative amounts of paclitaxel ($P = 0.002$; $P = 0.0003$). The amounts of paclitaxel administered between the first and last assessments (175–1225 mg/m²) were related to concomitant changes in VPT ($P = 0.034$). Paclitaxel had no clear neurotoxic threshold; if present, it lies below 540 mg/m². Rather, VPT appeared to increase 0.1 μm per 400 mg/m² over the entire range of 175–1225 mg/m² of paclitaxel. Clinical neuropathy prevailed in 0/8 patients at screening and in 5/10 patients at the final assessment ($P = 0.029$). Neuropathy never exceeded grade 1. Thus, although neurotoxicity of paclitaxel is frequent and cumulative, it remains mild or subclinical up to at least 1400 mg/m² administered over eight cycles.

Key words: breast carcinoma, neuropathy, neurotoxicity, paclitaxel, vibration threshold
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INTRODUCTION

THE ROLE of paclitaxel (Taxol) as a new antineoplastic agent has not been fully established, but it seems promising in the treatment of a variety of tumours, including ovarian, breast, head and neck and non-small cell lung cancer [1–3]. The main side-effects of paclitaxel are anaphylactoid reaction, granulocytopenia and polyneuropathy. The neuropathy has been characterised as being predominantly sensory, and both axonal and demyelinating [4]. Neuropathy has usually been observed at doses per course of 200–600 mg/m² or higher [1, 3–7]. It has been suggested that neuropathy is rare at below 200 mg/m² per course [8, 9] and that paclitaxel can safely be administered up to 250 mg/m² per cycle [6].

It thus appears that paclitaxel may have cumulative neurotoxicity. In various malignant diseases, neuropathy frequently was found at the highest doses [10]. Others reported that the occurrence of neuropathy appears to be associated with the area under the concentration–time curve of paclitaxel [11]. In one report, the neuropathy was worse with cumulative amounts higher than 600 mg [7]. In this study, however, patients were treated not only with paclitaxel, but also with cisplatin, which is well-known to be neurotoxic up to 4 months after cessation of

treatment [12]. In all these studies, paclitaxel was administered at doses above the assumed safe level of 200 mg/m^2 per cycle [6, 9]. In the present study, we administered paclitaxel at doses of 135 or 175 mg/m^2 to patients with breast carcinoma. The purpose of our study was to examine prospectively whether paclitaxel has a neurotoxic threshold, and whether cumulative neurotoxicity occurs if given at doses per cycle, which are as yet not known to induce neuropathy.

PATIENTS AND METHODS

This study was part of a prospective study to compare the response rate of metastatic breast cancer to paclitaxel at two different dose levels (135 and 175 mg/m^2). Paclitaxel was given as a 3-h continuous intravenous infusion, every 3 weeks. Patients were treated with an intended maximum of 10 cycles. Eligibility criteria included a World Health Organisation (WHO) performance status of 0–2, and prior treatment with one or two regimens as either adjuvant chemotherapy and/or chemotherapy for metastatic disease. No patient had previously received vinca alkaloids.

Neurological assessment

The overall severity of sensory neuropathy was graded according to the WHO recommendations for grading of acute and subacute toxicity (grades 0–4). More detailed assessment of neuropathy consisted of a number of measurements, as described previously [12, 13]. All measurements were performed by one investigator without reference to the results of previous assessments in the same patient.

Neuropathic symptoms were graded on three different scales: for pain (by 11-point numerical rating scale from 0–100); for paresthesias (by five-point scale rated as absent, temporary, continuous light, continuous severe or unbearable paresthesias); for additional symptoms (as presence or absence of six other prespecified sensory symptoms; semi-quantitative range 0–6).

Neuropathic signs were assessed by five semiquantitated neurological examinations: the presence or absence of sensation of position, vibration and pinprick at the great toe (semiquantitative range 0–3); tendon reflexes at knee and ankle (semiquantitative range −4–+4); two-point discrimination distances at the hand and shin (range 5.5–18 cm); seconds before sidestep during Romberg's manoeuvre (maximum 10 s); steps before sidestep during tandem gait (maximum 10 steps).

Vibratory perception thresholds (VPT) were measured with a Vibrameter (Somedic AB, Stockholm, Sweden) performed as described previously [12, 13]. By this method, a vibratory stylus is placed on the dorsum of the second metacarpal bone of the left hand. The vibration of the stylus is increased from submarginal, until the patient indicates the perception of vibration. Next, a supramarginal vibration is decreased until the patient indicates disappearance of vibration sensation. The vibratory perception threshold is the logarithm of the average of these two limits. The vibrameter uses a vibratory frequency of 100 Hz and corrects for pressure-induced alterations in vibratory amplitude. Age-related normal values were obtained from the manufacturer [14].

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Statistical analysis

All variables were checked for normal distribution before further analysis. In this case, Student's *t*-tests were used for comparison of two sets of data. Analysis of variance, supplemented with Duncan's test, was performed for comparison of more than two different measurements. In case of homogeneously distributed data (checked by modified Shapiro-Wilk statistics [15]), associations were investigated by linear regression analysis. Otherwise, Kendall's rank correlation was used. Normally distributed data were expressed as mean ± 1 S.D., unless otherwise indicated.

RESULTS

19 patients were eligible for the study. Table 1 shows the patients' characteristics. 10 patients were treated with 135 mg/m^2; 9 patients received 175 mg/m^2. Neurological examinations were performed at various stages during follow-up. One patient withdrew before the screening visit. The total number of assessments was 45: eight before the first cycle of paclitaxel; two after the first cycle; 10 after the second cycle; two after the third cycle; 10 after the fourth cycle; one after the fifth cycle; six after the sixth cycle; six after the eighth cycle. In 15 patients, more than one assessment was made (2.8 assessments on average, range two to five).

According to WHO criteria, neuropathy was not present in any of the 8 patients who were examined at the screening visit. Neuropathy grade 1 was found in 5 out of 10 patients who had received 700–1400 mg/m^2 of paclitaxel at their last assessment. Although temporary or continuous light paresthesias were reported regularly during the second to fifth course, no increase in the incidence of these or other symptoms was found. Pain was not mentioned on any occasion.

The neuropathic parameters, obtained from 45 assessments of all 18 patients, were related to the cumulative dose of paclitaxel. Repetitive assessments were regarded as separate measurements in this part of the analysis. The associations between cumulative amounts of paclitaxel and neuropathic parameters were investigated by rank correlation analysis, since these were mostly non-linear or heteroscedastic. The cumulative amounts of paclitaxel were significantly related to the VPT (rank correlation coefficient $\tau = 0.33$; $P = 0.002$; see Figure 1) and to reflex scores ($\tau = -0.38$; $P = 0.0003$). No meaningful relationships were found with the scores for two-point discrimination, Romberg manoeuvre, tandem gait or any of the neuropathic symptom scores ($P > 0.40$–0.90).

Table 2 shows the average VPT that corresponds with increas-

Table 1. *Patients' characteristics*

	No. of patients
Number of patients eligible	19
Number of patients evaluable	18
Age (years)	
Median (range)	51 (29–72)
WHO performance status	
Median (range)	1 (0–1)
Prior chemotherapy (no. of patients)	
Cyclophosphamide	19
Fluorouracil	19
Methotrexate	8
(Epi-)Doxorubicin	15

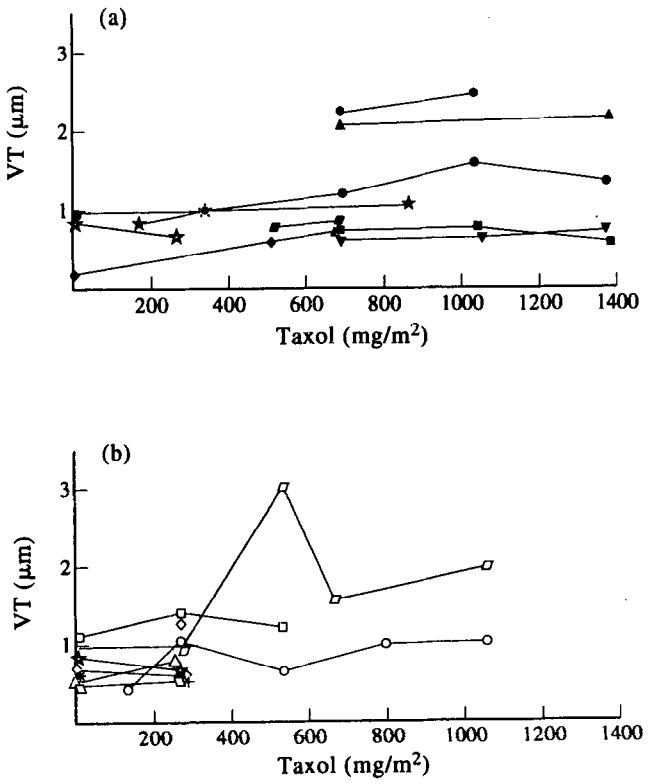

Figure 1. Association between vibratory thresholds (VPT, in μm) and individual cumulative dosages of Taxol (in mg/m²) for 45 assessments in 18 patients (rank correlation coefficient $\tau = 0.33$; $P = 0.001$). Closed symbols, 135 mg/m²; open symbols, 175 mg/m². Each line represents 1 patient, and 3 patients are represented by a single point, where only one assessment was made.

ing cumulative levels of paclitaxel. Relationships were similar among the groups of patients treated with 135 or 175 mg/m².

In the 15 patients whose measurements were repeated during the study, VPT increased significantly from 0.90 ± 0.56 μm at the first assessment to 1.13 ± 0.63 μm at the last assessment ($P = 0.026$, Student's paired t-test). The corresponding cumulative amounts of paclitaxel increased on average from about 260 mg/m² (range 0–700 mg/m²) at the first assesesment to 850 mg/m² (range 700–1400) at the last. The amounts of paclitaxel that were administered to the patients between these neurological assessments (the maximal interim cumulative amount) were linearly correlated with concomitant changes in vibratory thresholds ($r = 0.55$, $P = 0.034$). The equation of the regression line was:

$$\Delta \text{VT} = b + a \times \Delta \text{paclitaxel}, \quad (1)$$

Table 2. Cumulative amounts of paclitaxel versus VPT

Cumulative amount of paclitaxel (mg/m²)		VPT (μm) Mean ± S.D.	n
Screening	0	0.67 ± 0.29	8
Courses 1–2	< 500	0.87 ± 0.40	1
Courses 3–6	500–1000	1.24 ± 0.71	15
Courses 6–8	> 1000	1.36 ± 0.69	10

* $P < 0.05$; † $P < 0.025$ by analysis of variance with Duncan's test.

Table 3. Maximal interim cumulative amounts of paclitaxel versus concomitant changes in VPT

Interim cumulative amount of paclitaxel (mg/m²)*	Average change in vibratory threshold² (μm)†	
	Mean ± S.D.	n
< 500	0.06 ± 0.20	6
500–700	0.15 ± 0.28	5
> 700	0.58 ± 0.40	4

* Total amount of paclitaxel, administered between first and last neurological assessments. † Change in VPT between first and last assessments. ‡ $P < 0.05$; § $P < 0.025$ by analysis of variance with Duncan's test.

where Δ VT is the change in vibratory threshold between the last and the first assessment; Δ paclitaxel is the corresponding interim cumulative amount of paclitaxel (in mg/m²); $a = 6.15 \times 10^{-4}$ [standard error (SE) = 2.58×10^{-4}; $P = 0.034$]; $b = -0.135$ (SE = 0.170; $P > 0.40$).

This association is further shown in Table 3. No such associations were found with the other neuropathic parameters. The correlations were similar between two treatment regimens (135 or 175 mg/m²).

An increase in the cumulative amount of paclitaxel is hence clearly associated with an increase in VPT. A significant number of VPTs became abnormal during treatment. 2 of the 8 patients that were evaluated at the screening visit already had an elevated VPT, while VPT was abnormal in 9 out of 10 patients who had received at least 700 mg/m² of paclitaxel at their last assessment.

To establish whether paclitaxel had a neurotoxic threshold, rank correlation analysis was repeated after stepwise restriction of the range of values of cumulative amounts of paclitaxel from 1400 mg/m² downward. Correlations remained significant over a wide range of values, from 0–1400 mg/m² ($P = 0.001$; $n = 45$) down to 0–540 mg/m² ($P = 0.046$; $n = 25$). This indicates that paclitaxel has a rather low neurotoxic threshold, if any. These results are compatible with paclitaxel neurotoxicity that increases over the entire range of its cumulative amounts. From equation 1, it can be calculated that the vibratory threshold increases by 0.1 μm, on average, with every three courses of 135 mg/m² and with every two courses of 175 mg/m² paclitaxel.

DISCUSSION

In the present study patients were treated with two different doses of paclitaxel, 135 and 175 mg/m², below the assumed safety limit for toxicity [6, 9]. Patients were studied at a wide range of cumulative amounts of paclitaxel, from 135 to 1400 mg/m², administered during one to eight cycles. Neuropathy was evaluated by semi-quantitated assessment of signs and symptoms, and by measurement of VPT. The study was aimed at assessment of neuropathy at regular intervals in the two groups of patients. Unfortunately, not all patients could be evaluated according to protocol. There was no indication that non-compliance was related to the occurrence of neuropathy. Despite these imperfections, clear results were obtained, indicative of unequivocal effects of paclitaxel on the peripheral nervous system.

Disappearance of reflexes and elevation of VPT were found to be associated with the amounts of paclitaxel that the patients had received. Quantitative VPT assessment constitutes the most

reliable and most sensitive of these neuropathic characteristics [13, 14]. VPT is closely correlated with most clinical features of cisplatin neuropathy [12], and has been used as the single most important parameter of changes in cisplatin-induced polyneuropathy, during treatment with an ACTH (4–9) analogue [12]. In the present study, changes in VPT between the first and the last measurements were closely related to the cumulative amounts of paclitaxel that were administered. On average, VPT increased 0.1 μm for every 400 mg/m^2 of paclitaxel. From the normal relationship between VPT and age [14], it can be estimated that an increment of 0.1 μm corresponds to an increase in age of 10 years, for an average 50-year-old healthy individual. VPT had thus gradually become abnormal in 9 out of the 10 patients who were last assessed after administration of at least 700 mg/m^2 of paclitaxel. 5 of these 10 patients had clinical symptomatic neuropathy (50%). One of these 5 patients was treated with 135 mg/m^2 per cycle; the other four with 175/mg/m^2. This reflects the larger proportion of patients receiving 175 mg/m^2 per cycle, among those who reached a cumulative amount of 700 mg/m^2 or more (2 versus 8 patients). By contrast, none of the 8 patients who were examined before paclitaxel was dispensed had neurological signs. Neuropathy was first noted after two courses of paclitaxel, in 30% (3/10) of the patients who were studied at that time. The neuropathy was mild and paresthetic in all cases and never exceeded grade 1, according to the WHO criteria. No dose reduction or withdrawal from treatment was necessary because of neuropathy. At the relatively low single doses of paclitaxel employed in this study, there was no indication that the severity of neuropathic symptoms increased with higher cumulative amounts. Grade 2–3 neuropathy has been reported in trials when higher doses of paclitaxel were used [5, 11]. Neuropathy was the dose-limiting toxicity at paclitaxel doses of 250 mg/m^2 or higher, per cycle [6, 9]. Although cumulative neurotoxicity had already been reported at higher dosages [3], this report is the first showing cumulative toxicity at lower dosages with prospective neurologic assessments.

The neurotoxic effects of paclitaxel are probably related to its unique cytotoxic mechanism, by enhancement of the formation of microtubules bundles. It thus interferes with the mitotic spindle in cellular division and deforms the cytoskeleton in several tissues, including dorsal ganglia, axons and Schwann cells [4, 16–18]. Newly derived axonal sprouts seem particularly sensitive to paclitaxel [19, 20].

We conclude that paclitaxel has a cumulative neurotoxicity which increases with each cycle, although without clear indications of a neurotoxic threshold, if the dose per cycle is low (135 or 175 mg/m^2). If a clinical neuropathy develops with these regimens, the toxicity is mild (grade 1) up to a cumulative dose of 1400 mg/m^2.

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