Neurotoxicity has emerged as one of the most important and often dose-limiting toxicities associated with weekly paclitaxel therapy (1–6). Severe hematologic toxicities have become less frequent in short infusions over 1 or 3 hours, compared with former 24-hour applications, and can be managed with growth factors (1–5, 7). Paclitaxel is well known to cause both sensory and motor peripheral neuropathy by inducing axonal degeneration and demyelination (8–12). We have previously conducted a randomized clinical trial focusing on the development of a peripheral neuropathy as the primary end point in weekly paclitaxel infusions over 1- or 3-hour duration. However, a prediction of whether it would be of advantage to infuse over 1- or 3-hour was complicated by the fact that a reduction of infusion time decreases the area under the curve (AUC) of both total and unbound paclitaxel but increases the AUC of its vehicle Cremophor EL, which is known to have its neurotoxic potential as well (13, 14). In this prior trial, we could show that after 12 weeks of therapy the majority of our patients had developed a peripheral neuropathy without significant differences between the two infusion groups (6).

Prior pharmacodynamic investigations already revealed that the AUC of total paclitaxel (15–17) and unbound paclitaxel (15) and the time above total paclitaxel concentrations of 0.05 μmol/L (Tₜₐ₈₀₅) might be associated with the extent of granulocytopenia, but the relations of paclitaxel pharmacokinetics with neurotoxicity are poorly understood. The question whether a fixed dosing of paclitaxel might be of advantage compared with the common body surface area–based administration in the context of efficacy and toxicity has not been answered consistently (19, 20). Taken together, this leads to a strong demand for a further optimization of paclitaxel dosing and scheduling. Using the clinical (6) and pharmacokinetic (15) data acquired in our prior trial, the present investigation

Association of Paclitaxel Pharmacokinetics with the Development of Peripheral Neuropathy in Patients with Advanced Cancer

Stephan Mielke,1 Alex Sparreboom,3,5 Seth M. Steinberg,4 Hans Gelderblom,6 Clemens Unger,2 Dirk Behringer,1 and Klaus Mross2

Abstract

Purpose: The shortening of infusion time from 3 to 1 hour decreases the systemic exposure (area under the curve, AUC) of total and unbound paclitaxel but increases the AUC of its vehicle Cremophor EL, whereas the time above total paclitaxel concentrations of 0.05 μmol/L (Tₜₐ₈₀₅) remains almost constant. As both Cremophor EL and paclitaxel are neurotoxic, we evaluated their pharmacodynamic effects on the development of peripheral neuropathy as the most important nonhematologic toxicity.

Experimental Design: Patients with advanced cancer of different origin were randomized to receive a maximum of 12 weekly-given 1- or 3-hour infusions of 100 mg/m² paclitaxel (Taxol). Twenty-four patients were assessable for both pharmacokinetics and peripheral neuropathy development evaluated by a clinical scoring system including sensory symptoms, strength, tendon reflexes, and vibratory sense.

Results: Patients with peripheral neuropathy development (n = 14) received more weeks of therapy (P = 0.056) and showed significantly higher Tₜₐ₈₀₅ (P = 0.022) and overall systemic drug exposures (weeks of therapy × AUC) for total paclitaxel (P = 0.002) and unbound paclitaxel (P = 0.003) than those without peripheral neuropathy. In Kaplan-Meier analyses, Tₜₐ₈₀₅ ≥ 10.6 hours (P = 0.023), AUC of total paclitaxel ≥ 4.7 μg/mL × hour (P = 0.047), and AUC of unbound paclitaxel ≥ 0.375 μg/mL × hour (P = 0.095) were identified as being potential factors for peripheral neuropathy development. In a Cox regression analysis, only Tₜₐ₈₀₅ ≥ 10.6 hours remained as an independent risk factor (relative risk, 18.43; P = 0.036) after adjusting for prior vincamycin (relative risk, 11.28; P = 0.038).

Conclusions: From the results obtained in this study, it is concluded that exposure to paclitaxel but not Cremophor EL is associated with peripheral neuropathy development.

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addressed the question whether and to what extent pharmacologic variables contributed to the development of a peripheral neuropathy as the most important nonhematologic toxicity.

**Patients and Methods**

**Study design and patients.** The subset of 24 patients investigated in this pharmacodynamic study was obtained from a pharmacokinetic analysis group (n = 29; ref. 15) from a larger prospective and randomized multicenter trial designed to investigate the effects of weekly 1- or 3-hour paclitaxel infusions on cumulative peripheral neuropathy as the primary end point in patients with locally advanced or metastatic cancer for whom a monotherapy with paclitaxel was a therapeutic option (n = 121; ref. 6). It was the aim of the present study to analyze the influence of the obtained paclitaxel administration's pharmacokinetic variables on cumulative peripheral neuropathy development.

**Eligibility criteria and randomization.** Patients with histologically proven, locally advanced or metastatic cancer, for whom paclitaxel as monotherapy was a therapeutic option, were candidates for this study. Exclusion criteria included age <18 years or >75 years with Eastern Cooperative Oncology Group performance status of >2; life expectancy < 75

<table>
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<td>Numbness/paraesthesia</td>
<td>Functionally disabling</td>
</tr>
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<td></td>
<td>in the feet</td>
<td>in feet and fingers</td>
<td>numbness/paraesthesia</td>
</tr>
<tr>
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<td>Weak toe extension and</td>
<td>General/diffuse weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>weak finger abduction</td>
<td></td>
</tr>
<tr>
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<td>Single reflexes reduced</td>
<td>Single reflexes absent</td>
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</tr>
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<td>(6/8)</td>
<td>(&lt;4/8)</td>
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</tr>
<tr>
<td>D. Vibratory sense*</td>
<td>Normal (8/8)</td>
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</table>

**Table 1.** Scoring system employed for the graduation of paclitaxel-induced peripheral neuropathy as previously published (6) and modified after Berger et al. (12) and Chaudhry et al. (11)

NOTE: The individual score was obtained as the sum of the areas A to D and could therefore range from 0 (best) to 12 (worst). Clinically significant peripheral neuropathy was defined as an event when the peripheral neuropathy score exceeded the value 3 the first time (6).

*Vibratory sense had to be obtained by the tuning fork test.
Freiburg, Germany) during and until 48 hours after the end of paclitaxel administration (14 time points for 3-hour infusion and 12 time points for 1-hour infusions) and delivered to the Tumor Biology Center of Freiburg as the study center responsible for these analyses. All samples were collected in 10-mL polypropylene tubes containing 75 IU of ammonium-heparinate (Sarstedt, Germany), separated by centrifugation (10 minutes at 2,000 × g), aliquoted in 1.5-mL fractions and stored at −20°C until analysis. Concentrations of total paclitaxel were determined by reverse-phase high-performance liquid chromatography, whereas Cremophor EL analyses were based on a colorimetric dye-binding microassay. For measurement of unbound paclitaxel plasma concentrations, equilibrium dialysis using a [C-3H]paclitaxel tracer was employed.

Statistical analysis. For the statistical evaluation of the effect of the pharmacokinetic variables AUC and Cmax of paclitaxel, unbound paclitaxel, and Cremophor EL as well as T >0.05 on peripheral neuropathy development, which were obtained at the first drug application, the assumption was made that these variables remained constant during the whole course of therapy. As an initial analysis, to determine if there were differences in pharmacokinetic variables between patients with or without peripheral neuropathy development when viewed simply as a dichotomous variable, we created scatter plots and applied an unpaired two-tailed t test after confirming normality. Ps ≤ 0.05 were considered to be significant and are presented without adjustment for multiple comparisons in this exploratory analysis. Furthermore, we calculated the overall systemic drug exposure as a product of AUC∞ and weeks of therapy (overall systemic drug exposure = AUC∞ × weeks of therapy) and checked again for group differences. The nonparametric Mann-Whitney test was used to check for group differences in therapy duration and T >0.05 because these particular variables were not normally distributed.

As a more rigorous analysis, because the development of a peripheral neuropathy in course of paclitaxel therapy may be treated as an event with probability increasing as a function of weeks of therapy, another evaluation was done to determine if the pharmacokinetic variables AUC, Cmax, and T >0.05 could be used to describe the probability of developing a peripheral neuropathy as a function of weeks of therapy. To do so, exploratory analyses using the Kaplan-Meier method and the log-rank test to determine the degree to which individual pharmacokinetic variables might be associated in a univariate fashion with time to development of a peripheral neuropathy were done first (21). Values obtained for AUC, Cmax, and T >0.05 were divided into quartiles to determine their association with the primary outcome peripheral neuropathy, to identify if these results were consistent in a linear fashion with the outcome, or if dichotomizing at a quartile or the median may be more useful. For this univariate analysis, we employed the log-rank test to examine for group differences. All of the resulting Ps are two tailed and because this is interpreted as an exploratory analysis, have not been adjusted for multiple comparisons. Finally, those factors that seemed to have potential effect in the univariate analyses were then evaluated in a Cox proportional hazards model to determine if they were associated with the outcome when considered jointly (22). All graphs presented in this publication have been plotted employing Prism 4.00 for Windows software (Graph Pad Software, San Diego, CA).

Results

Participants and treatment delivery. Pharmacokinetic data were available for 29 patients. Five of them were not assessable for this analysis due to incorrect infusion durations (n = 2), unallowed dose reductions (n = 2), and an incomplete follow-up evaluation of the peripheral neuropathy score (n = 1). Thus, this pharmacokinetic analysis was ultimately based on 24 patients. Their characteristics at baseline are displayed in Table 2. Four of these patients experienced a single event of delayed (>14 days) treatment delivery (in particular 15, 17, 19, or 21 days) but were still considered eligible for this analysis. One patient refused further therapy after one completed cycle, so that only the first 6 weeks of therapy could be considered for this analysis. Within the maximum therapy duration of 12 weeks, 10 of 24 patients developed a clinically significant peripheral neuropathy. No group differences (P = 0.63) between 1- and 3-hour infusions could be observed (Fig. 1A), but patients with peripheral neuropathy development received more paclitaxel infusions than those without (Fig. 1B). A single patient with 1-hour infusions exceeded the peripheral neuropathy score of 6 at week 8 and had to be taken off protocol therapy. In course of their therapy 5 of 24 patients received dose reduction of 25% on week 3 (3-hour infusion), 7 (1-hour infusion), 7 (3-hour infusion), 11 (3-hour infusion), or 12 (1-h infusions) due to a peripheral neuropathy score from 4 to 6. No dose reduction due to other causes were done, so that all 24 patients received the same dose of paclitaxel until they developed a peripheral neuropathy or were taken off protocol therapy. Univariate unadjusted log rank analyses showed age (60-72 versus 42-59 years; P = 0.006) and prior therapy with

<table>
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</tr>
<tr>
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<td>Ovary</td>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
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<tr>
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<td>1</td>
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</tr>
<tr>
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<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Chemotherapy containing Vinca</td>
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<td>3</td>
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</tr>
<tr>
<td>Chemotherapy containing platinum</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

NOTE: A total of 24 patients were assessable for both pharmacokinetics and toxicity. Patients had been randomized to receive either 1- or 3-h paclitaxel infusions. Based on the clinical peripheral neuropathy score, 10 patients developed a peripheral neuropathy during the course of their therapy, whereas 14 patients remained free of peripheral neuropathy.

Abbreviations: PNP, peripheral neuropathy; ECOG, Eastern Cooperative Oncology Group.
vindamycin ($P = 0.033$) to be potentially related to peripheral neuropathy development (data not shown).

**Pharmacodynamics of paclitaxel and Cremophor EL.** This pharmacodynamic analysis was based on the variables AUC and $C_{\text{max}}$ which have been obtained for total paclitaxel, unbound paclitaxel, and Cremophor EL at the first paclitaxel application. For 23 patients, the $T_{\geq 0.05}$ was available. As a first step, we tested to see if there were group differences between patients with and without peripheral neuropathy development regardless of when their peripheral neuropathy development took place over time. No differences could be found for the peak concentrations of total paclitaxel, unbound paclitaxel, and Cremophor EL (Fig. 2A-C), but patients with peripheral neuropathy development showed a higher average of systemic exposure to total paclitaxel and unbound paclitaxel but not to Cremophor EL than those without peripheral neuropathy (Fig. 2D-F). However, none of these group differences was significant. In a second analysis, we considered the effects of therapy duration by calculating the overall systemic drug exposure and found that patients with peripheral neuropathy had significantly higher overall systemic drug exposures for total paclitaxel ($P = 0.002$) and unbound paclitaxel ($P = 0.003$) but not for Cremophor EL ($P = 0.1$) than those without peripheral neuropathy development (Fig. 2G-I).

Considering the duration of therapy, we did Kaplan-Meier analyses investigating the probability of developing a peripheral neuropathy over time. To do this analysis, initially values obtained for the AUC or $C_{\text{max}}$ for total paclitaxel, unbound paclitaxel, and Cremophor EL were divided into one lower and one higher level subgroup and compared with each other. These exploratory analyses showed that patients with AUC levels of $\geq 4.7 \mu g/mL \times$ hour for total paclitaxel and $\geq 0.375 \mu g/mL \times$ hour for unbound paclitaxel had a higher probability of developing peripheral neuropathy than those with levels of $<4.7 \mu g/mL \times$ hour ($P = 0.047$; Fig. 3A) or $<0.375 \mu g/mL \times$ hour ($P = 0.095$; Fig. 3B). However, only the group difference for total paclitaxel was statistically significant. For Cremophor EL, no group differences could be observed ($P = 0.70$; Fig. 3C). A similar analysis was done for the peak concentrations but failed to provide significant group differences (data not shown).

Patients with peripheral neuropathy showed significantly ($P = 0.022$) higher $T_{\geq 0.05}$ than those without peripheral neuropathy (Fig. 4A). For one patient, no value for $T_{\geq 0.05}$ was available, so that this particular analysis was based on a subset of 23 patients. Subdividing this group at tertiles and applying the Kaplan-Meier method, patients with $T_{\geq 0.05} > 10.6$ hours had a higher ($P = 0.023$) probability of developing a peripheral neuropathy than those with times below 10.6 hours (Fig. 4B).

**Cox regression analysis.** Based upon the prior exploratory analyses, prior vindamycin, age (60-72 versus 42-59 years), an AUC of total paclitaxel of $\geq 4.7 \mu g/L$, an AUC of unbound paclitaxel of $\geq 0.375 \mu g/L$, and a $T_{\geq 0.05} \geq 10.6$ hours have been found to be potentially promising factors for a Cox regression analysis. Initial models showed that age could be discarded as a factor because of its relative unimportance compared with the other variables. Models without $T_{\geq 0.05}$ could be based on 24 patients, whereas a model that included this variable was based on 23 assessable patients. Prior therapy with vindamycin remained an independent variable in both models. The relative risks, confidence intervals, and $P$ of the Cox analysis are presented in Table 3. In particular, when all three variables are considered simultaneously, model 1 shows no significant effect of AUC of total paclitaxel or unbound paclitaxel when taking prior vindamycin into account, whereas model 2 suggests that the $T_{\geq 0.05} \geq 10.6$ hours threshold remains significant after adjusting for prior vindamycin (Table 3).

**Discussion**

Both the clinical availability of growth factors and the fact that the reduction of infusion time from 24 to 3 hours diminished severe hematologic toxicities by reducing the AUC of paclitaxel contributed mainly to patient safety in current paclitaxel schedules (2, 7, 23). Nevertheless, neurotoxicity, predominantly seen as cumulative peripheral neuropathy (6, 8–10, 23), has resulted in demands for further improvement, especially as treatment options are rare or nonexistent and the application of neuroprotective agents such as
amifostine seem to lack definite benefit thus far (24). For all these reasons, the present study was undertaken to focus primarily on neurotoxicity and contributes in at least a preliminary fashion to the understanding of the complex interplay between pharmacokinetic variables and peripheral neuropathy development in infusions of 1- or 3-hour duration, which have meanwhile become a widely used standard. From previous experience, we found the applied scoring system based on patient symptoms and a clinical examination to be a valuable instrument for providing reliable information on peripheral neuropathy development especially when acquired weekly (6). However, the addition of neurophysiologic testing for peripheral neuropathy evaluation can be of predictive value as recently shown for patients treated with a combination paclitaxel and cisplatin (25).

Whereas various other studies have already discussed the association between paclitaxel pharmacokinetic variables and hematologic toxicity (15–18), this is to our knowledge the first comprehensive evaluation of pharmacodynamic effects of paclitaxel on peripheral neuropathy development. Considering the cumulative nature of peripheral neuropathy development, it was critical for this analysis to investigate the influence of the obtained pharmacokinetic variables using a statistical approach incorporating the time to peripheral neuropathy development. Selecting Kaplan-Meier analyses as the statistical tool, we found that mainly the AUCs of total paclitaxel and unbound paclitaxel contributed to the peripheral neuropathy development in univariate analyses, although these variables were not found to be independently contributing in the Cox model. This effect was also noted when estimating the overall systemic drug exposure as a product of AUC and the number of chemotherapy applications. As pharmacokinetic analyses of paclitaxel in plasma are complicated by the nonlinear behavior of this drug, which is most likely based on interactions with its vehicle Cremophor EL (26), it was important for these analyses to determine also unbound, pharmacologically active drug concentrations of paclitaxel (15). Nevertheless, at a dose level of 100 mg/m² paclitaxel as it has been given in this trial, it is likely that the AUC of total paclitaxel remained in the linear range of the dose-exposure relationship (15, 27–29).

Physiologically relevant concentrations of Cremophor EL are known to cause axonal swelling, vesicular degeneration, and demyelization in preclinical models, suggesting that increased exposure to this vehicle could lead to more treatment-related neurotoxicity (13). Interestingly, in the current analysis, no effects of Cremophor EL exposure measures on peripheral neuropathy development could be observed. This is despite the fact that the AUC for Cremophor EL is increased by the reduction of infusion time, in contrast to that of paclitaxel (15). Furthermore, we could not detect any influence of the Cremophor EL peak concentrations, which also differs significantly between 1- and 3-hour infusions, on the neurotoxic outcome. These findings are in contrast to results obtained in animal models (14, 30) but coincide with recent observations from two phase I clinical trials showing that peripheral neuropathy remained an important and often dose-limiting toxicity after administration of Cremophor EL–free, albumin-stabilized nanoparticle (31) or polymeric micellar (32) paclitaxel formulations. This altogether provides further evidence of the conjecture that the intrinsic toxic effects of paclitaxel are more important than those of Cremophor EL.
with regard to peripheral neuropathy development. Both of these phase I studies described an association between observed neuromuscular grade 3 toxicities and increased AUC or C\textsubscript{max} levels of paclitaxel; however, these differences were based on very limited number of incidents (31, 32). It should be pointed out that we investigated the pharmacodynamic effects of Cremophor EL and paclitaxel separately from each other, whereas future models simultaneously considering measures of exposure to both paclitaxel and Cremophor EL could further refine the observed associations.

Based on previously published data reporting the association between concentrations of paclitaxel exceeding a particular threshold of 0.05 \(\mu\)mol/L (\(T_{t>0.05}\)) and the extent of granulocytopenia (17, 18), we included this variable into our analysis as well. We found \(T_{t>0.05}\) to contribute to peripheral neuropathy development in the univariate analyses but also an independent factor in the Cox model. The hazard ratio of peripheral neuropathy development for patients experiencing concentrations of paclitaxel above 0.05 \(\mu\)mol/L for 10.6 hours or longer was estimated to be 18, although with very wide confidence intervals. Other studies failed to find a relation between pharmacokinetics and neurotoxicity (17, 33, 34), which could be likely because of the fact that neurotoxicity...
was not a primary end point in these trials. Further models used concentrations of paclitaxel above 0.1 \( \mu \text{mol/L} \) (\( T_{>0.1} \)) as a threshold and found it to be related to hematologic toxicity (18, 35) and therapeutic efficacy (36). As our findings are based on a relatively limited number of patients, the conduction of further clinical studies investigating pharmacodynamic effects on peripheral neuropathy as primary end point would be desirable. In this context, further both empirically based (17, 18, 35) and mechanism-based estimates (37) that remained unstudied in our analysis should be investigated for their potential effects on peripheral neuropathy development.

The delivery of docosahexaenoic acid-paclitaxel, a fatty acid–conjugated form of paclitaxel that was primarily developed to enhance the drug uptake into solid tumors, revealed no moderate or severe neurotoxicity (38). The administration of docosahexaenoic acid-paclitaxel increased the half-life of paclitaxel significantly resulting in concentrations above 0.01 \( \mu \text{mol/L} \) (\( T_{>0.01} \)) for 6 to 7 days (38). Our data suggests that peripheral neuropathy development is associated with a particular threshold of drug exposure. Thus, the extended exposure to these low concentrations of paclitaxel associated with the administration of docosahexaenoic acid-paclitaxel might not have reached the threshold required for affecting peripheral nerves. Another, more simple explanation for these findings could be again the fact that neurotoxicity was not the primary end point of this study.

An unexpectedly identified variable with moderate statistical significance in both Cox models was prior therapy with vincamycin, which exclusively appeared as a factor potentially associated with development of peripheral neuropathy in this particular subset of patients but not in our primary clinical trial (6). One explanation for this discrepancy could be the fact that only two study centers were allowed to participate in the present substudy, which could have increased the reliability and validity of the acquired data.

In this study, \( T_{>0.05} \) was the most important pharmacokinetic variable affecting the final outcome of our patients. As 1- and 3-hour infusions do not significantly differ in their \( T_{>0.05} \) (15), this study contributes to the explanation why no significant differences in terms of peripheral neuropathy development have been seen in the primary clinical trial (6). From these experiences, we conclude that both 1- and 3-hour infusions are equally safe with respect to neurotoxicity. Furthermore, we believe that a further optimization in paclitaxel scheduling by adapting the infusion duration alone does not seem achievable. We strongly encourage further research in this area, which should include the development and investigation of neuroprotective agents accompanying paclitaxel therapy. Recent data revealed a decrease of nerve growth factor levels in plasma to be related to and predictive for peripheral neuropathy development (39), which could also be a target for a clinical application.

Acknowledgments

We thank Professor Roland Mertelsmann (Department of Hematology and Oncology, University Medical Center of Freiburg, Germany) for his support.


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