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K. Mross · N. Holländer · B. Hauns · M. Schumacher
H. Maier-Lenz

The pharmacokinetics of a 1-h paclitaxel infusion

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Abstract *Purpose*: To characterize the disposition of paclitaxel (PAC) after a 1-h infusion in humans and define if possible a pharmacodynamic relationship between PAC disposition and the observed toxicity. *Patients and methods*: PAC pharmacokinetics were studied in 43 courses of therapy in 30 patients (30 first course, 13 PK third course). PAC was administered at 150, 175, 200, 225 and 250 mg/m^2 by a 1-h infusion to patients with advanced cancer (lung, breast, ovarian, cervix, and head and neck). PAC was quantified by high-performance liquid chromatography (HPLC). Pharmacokinetic parameters were calculated by non-compartmental and model-dependent methods. *Results*: Increases in the area under the curve and the peak plasma concentration were not proportional to increases in the dose. However, the deviation from linearity is rather moderate. The dose-limiting toxicity was central neuropathy which was not associated with pharmacokinetic deviations. Owing to the absence of grade 3 or 4 myelotoxicity, no clear correlation between this toxicity and pharmacokinetic parameters could be established. *Conclusion*: Within the evaluated dose range of the 1-h infusion there was only a moderate nonlinear disposition of PAC in humans and therefore a dose of 225 mg/m^2 is recommended as safe. The observation of central neuropathy could not be directly related to a pharmacokinetic parameter. The complexity of the formulation which included Cremophor EL and ethanol may offer an explanation for the observed central neurotoxicity.

K. Mross (✉) · B. Hauns · H. Maier-Lenz
Department of Medical Oncology and Clinical Pharmacology, Tumor Biology Center at the Albert-Ludwigs-University Freiburg, Breisacherstrasse 117, 79106 Freiburg, Germany
e-mail: mross@tumorbio.uni-freiburg.de

N. Holländer · M. Schumacher
Institute of Medical Biometry and Medical Informatics, Albert-Ludwigs-University, Germany

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Introduction

Since 1987 several clinical studies have evaluated the administration of paclitaxel (PAC) by 120-h [31], 72-h [4], 24-h [33], 6-h [34], 3-h [27], and 1-h [14] infusion. The speed of PAC development was initially hampered by hypersensitivity reactions which were observed in patients treated with five repeated daily 1-h infusions [13]. Therefore the duration of the infusion was increased to 24 h or even longer because it appeared that the trials that had used longer infusion durations had a lower incidence of hypersensitivity reactions.

Two other aspects that have been the subject of study are the optimal dose and infusion time of PAC. In a randomized trial of PAC in relapsed ovarian cancer, 175 mg/m^2 versus 135 mg/m^2 and 24-h versus 3-h infusion have been evaluated [9]. The 24-h infusion has been approved in the US by the Food and Drug Administration for routine use. In Europe the 3-h infusion schedule has been approved and is the most common procedure for PAC administration and allows hospitalization to be avoided. However, a 3-h infusion is still rather cumbersome in the outpatient setting because premedication is still necessary at least 1 h before PAC administration. A further decrease in the infusion time to 1 h has been undergoing evaluation since 1994 [14]. In a randomized phase I/II trial either 135 mg/m^2 was given as a single dose over 1 h or 135 mg/m^2 was administered in divided daily doses for 3 days, each over 1 h. No significant differences in toxicity were found. In a further randomized trial 135 and 200 mg/m^2 PAC (1-h infusion) were studied in non-small-cell lung cancer patients [15]. The response rate was significantly higher in patients who received the 200 mg/m^2 dose than in those who received 135 mg/m^2 (31% versus 12%, $P < 0.05$) and myelosuppression was mild even at the higher dose (200 mg/m^2) with only 12% of courses resulting in grade

3 or 4 leukopenia. Even in 1997 the same investigators stated that the optimum dose and schedule of PAC remains under investigation [12] while they are now combining 225 mg/m^2 PAC with carboplatin AUC 6 (Calvert formula).

The missing classical phase I dose-escalation study with PAC 1-h infusion has recently been performed [21]. This study has confirmed that this schedule leads to only minor myelosuppression even at the highest dose level and has determined for the first time the dose-limiting toxicity (DLT) which is a reversible central neuropathy at a dose of 250 mg/m^2. Pharmacokinetic studies carried out in 1993 and 1995 of different PAC dosages (135–225 mg/m^2) and different infusion times (3 h and 24 h) have shown that the disposition of PAC seems to be nonlinear [10, 17, 19], which has important practical implications for the optimal clinical use of PAC. We present the results of a pharmacokinetic study which was performed in addition to a clinical dose-escalation phase I study [21].

Patients and methods

The pharmacokinetics of PAC were studied in 43 cycles of therapy administered to 30 patients. Patients were required to have proven locally advanced, locally recurrent or metastatic cancer of different origins (lung, breast, ovarian, cervix, and head and neck). The median age was 56 years (range 27–74 years), and the median performance status was 1 (range 0–2). No patient had evidence of major alterations in hepatic, renal, or cardiac function at the time of study. PAC was escalated from a starting dose of 150 mg/m^2 to 250 mg/m^2 which was the maximum tolerated dose (MTD) at which DLT (central neuropathy) was observed in two out of five patients.

Ampoules containing 30 mg PAC formulated in Cremophor EL/ethanol (1:1 vol/vol) were provided by Bristol Myers Squibb (München, Germany). For patient administration, paclitaxel was diluted in 500 ml 5% dextrose in water and given to the patient via a peripheral or central venous catheter using a motor-driven programmable infusion pump (Model 598, IVAC Corporation, San Diego, Calif.) over a 1-h period. Premedication was uniform for all patients and consisted of 20 mg dexamethasone, 2 mg clemastine, and 300 mg cimetidine, all three drugs administered intravenously 30 min prior PAC. The protocol was approved by the local ethical committee. All patients gave their written informed consent before entering the clinical and pharmacokinetic study.

Pharmacokinetic study design

Evaluation of PAC pharmacokinetics was planned for the first, third and sixth treatment cycle. Evaluation of the sixth treatment cycle was not possible owing to the small number of patients who received all six cycles. In each patient a blank plasma for evaluation of possible interfering peaks in high-performance liquid chromatography (HPLC) was drawn before PAC was administered. Blood samples for analysis of PAC were obtained at 0.5, 1, 1.5, 2, 3, 4, 12, and 24 h after the start of PAC infusion. All blood samples were drawn from a vein in the arm opposite to that used for PAC infusion. Samples were collected in 10-ml polypropylene tubes containing 75 IU ammonium-heparinate (Sarstedt Monovette System, Germany). Plasma was immediately separated by centrifugation at 2000 *g* for 10 min at 4 °C, aliquoted in 1.5-ml fractions in polypropylene vials and stored at −20 °C until analysis.

HPLC determination of paclitaxel

PAC and 7-epi-PAC (a degradation product of PAC used as internal standard) were provided by Bristol Myers Squibb, München, Germany. PAC and 7-epi-PAC in plasma were determined by a previously described HPLC method [35]. This method was adapted and validated in our analytical laboratory. Standard curves (range 10–1500 ng/ml) for the quantitation of PAC were prepared for each patient using plasma samples from healthy volunteers. Different amounts of PAC as well as the internal standard (7-epi-PAC) were added to blank plasma samples. A solid-liquid extraction procedure was used. Samples were isocratically eluted and monitored using a UV detector at 227 nm. Patient samples were spiked with the internal standard and processed in the same way as samples for the calibration line. Concentrations of PAC were calculated by determining the ratio of the PAC signal to the internal standard signal in that sample and comparison of that ratio with a concomitantly performed standard curve. There was no material in pretreatment plasma samples that interfered with the peaks of PAC and 7-epi-PAC. The standard curves were calculated by the use of a 1/c (where c is concentration) weighted linear regression method. PAC standard curves were linear between 10 and 1500 ng/ml with an r^2 value greater than 0.99 in all instances (the assay is in fact linear up to 10,000 ng/ml). The limit of detection was 2 ng/ml (accuracy >10%) and the limit of quantification was 10 ng/ml (accuracy <10%). The coefficient of variance (CV) for the within-day precision ranged from 0.3 to 3.0, and the CV for the day-to-day precision ranged from 0.8 to 3.1. The recovery ranged from 103% (50 ng/ml) to 92% (1500 ng/ml).

Pharmacokinetic analysis

The pharmacokinetics of PAC were evaluated by both noncompartmental and model-dependent methods. For model-dependent analysis a two-compartment model was used. The plasma concentration time curves were modeled by the biexponential function $c_p(t) = A \times e^{-\alpha t} + B \times e^{-\beta t}$. Based on the observations after infusion (i.e. using seven data points starting at t_{max}), A, B, α and β were estimated by using nonlinear least-squares regression with weights 1/c. This weighing scheme was chosen because of the variability of the underlying HPLC method noticed during the assay validation procedure [16]. In particular, the observed decrease in CV with increasing dose for the within-day precision did not support the model assumption of a constant coefficient of variation. A detailed description of the corresponding analysis cannot be given in this paper. Reference 16 can be obtained via http://www.fdm.uni-freiburg.de/Preprints/Preprints.html or via personal communication.

Half-lives and volume of distribution at steady-state were obtained as $t_{1/2,\alpha} = \log(2)/\alpha$, $t_{1/2\beta} = \log(2)/\beta$ and $Vd_{ss} = (k_{21} + k_{12}/k_{21}) \times (\text{dose}/A + B)$ where $k_{12} = (\alpha + \beta) - k_{21} - k_{e1}$ is the transfer rate from the central to the tissue compartment, $k_{21} = \alpha + (\beta - \alpha) \times (A/[A + B])$ is the transfer rate from the tissue to the central compartment and $k_{e1} = \alpha \times \beta / k_{21}$ denotes the elimination rate of the drug, all of them assumed to be constant [11]. For all calculations the statistical software package SAS [23, 26] was used. The total area under the curve was estimated by $AUC_{tot} = AUC_{0-24h} + c_p(24h)/\beta$ where AUC_{0-24h} was calculated by the trapezoidal rule [2] and the extrapolation from the last observed plasma concentration [c_p(24 h)] to infinity was based on β. The total body clearance was calculated by $Cl_{TB} = \text{dose}/AUC_{tot}$.

To investigate the possibility of nonlinearity of PAC, we compared the data with a line from the origin (dose = 0, $C_{max}/AUC_{tot} = 0$) through the mean value for 150 mg/m^2. This line would be expected if C_{max} and AUC_{tot}, respectively, increased linearly in proportion to dose. Furthermore, we fitted a regression function for AUC_{tot} and C_{max} by using a linear and quadratic term for dose, $\beta_1 \times$ dose and $\beta_2 \times$ dose^2. The estimated regression function was compared with a linear regression line, $\beta_0 + \beta_1 \times$ dose, obtained for the dose range of the present study.

Results

Pharmacokinetics of PAC

The median c(t) curves for each dose level are depicted in Fig. 1. Pharmacokinetic parameters obtained for the first treatment cycle of PAC are listed in Table 1, which includes the results from 30 patients. Pharmacokinetic parameters from the third cycle of PAC are listed in Table 2, which includes the results from only 15 patients because patients with progressive disease after the first or second treatment course were removed from the study. Furthermore, in the third cycle two patients were not evaluable because of missing blood samples.

Clearly, the increases in AUC_{tot} and C_{max} were not proportional to the increases in the PAC dose (Figs. 2 and 3). In both cycles the deviation from linearity was more obvious for C_{max}. However, although these results are similar to those of prior studies nonlinearity was rather moderate in the present study. As compared, for example, with the results of Kearns et al. [19], who considered doses between 135 and 300 mg/m^2, the curvature of the fitted regression function is rather weak and mainly results from the start at the origin. Restricting the interpretation to the evaluated dose range (150–250 mg/m^2) the data can equally well be described by a linear regression line with a non-zero intercept term (which is of course not proportional). A larger difference between the linear and quadratic versus the linear regression function would have been expected for a strong nonlinear relationship. These results are not surprising since in previous investigations nonlinearity was especially apparent for higher dose levels. In our

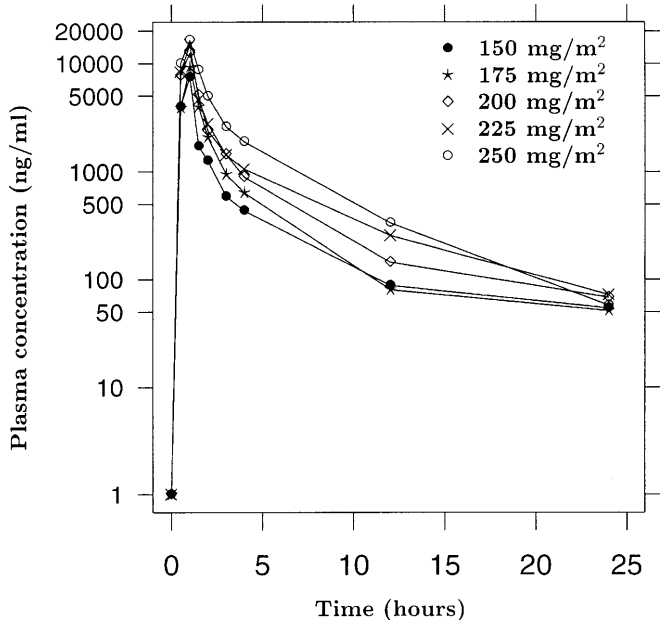

Fig. 1 c(t) curves of PAC in plasma samples from five patient cohorts (dose range 150 to 250 mg/m^2, first treatment cycle)

Table 1 Pharmacokinetic parameters obtained during the first treatment cycle

Dose (mg/m^2)	$AUC_{tot}(0–\infty)$ (ng/ml · h)		Extrapolated area (% of AUC_{tot})		C_{max} (ng/ml)		$t_{1/2}\alpha$ (h)		$t_{1/2}\beta$ (h)		V_{SS} (l/m^2)		Cl_{tot} (l/h/m^2)	
	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD
150	11,734	14,410 ± 6286 (n = 3)	1.7	1.9 ± 0.35 (n = 3)	7449	7554 ± 1190 (n = 3)	0.19	0.21 ± 0.05 (n = 3)	3.22	3.35 ± 0.91 (n = 3)	72	76 ± 16 (n = 3)	12.78	11.64 ± 4.23 (n = 3)
175	15,434	14,523 ± 1936 (n = 3)	1.5	1.6 ± 0.36 (n = 3)	9252	8641 ± 985 (n = 3)	0.33	0.30 ± 0.10 (n = 3)	2.79	3.27 ± 0.95 (n = 3)	72	65 ± 15 (n = 3)	11.25	12.18 ± 1.77 (n = 3)
200	21,277	23,788 ± 6898 (n = 12)	1.2	1.3 ± 0.82 (n = 12)	12,560	12,815 ± 3313 (n = 12)	0.27	0.27 ± 0.06 (n = 12)	3.03	3.07 ± 0.97 (n = 12)	43	46 ± 17 (n = 12)	9.42	9.00 ± 2.32 (n = 12)
225	25,821	26,506 ± 6973 (n = 7)	2	1.7 ± 0.57 (n = 7)	14,948	14,555 ± 2512 (n = 7)	0.31	0.33 ± 0.11 (n = 7)	3.70	0.33 ± 0.11 (n = 7)	61	58 ± 20 (n = 7)	8.74	8.98 ± 2.30 (n = 7)
250	36,506	35,018 ± 12,758 (n = 5)	0.6	0.7 ± 0.24 (n = 5)	16,481	19,167 ± 5324 (n = 5	0.26	0.33 ± 0.14 (n = 5)	2.84	3.10 ± 1.08 (n = 5)	35	36 ± 6 (n = 5)	6.85	8.05 ± 3.19 (n = 5)

Table 2 Pharmacokinetic parameters obtained during the third treatment cycle

Dose (mg/m^2)	AUC_{tot} (0–∞) (ng/ml · h)		Extrapolated area (% of AUC_{tot})		C_{max} (ng/ml)		$t_{1/2\alpha}$ (h)		$t_{1/2\beta}$ (h)		V_{SS} (l/m^2)		Cl_{tot} (l/h/m^2)	
	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD
150	–	8394	–	0.0	–	5109	–	0.28	–	1.88	–	62	–	17.90
		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)
175	–	26,488	–	1.2	–	13,594	–	0.37	–	3.20	–	33	–	6.56
		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)
200	18,527	18,489 ± 6125	1.5	1.4 ± 0.47	10,267	11,297 ± 2589	0.33	0.35 ± 0.12	3.90	3.78 ± 1.04	55	57 ± 23	10.80	11.92 ± 4.38
		(n = 5)		(n = 5)		(n = 5)		(n = 5)		(n = 5)		(n = 5)		(n = 5)
225	32,557	31,239 ± 3294	1.8	2.0 ± 1.6	18,321	17,746 ± 2568	0.26	0.26 ± 0.09	3.02	3.25 ± 0.60	41	42 ± 10	6.94	7.25 ± 0.74
		(n = 5)		(n = 5)		(n = 5)		(n = 5)		(n = 5)		(n = 5)		(n = 5)
250	–	25,192	–	0.4	–	19,312	–	0.19	–	2.05	–	39	–	9.92
		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)		(n = 1)

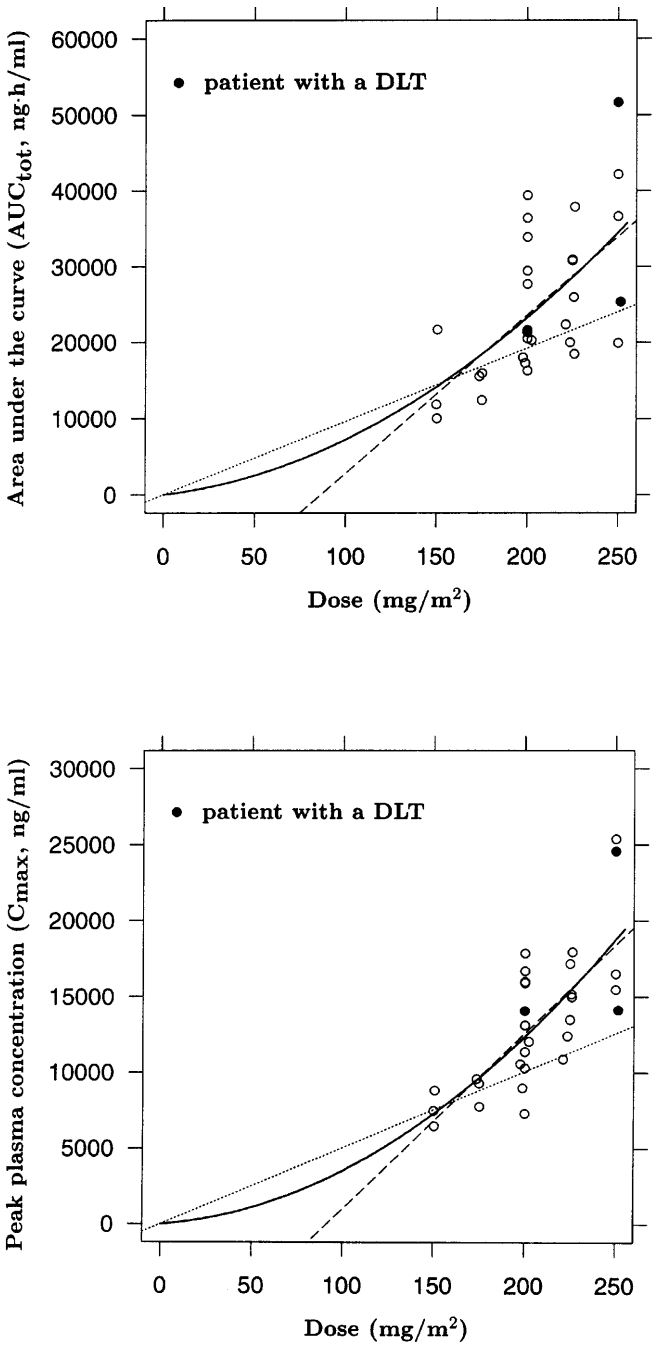

Fig. 2 Correlation between area under the curve and dose and between peak plasma concentration and dose (first treatment cycle). Patients with DLT are labelled (*solid circles*). The *dotted line* represents linearity, the *solid line* shows the fitted regression function using a linear and a quadratic term for dose and the *long dashed line* shows the linear regression function estimated within the observed dose range

study DLT was observed at 250 mg/m^2 and therefore we did not investigated higher dose levels as did Kearns et al. [19] and Beijnen et al. [3], for example.

There was no indication of cumulative effects in the pharmacokinetic terms, but firm conclusions are difficult because of the very small patient cohorts available for

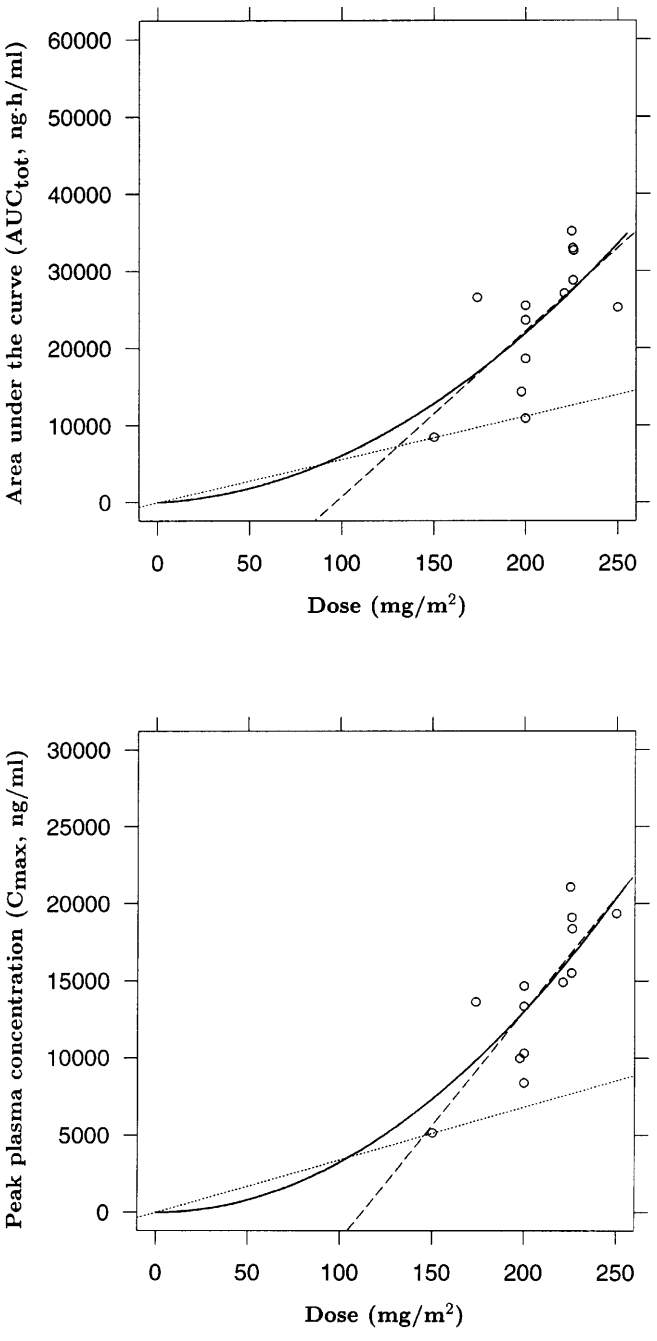

Fig. 3 Correlation between area under the curve and dose and between peak plasma concentration and dose (third treatment cycle). The *dotted line* represents linearity, the *solid line* shows the fitted regression function using a linear and a quadratic term for dose and the *long dashed line* shows the linear regression function estimated within the observed dose range

comparison. The results reveal considerable inter- and intraindividual variability of the pharmacokinetic parameters. The former is clear from Tables 1 and 2 and the latter is illustrated in Fig. 4, which is based on the results from 15 patients receiving the first and third course. The dashed lines correspond to a deviation of −25%, 0% and 25%. Several patients showed a substantial deviation between the two cycles. Strong decreases and strong increases in the values of C_{max} and AUC_{tot} were observed. The factors that are under the control of the investigator have been discussed in detail recently [16].

Those patients with a DLT (two central and one peripheral neuropathy) showed no significant deviations from the pharmacokinetic parameters of the entire study population (these patients are labelled in Fig. 2). Although no grade 4 toxicity was observed at the two

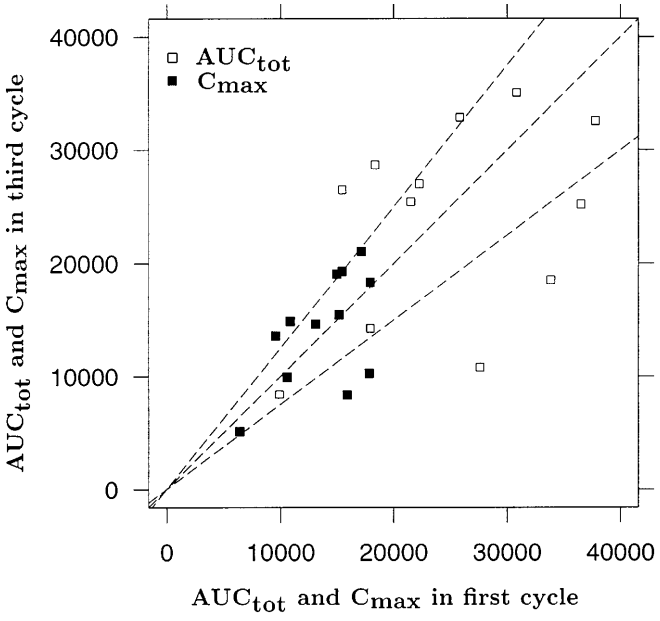

Fig. 4 Variance between AUC_{tot} and C_{max} determined during the first and the third treatment cycles

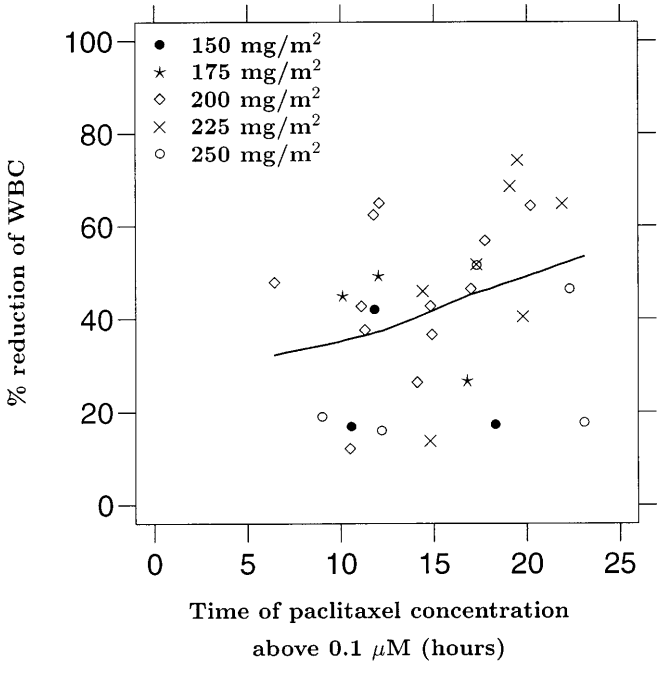

Fig. 5 Correlation between time above a PAC concentration of 0.1 μM and reduction in the WBC count

highest dose levels a reduction in the white blood cells (WBC) with increasing dose was observed. The reductions in WBC were 25% (150 mg/m^2), 40% (175 mg/m^2), 45% (200 mg/m^2), 51% (225 mg/m^2) and 30% (250 mg/m^2). At 24 h (the last measurement point) the plasma concentrations of PAC were always higher than 0.05 μM (=17.1 ng/ml). PAC concentrations above a threshold value of 0.1 μM (=85.4 ng/ml) were observed for 13.6 h (150 mg/m^2), 13.0 h (175 mg/m^2), 13.5 h (200 mg/m^2), 18.1 h (225 mg/m^2) and 16.8 h (250 mg/m^2) (mean values; time was derived from the fitted bi-exponential function). No significant relationship (e.g. according to an E_{max} model) was seen when the percentage reductions in white blood cells were plotted against the corresponding time above 0.1 μM paclitaxel in all patients. The myelotoxicity was related to the dose or to the time above a certain threshold concentration (Fig. 5). The smoothing line suggests a slight but not significant increase. The fact that we did not observe any reduction in WBC greater than 80% (only 8/30 patients, or 27%, had a WBC reduction between 50% and 80%) agrees with the absence of any significant and clinically relevant myelotoxicity of 1-h PAC infusion.

Discussion

The data from the present study complement and expand previous knowledge of the clinical pharmacology of PAC, especially for the 1-h infusion procedure for PAC administration. Most pharmacokinetic data on paclitaxel have been gathered during phase I clinical trials in which the drug was given as a 1-h infusion (dose range 15 to 30 mg/m^2) [13], 3-h infusion (dose range 135 to 225 mg/m^2) [10], 6-h infusion (dose range 15–275 mg/m^2) [34], and 24-h infusion (dose range 110–390 mg/m^2) [25, 33]. Because severe hypersensitivity reactions were identified early in the course of phase I clinical trials when PAC was administered as short infusions without premedication [1], the length of administration was increased and a premedication regimen that included steroids and H_1 and H_2 histamine receptor blockers was introduced [32]. After cessation of the infusion, the disappearance of PAC from the plasma was generally found to be biphasic, indicating both a distribution and an elimination phase. However, by using very sensitive assays and longer plasma sampling periods (0–48 h instead of 0–24 h), an extra disposition phase appeared and a three-exponential decay gave a better description of the postinfusion c(t) curves than did a biphasic description [18].

To take nonlinearity into account, more sophisticated two- and three-compartment models introducing a Michaelis-Menten kinetic into distribution and elimination have been proposed by Sonnichsen et al. [29] and Gianni et al. [10]. In our study the limited number of data points per patient did not allow the fitting of such more complex models. However, nonlinearity was only moderate and the fit for the individual observed plasma PAC versus time profiles obtained using a linear two-compartment model was quite good. The elimination half-life, the volume of distribution and the plasma clearance calculated for a 1-h infusion of PAC are similar to those summarized recently [24].

Early phase I studies with PAC indicated a linear pharmacokinetic behaviour with the clearance independent of dose and, consequently, a linear relationship between area under the c(t) curve (AUC) and dose. However, a comprehensive retrospective analysis has shown a linear relationship between dose (50–275 mg/m^2) and AUC for PAC given as a 24-h infusion, indicating linear kinetics. Combining data from different studies in which PAC was given as a 6-h infusion has shown nonlinear pharmacokinetics with doses higher than 250 mg/m^2. The same phenomenon has been shown for a 3-h infusion [3]. This nonlinear pharmacokinetic behaviour at higher dose levels has been confirmed in a prospective study [10] and can be explained by a saturable elimination system. It has been shown that 6α-hydroxy-PAC is the major, but 30 times less active, metabolite of PAC. Both the hydrophobic PAC and the less hydrophobic 6α-hydroxy-PAC are excreted mainly via the bile. Saturation or inhibition of biliary excretion would result in an increase in the AUC. The pharmacokinetic data were consistent with a saturable elimination system according to which low plasma concentrations would appear to be cleared faster than high concentrations [10].

Shortening the infusion time (from 24 h via 3 h to 1 h) would possibly mean overtaxing the elimination system for a certain time until the PAC concentration in plasma is below the saturation point. Such a clear relationship could not be established in our pharmacokinetic study (1-h infusion), but possibly we did not reach a dose level at which such saturation/inhibition processes become apparent. However, our data do not exclude such an interpretation because a slight deviation from linearity was seen.

The clinical phase I study of 1-h PAC infusion established for the first time the DLT for this schedule at 250 mg/m^2 which is the MTD [21]. The nonlinear pharmacokinetic behaviour of PAC as a 24-h infusion and as a 3-h infusion has been observed at doses higher than the MTD for the 1-h infusion. No significant myelotoxicity (grade 3 or 4) according to WHO criteria was observed, although PAC plasma concentrations were above threshold levels of 0.05 μM and 0.1 μM, respectively, for 8 to >24 h. A decrease of 50% in WBC was observed within a sigmoidal E_{max} model for approximately 15 h with PAC plasma concentrations above 0.1 μM [19]. With the same model a decrease of 50% in ANC has been observed with PAC plasma concentrations above 0.05 μM [10]. The exact WBC and ANC nadirs are in general not determined accurately because the nadirs differ from patient to patient and daily blood counts are normally not performed. An evaluation of our data did not show such a sigmoidal (time above 0.1 μM) response curve. The patient cohorts were largest

at the dose levels of 200 mg/m^2 ($n = 12$) and 225 mg/m^2 ($n = 7$). At these two dose levels the mean times above 0.1 μM were 13.5 and 18.1 h, respectively, and the reduction in WBC was highest (45% and 51%). The patient cohorts at the other three dose levels (150, 175 and 250 mg/m^2) were too small to draw any meaningful conclusions. Much more pharmacokinetic data and more precise data (WBC and ANC at the real nadir) are necessary for a clear pharmacodynamic correlation.

Still another factor is Cremophor EL, one of the constituents of the complex formulation of PAC. Cremophor EL is known to be a cell membrane-active substance interfering with p-glycoprotein 170 (Pgp-170), the gene product of the multidrug-resistance (MDR) gene [37]. This compound can inhibit Pgp-170, which is highly expressed in the bile duct epithelial cells and thus could alter the excretion of PAC and metabolites into the bile. Cremophor EL may also play a crucial role in the observed central neurotoxicity, because Pgp-170 is also highly expressed in the blood-brain barrier epithelial cells. This compound has a small volume of distribution (3.0 $\pm$ 0.34 l/m^2) and its distribution is therefore limited to the central blood compartment [6]. Cremophor EL inhibits neurite outgrowth, causes deficits in rapid axonal transport and leads to structural abnormalities in a neuroblastoma neuronal-cell model [22], induces axonal swelling, degradation and demyelination in dorsal root ganglion neurons of rats [36], and accounts for nearly all the neurotoxicity of clinically formulated cyclosporin A in vitro [5] when given intravenously. No such neurotoxicity is observed following oral drug administration of cyclosporin A [8] which can easily be explained by the fact that Cremophor administered orally is not absorbed as a result of hydrolysis in the GI tract [30].

Because we found no abnormal PAC pharmacokinetic parameters in those patients who developed central or peripheral neurotoxicity grade 3 (the DLT) other explanations have to be considered. The known neurotoxic properties of Cremophor EL suggest a causal relationship. The total amount of ethanol, the other major constituent of the PAC formulation, at the highest dose level (250 mg/m^2) was 20–25 ml which cannot be the reason for a grade 3 central neurotoxicity. Finally, docetaxel another taxoid which has been formulated without Cremophor EL shows less neurotoxicity [7]. All known aspects together led us to generate the hypothesis that the neurotoxicity of PAC is possibly caused by PAC and Cremophor EL. Research related to this problem should focus on this compound, have the aim of developing a new formulation or search for water-soluble analogs.

In conclusion, a 1-h infusion of PAC is safe within a dose range of 150–225 mg/m^2 because no DLT was observed and nonlinearity can be ignored up to 225 mg/m^2. A stronger nonlinearity (which may be dangerous for the patient) at doses above 250 mg/m^2 cannot be ruled out, but these doses are not recommended because of the observed DLT. It is not known how elevated liver function parameters can influence the pharmacokinetics of a 1-h infusion schedule. As the short-infusion PAC schedule, either weekly at lower doses (80–100 mg/m^2) or every 3 weeks (200–225 mg/m^2) [12], becomes increasingly routine, more information on the pharmacokinetics and pharmacodynamics of this schedule should become available, bearing in mind that this schedule is not yet approved by the federal authorities. Finally, the premedication cocktail itself could influence the pharmacokinetics, because biotransformation (metabolism) of PAC is catalyzed by the cytochrome P-450 system. H_2 histamine antagonists may have variable modulatory effects on the activities of many hepatic P-450 enzymes [20, 28].

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