Clinical Pharmacokinetics and Pharmacodynamics of Paclitaxel: A 3-Hour Infusion versus a 24-Hour Infusion

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ABSTRACT

The present study was conducted to compare the pharmacokinetics and pharmacodynamics (PD) of paclitaxel between Phase I trials of 3- and 24-h infusions and to determine the most informative pharmacokinetic parameter to describe the PD. Twenty-seven patients were treated in a Phase I study of paclitaxel by a 3-h infusion at one of six doses: 105, 135, 180, 210, 240, and 270 mg/m². Pharmacokinetic data were obtained from all patients. Paclitaxel concentrations were measured in the plasma and urine using HPLC. The pharmacokinetics and PD were compared with those of a Phase I trial of paclitaxel by a 24-h schedule previously performed. The maximum tolerated dose of paclitaxel by a 3-h infusion was determined to be 240 mg/m². The major toxicities were granulocytopenia, neuromuscular toxicities, and hypotension. Apparent differences in pharmacodynamic relationships for the change in granulocytes with dose, peak concentration, and areas under the concentration versus time curve were observed between the 3- and 24-h schedules. However, the relationship between the duration of plasma concentration above 0.05 µM and the change in granulocytes could be fitted to the same sigmoid maximum effect model in either schedule (P < 0.01). There were no clear relationships between peripheral neuropathy or hypotension and any pharmacokinetic parameters. The pharmacokinetics and PD of paclitaxel were schedule dependent. The duration of plasma concentration above 0.05 µM could be a common pharmacokinetic parameter predicting granulocytopenia for both schedules.

INTRODUCTION

Paclitaxel is a novel diterpenoid originally isolated from the stem bark of the western yew, Taxus brevifolia (1). Clinically, it has been shown to have significant antitumor activity in ovarian cancer (2, 3), breast cancer (4, 5), lung cancer (6), and head and neck cancer (7). Until recently, various infusion schedules, including 1–6-h (8, 9), 3-h (10, 11), 6-h (12, 13), 24-h (14), 96-h (15) infusions and 5-day intermittent schedule (16), have been tried. Nevertheless, at the present time, the optimal dose and schedule of paclitaxel remains unknown.

In vitro studies in several cell lines showed that both concentration and schedule may affect the biological effect of paclitaxel (17–19). The previous clinical study in a 2 × 2 factorial design, 2 doses (135 mg/m² and 175 mg/m²) and 2 infusion schedules of paclitaxel (3 and 24 h), demonstrated that a 3-h infusion could produce the same response rate and a much lower frequency of neutropenia and neutropenic fever (20, 21). The results as of yet cannot be extrapolated to other patient populations. To clear the mechanism of different pharmacodynamic behaviors between different infusion schedules and to design the rational treatment schedule, detailed pharmacokinetic analyses are essential.

We conducted two independent Phase I studies of paclitaxel: (a) by a 24-h infusion schedule using the lowest dose of 49.5 mg/m² and (b) by a 3-h infusion schedule using six dose levels. Clinical features and pharmacokinetics of the Phase I study by the 24-h schedule were reported previously (22). The toxicities of paclitaxel were quite different between the two administration schedules. Granulocytopenia was more severe in the 24-h schedule, while the 3-h schedule more frequently induced peripheral neuropathy and myalgia. In addition, hypotension was observed only in the 3-h infusion. The MTDS of paclitaxel were also different, 180 mg/m² for the 24-h schedule and 240 mg/m² for the 3-h schedule. The purposes of this study were: (a) to compare the PK and PD of paclitaxel between Phase I studies of 3- and 24-h infusion, (b) to examine the relationship between PK and PD, and (c) to determine the most informative pharmacokinetic parameter to describe the PD.

PATIENTS AND METHODS

Patient Selection

Between March 1993 and December 1993, 30 patients were entered into a Phase I trial of paclitaxel by a 3-h schedule, and 27 of them were treated with paclitaxel at the National Cancer Center Hospital (Tokyo, Japan) and National Cancer Center Hospital East (Chiba, Japan). All patients had a histo-

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2 To whom requests for reprints should be addressed.

The abbreviations used are: MTD, maximum tolerated dose; PK, pharmacokinetics; PD, pharmacodynamics; ECOG, Eastern Cooperative Oncology Group; Cmax, maximum plasma concentration; AUC, area under the concentration versus time curve; MRT, mean residence time; CL, total clearance; % D, percentage decrease; DLT, dose-limiting toxicity; Vss, volume of distribution at steady state; t1/2, apparent elimination half-life.
logically or cytologically proven solid tumor refractory to conventional therapy or for which no effective therapy exists.

Eligibility criteria included the following: (a) ages between 15 and 74 years; (b) an ECOG performance status of 0, 1, and 2; (c) full recovery from toxic effects of prior therapy; (d) adequate hematopoietic (WBC ≥ 4,000/mm³, hemoglobin ≥ 10.0 g/dl, and platelets ≥ 100,000/mm³), renal (creatinine ≤ 1.5 mg/dl and urea nitrogen ≤ 25 mg/dl), and hepatic (total bilirubin ≤ 1.5 mg/dl, transaminase and alkaline phosphatase ≤ 2 times upper normal limits) function; (e) stable sinus rhythm with no clinical heart disease; and (f) absence of moderate or severe peripheral neuropathy. The protocol was accepted by the Institutional Review Board. Written informed consent was obtained from all patients according to the institutional guidelines.

The Phase I study by a 24-h infusion, the entry period of which was October 1991 and August 1992, was conducted at the National Cancer Center Hospital, and eligibility criteria were the same as those for the 3-h infusion schedule (22).

Drug Administration and Dose Escalation

For the study, paclitaxel was supplied by Bristol-Myers Squibb K.K. (Tokyo, Japan) as a concentrated sterile solution with 6 mg/ml in a 5-ml vial in polyoxyethylated castor oil (Cremophor EL) and dehydrated alcohol (1:1 v/v). The drug was administered as a continuous i.v. infusion over 3 h in 500 ml 5% glucose. On the other hand, one half of the total dose was diluted in 500 ml 5% glucose and infused over 12 h for two treatments in the 24-h schedule. Glass or polypropylene bottles and polyethylene-lined nitroglycerin tubes with in-line filters of 0.22 μm were used.

The patients were pretreated with 20 mg i.v. dexamethasone 7 and 14 h before paclitaxel, 50 mg i.v. ranitidine, and 50 mg diphenhydramine p.o. 30 min before paclitaxel to prevent the hypersensitivity reaction. Continuous electrocardiogram telemetry was performed during and after the infusion of paclitaxel for 24 h. Patients in the 3-h schedule received paclitaxel at one of the six doses: 105, 135, 180, 210, 240, and 270 mg/m². At least three patients were treated at each dose level. MTD was defined as the dose level at which two of three to six patients experienced the following end points: (a) grade ≥ 3 nonhematological toxicity, (b) grade 4 leukaemia or thrombocytopenia, and (c) grade 4 granulocytopenia for more than 7 days. The final determination of MTD or further dose escalation was made by a monitoring committee consisting of three independent members. The dosage that is one level lower than the MTD was defined to be the recommended dose for Phase II studies. ECOG Common Toxicity Criteria (23) were used for evaluating the toxicities.

The doses given in the Phase I study by the 24-h infusion schedule were 49.5, 75, 105, 135, and 180 mg/m² (22).

Criteria of Response

Responses were evaluated in patients with measurable diseases in accordance with the ECOG criteria (23).

Pharmacokinetics

Pharmacokinetic Sampling. Plasma and urine samples for pharmacokinetic evaluation of paclitaxel were collected from all patients in the 3-h schedule group in their first course of therapy. Heparinized blood samples were obtained before the treatment and at the following times: 90 min into the paclitaxel infusion, at the end of the infusion, at 5, 15, and 30 min, and at 1, 2, 3, 4, 6, 12, 24, and 48 h after the end of the infusion. Urine samples were collected before treatment with paclitaxel and during 0–15, 15–27, 27–51, and 51–75 h after the beginning of paclitaxel infusion. Immediately separated plasma and urine were frozen at −40°C until assayed. In the 24-h schedule, blood sampling was done before infusion, at 1, 3, 6, 12, 18, and 24 h during the infusion, as well as at 5, 15, 30 min and 1, 2, 3, 4, 6, 12, 18, 24, and 36 h after the infusion.

Analytical Technique. Concentrations of paclitaxel in plasma and urine were determined using HPLC with n-hexyl p-hydroxy benzoate (Tokyokasei, Tokyo, Japan) as an internal standard. The HPLC system consisted of a LC-9A chromatograph system (Shimadzu, Kyoto, Japan), SIL-6B autoinjector, SPD-6AV UV detector at 227 nm, and chromatopac C-R4A data-processor. Plasma samples (0.5 ml) diluted with 2 ml water were applied to a solid-phase extraction column, Sep-Pak C₁₈ cartridge (Waters Associates, Milford, MA), and conditioned with 5 ml acetonitrile followed by 10 ml water. Internal standard solution diluted with water (2 ml, 1 μg/ml) was added to the column and the column was washed with 2 ml 30% acetonitrile in water. Paclitaxel and n-hexyl p-hydroxy benzoate were eluted with 4 ml acetonitrile. The eluant was evaporated to dryness under reduced pressure at 40°C. The residue was reconstituted in 200 μl 45% acetonitrile-55% 2 mm H₂PO₄, and 100 μl of the reconstituted sample were injected onto the HPLC column. The samples over 2 μg/ml were diluted with water to more than five times and processed. HPLC was performed on Inersil ODS-5 (4.6 × 150 mm, 5 μm; GL Science, Tokyo, Japan). The mobile phase was acetonitrile-0.01 m KH₂PO₄ (45:55) at a flow rate of 1.5 ml/min. The retention time of paclitaxel and n-hexyl p-hydroxy benzoate was 12 and 17 min, respectively. The recovery of paclitaxel was as high as that of n-hexyl p-hydroxy benzoate (>98%). The paclitaxel concentration was quantitated by linear regression analysis of the peak height ratio (paclitaxel: n-hexyl p-hydroxy benzoate) versus the standard curve generated from the solution of paclitaxel with n-hexyl p-hydroxy benzoate diluted with acetonitrile-2 mm H₂PO₄ (45:55). Urine samples were processed in a similar manner and analyzed under similar conditions. A linear relationship was obtained in the range of 0.015–2.0 μg/ml in plasma and 0.02–2.0 μg/ml in urine. The accuracy and between-day precision at 2.0 μg/ml were within 6% for plasma and urine. The samples obtained in the 24-h schedule were also analyzed using the same assay procedure.

Pharmacokinetic Analysis. Pharmacokinetic parameters, C_max, AUC, t₁/₂, and MRT were obtained by a noncompartmental moment method. C_max was actually observed peak concentration. AUC and MRT were computed by trapezoidal integration with extrapolation to infinite time according to the following equations where C means the plasma concentration (24).

\[ \text{AUC} = \int_{0}^{\infty} C \, dt \]
Integration over time was performed over the period of 0–75 h, and the extrapolation function was calculated from the log linear portion of the terminal phase. Least-square linear regression analysis was used to ascertain the elimination rate constant (B) from the visually identified terminal linear portion of the log concentration-time curve. \( t_{1/2} \) was calculated by the equation \( t_{1/2} = \ln(2)/\beta \). The CL and the apparent volume of distribution at steady state (\( V_{ss} \)) were determined as follows (25):

\[
CL = \text{Dose} / \text{AUC}
\]

\[
V_{ss} = CL \cdot (\text{MRT} - \text{Infusion Time}/2)
\]

The duration that the paclitaxel concentration was above the threshold level was calculated on the log concentration versus time curve using actually measured data. The threshold levels analyzed in this study were 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, and 0.1 \( \mu \text{m} \). These values were selected arbitrarily from the concentration versus time curve. The amount of paclitaxel excreted into urine in the collection period was calculated from the urinary concentration and volume. The urinary recovery was expressed as the percentage of the dose administered.

Linear regression analysis was used, and Pearson’s correlation coefficients were obtained to test dose linearity of C\(_{\text{max}}\), AUC, and time above a threshold concentration.

**Pharmacodynamics**

The pharmacokinetic/pharmacodynamic relationships were modeled with the sigmoid maximum effect (\( E_{\text{max}} \)) equation:

\[
E(\%\ \text{change}) = E_{\text{max}} \cdot P^h / (P_{50}^H + P^h)
\]

where \( E_{\text{max}} \) represents the maximal elicitable effect and P represents the pharmacokinetic parameter. \( P_{50} \) is the value of the parameter by which 50% of \( E_{\text{max}} \) is elicited. The analyses were made between pharmacokinetic parameters, including dose, \( C_{\text{max}} \), AUC, and duration of plasma concentration above threshold levels, and pharmacodynamic effects of \% D in granulocyte count using the following equation:

\[
\%D = [(\text{Pretreatment granulocyte} - \text{Nadir granulocyte})/\text{Pretreatment granulocyte}] \times 100\%
\]

The computer program ADAPT (26) was used to estimate exponent H, known as the Hill constant, which determines the shape of the curve, and \( P_{50} \) by an IBM compatible computer. The relationships were analyzed for data of the 3-h infusion, 24-h infusion, and combined data of both infusion schedules, respectively. Selection of the best-fit pharmacokinetic parameter which describes PD most successfully was made by comparing the Akaike Information Criterion (27). The model which showed the minimum of the Akaike Information Criterion was estimated the best-fit one.

**RESULTS**

A total of 27 patients were entered into the Phase I trial of paclitaxel by the 3-h infusion. Eighteen patients were male and nine were female. The number of patients treated at each dosage level was as follows: 105 mg/m\(^2\), 3; 135 mg/m\(^2\), 3; 180 mg/m\(^2\), 3; 210 mg/m\(^2\), 5; 240 mg/m\(^2\), 7; 270 mg/m\(^2\), 6. Severe hypersensitivity reactions or cardiac arrhythmias were not documented. At first, three patients were treated at each dosing level. DLT was not observed at doses less than 240 mg/m\(^2\). At 240 mg/m\(^2\), the fourth patient developed prolonged and life-threatening grade 4 hypotension. The patient was a 53-year-old man with small cell carcinoma of the esophagus. He was heavily pretreated, but had no past history of ischemic heart disease or arrhythmia. He suddenly lost consciousness without other allergic reactions 5 min after completion of paclitaxel infusion. The systolic blood pressure fell down to 50 mm Hg without cardiac arrhythmias. Central venous pressure and pulmonary capillary wedge pressure were low, and systemic hydration and dopamine were necessary for one week to keep the blood pressure stable. Because two more patients were treated at 240 mg/m\(^2\) without hypotension, the next cohort was treated at 270 mg/m\(^2\). Hypotension was observed in three of six patients. The dose was reduced to 240 mg/m\(^2\) and one more patient experienced grade 3 hypotension. The next two patients received 210 mg/m\(^2\) without hypotension. The MTD was identified to be 240 mg/m\(^2\), and the recommended dose for Phase II study was 210 mg/m\(^2\). Eleven patients experienced grade 4 granulocytopenia, 17 patients grades 1–3 peripheral neuropathy, and 20 patients grades 1–3 myalgia/arthralgia. The peripheral neuropathy and granulocytopenia appeared to be dose related. Partial response was observed in one patient with heavily treated ovarian cancer. Granulocyte-colony-stimulating factor was used only for three patients after severe toxicities. Details of the clinical features by each level and repeated courses found in this Phase I study by the 3-h infusion will be reported elsewhere.

Comparing the results of the first course of 15 patients in the 24-h infusion (22), grade 4 granulocytopenia was less frequent (3-h, 40.7% versus 24-h, 66.7%), while mild to moderate peripheral neuropathy (3-h, 63.0% versus 24-h, 6.7%) and arthralgia/myalgia (3-h, 74.1% versus 24-h, 13.3%) were more frequent. Hypotension was documented only in the 3-h infusion group: one, grade 4; 2, grade 3; and 2, grade 1. Pharmacokinetic and pharmacodynamic analyses were performed for all 27 patients on the 3-h schedule and compared to those of patients on the 24-h schedule (22). A total of 18 patients were treated in the Phase I trial by the 24-h infusion. Pharmacokinetic analyses were performed for all 18 patients. Four patients in the 24-h infusion group were excluded from the analysis of \% D in granulocytes because three patients given the 180-mg/m\(^2\) dose were given prophylactic granulocyte-colony-stimulating factor after the determination of MTD and because pretreatment granulocyte count was not determined in one patient. The first cycle of paclitaxel treatment was analyzed for PK and PD.

**PK of the 3-h Infusion Schedule.** Table 1 lists the mean pharmacokinetic parameters of paclitaxel at each dose level in 27 patients treated by the 3-h infusion. The drug plasma concentration increased throughout the 3-h infusion period and began to decrease immediately upon cessation of the infusion.
Clinical Pharmacodynamics of Paclitaxel

Table 1 Pharmacokinetic parameters of paclitaxel (3 h)

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>Cmax (µM)</th>
<th>t₁/₂ (h)</th>
<th>AUC (µM·h)</th>
<th>Vss (liter/ml)</th>
<th>CL (ml/min·m²)</th>
<th>MRT (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>105</td>
<td>3</td>
<td>2.602 ± 0.627*</td>
<td>9.9 ± 2.0</td>
<td>9.23 ± 0.66</td>
<td>74.7 ± 11.6</td>
<td>223 ± 15</td>
<td>7.24 ± 0.33</td>
</tr>
<tr>
<td>2</td>
<td>135</td>
<td>3</td>
<td>3.944 ± 1.108</td>
<td>16.0 ± 6.9</td>
<td>13.14 ± 4.3</td>
<td>113.1 ± 69.4</td>
<td>214 ± 60</td>
<td>10.24 ± 3.88</td>
</tr>
<tr>
<td>3</td>
<td>180</td>
<td>3</td>
<td>5.232 ± 1.505</td>
<td>13.7 ± 5.8</td>
<td>19.28 ± 4.4</td>
<td>81.7 ± 37.9</td>
<td>190 ± 49</td>
<td>9.06 ± 4.15</td>
</tr>
<tr>
<td>4</td>
<td>210</td>
<td>5</td>
<td>7.898 ± 3.201</td>
<td>13.3 ± 1.5</td>
<td>27.15 ± 12.4</td>
<td>58.9 ± 24.7</td>
<td>179 ± 81</td>
<td>7.05 ± 0.64</td>
</tr>
<tr>
<td>5</td>
<td>240</td>
<td>7</td>
<td>9.017 ± 1.286</td>
<td>14.6 ± 2.9</td>
<td>31.19 ± 2.71</td>
<td>55.6 ± 14.7</td>
<td>151 ± 14</td>
<td>7.57 ± 1.16</td>
</tr>
<tr>
<td>6</td>
<td>270</td>
<td>6</td>
<td>13.913 ± 1.896</td>
<td>11.6 ± 1.0</td>
<td>47.67 ± 5.06</td>
<td>33.6 ± 7.4</td>
<td>112 ± 12</td>
<td>6.47 ± 0.68</td>
</tr>
</tbody>
</table>

* Values are means ± SDs.

Fig. 1 Log plasma paclitaxel concentration versus time curves at the same doses (105 mg/m² and 180 mg/m²) and at the MTDs (240 mg/m² or 180 mg/m²) for the 3- and 24-h infusion.

with t₁/₂ of 9.9–16.0 h and MRT of 6.47–10.24 h (Fig. 1). Both Cmax and AUC increased with increasing doses (r = 0.865, P < 0.001 for Cmax; r = 0.870, P < 0.001 for AUC), although the pharmacokinetic behavior appeared to be nonlinear (Fig. 2). The mean Cmax and AUC at a dose of 270 mg/m² were more than 3-fold greater than those at a dose of 135 mg/m². CL and Vss decreased with increasing doses (Table 1). The urinary excretion of paclitaxel over 75 h was less than 15% of the dose administered, which indicated that non-renal excretion is the primary route of drug elimination.

Comparison of PK between 3-h and 24-h Infusion Groups. Cmax and AUC in the 24-h infusion group also correlated with dose (r = 0.892, P < 0.001 for Cmax; r = 0.916, P < 0.001 for AUC; Ref. 22), although the PK did not show clear nonlinear or dose-dependent behavior (Fig. 2). Intercpatient variability of Cmax or AUC at these doses appeared to be larger for the 3-h infusion with up to 3-fold variability in AUC and Cmax. To compare the PK of the same dose and of the MTD in each schedule, Fig. 1 shows the representative plasma concentration-time curves for the 3- and 24-h infusion schedules, and Table 2 shows the pharmacokinetic parameters. At the same doses, Cmax and AUC were greater in the 3-h infusion group than in the 24-h infusion group, while Vss and MRT were much larger in the 24-h infusion group. At MTDs, the AUC for the 3-h infusion of 240 mg/m² was more than 2-fold greater than the AUC for the 24-h infusion of 180 mg/m².

Comparison of PD between 3-h and 24-h Infusion Groups. AUC and duration of plasma concentration (h) above (T >) 0.05–0.1 µM correlated with the % D in granulocytes with P values of less than 0.05, respectively, in the 3-h infusion schedule, using a sigmoid Emax model (Figs. 3C and 4). Among them, the best parameter predicting granulocytopenia was T > 0.09 µM with the minimum of the Akaike Information Criterion. In the 24-h schedule, dose, AUC, and T > 0.04–0.07 µM were demonstrated to correlate with the % D in granulocytes (Figs. 3, A and C, and 4). The best parameter predicting granulocytopenia in the 24-h schedule was T > 0.05 µM. When the pharmacodynamic models of the two infusion schedules were analyzed concomitantly, apparent differences in the relationship for % D in granulocytes with dose, Cmax, and AUC were observed (Fig. 3). On the other hand, the relationship between the % D in granulocytes and T > 0.04–0.07 µM could be described adequately by the same sigmoid Emax model for both infusion schedules (Table 3). The pharmacokinetic parameter for the best model was T > 0.05 µM (Table 3), where P_{50} is 14.3 h and H is 1.883. The final pharmacodynamic model of paclitaxel predicting % D in granulocytes on either schedule was made according to the following formula:

\[
% \text{D in granulocytes} = 100 \times \frac{T > 0.05 \mu M^{1.88} \times (150 + T > 0.05 \mu M^{1.88})}{(150 + T > 0.05 \mu M^{1.88})} (\text{Fig. 4}).
\]

P > 0.05 µM increased dose dependently at both schedules (r = 0.637, P < 0.001 for the 3-h infusion; r = 0.700, P < 0.001 for the 24-h infusion; Fig. 5). No relationship for peripheral neuropathy, myalgia, or hypotension with any pharmacokinetic parameters including Cmax, AUC, and duration of plasma concentration above threshold levels could be found by linear or nonlinear models (P > 0.1) in either infusion schedule. The pharmacokinetic parameters of the patient, who experienced prolonged and life-threatening grade 4 hypotension at 270 mg/m², were not significantly different from the mean values of the other patients who were administered the same dose (data not shown).

DISCUSSION

Paclitaxel is a promising new drug with a novel mechanism of action and broad clinical activity. This drug is distinctive in the point that an optimal schedule and dose has been considered early in its development (28). Until recently, various infusion schedules have been tried (8–16). However, the most effective dose and schedule remain undetermined (29). In the previous clinical trial comparing a 3-h infusion with a 24-h infusion, the doses were set up to be equal in both infusion schedules (20). Severe neutropenia was much more frequent in the 24-h infusion group. To design the rational treatment schedule, detailed

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Fig. 2  Dose linearity in $C_{\text{max}}$ (A) and AUC (B) in 27 patients in the 3-h infusion group and in 18 patients in the 24-h infusion group.

Table 2  Comparison of PK between a 3- and 24-h infusion

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>$C_{\text{max}}$ (µM)</th>
<th>$t_{1/2}$ (h)</th>
<th>AUC (µM·h)</th>
<th>CL (ml/min·m²)</th>
<th>$V_\infty$ (liter/ml)</th>
<th>MRT (h)</th>
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<tbody>
<tr>
<td>3-h infusion</td>
<td>105</td>
<td>3</td>
<td>2.602</td>
<td>9.9</td>
<td>9.23</td>
<td>223</td>
<td>74.7</td>
<td>7.24</td>
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<tr>
<td>180</td>
<td>3</td>
<td>5.232</td>
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<td>81.7</td>
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<tr>
<td>240*</td>
<td>7</td>
<td>9.017</td>
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<td>151</td>
<td>55.6</td>
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<td>7.57</td>
</tr>
<tr>
<td>24-h infusion</td>
<td>105</td>
<td>3</td>
<td>0.210</td>
<td>24.6</td>
<td>5.91</td>
<td>386</td>
<td>394</td>
<td>30.8</td>
</tr>
<tr>
<td>180b</td>
<td>6</td>
<td>0.673</td>
<td>13.1</td>
<td>13.24</td>
<td>270</td>
<td>151</td>
<td>21.2</td>
<td></td>
</tr>
</tbody>
</table>

* MTD by a 3-h infusion.

b MTD by a 24-h infusion.

Fig. 3  % D in granulocyte counts versus the doses (A), the $C_{\text{max}}$s (B), and the AUCs (C) in 41 patients treated by the two infusion schedules.

pharmacokinetic and pharmacodynamic analyses were expected to be helpful, and comparison of the equitoxic doses of each infusion schedule was to be required in the clinical setting.

We conducted a Phase I trial by a 3-h infusion and the results were compared with those of a Phase I trial by a 24-h infusion conducted previously (22). We found the MTD of the
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3-h infusion to be 240 mg/m² compared with 180 mg/m² of the 24-h infusion. DLTs of 3-h infusion were peripheral neuropathy and hypotension, in addition to granulocytopenia found as DLT in the 24-h infusion. Each trial was accompanied with precisely performed pharmacokinetic and pharmacodynamic analyses. In this context, the detailed comparative pharmacokinetic and pharmacodynamic analyses between two Phase I trials have been shown.

Nonlinear increase in both C_{max} and AUC and decreasing CL and V_{ss} with increasing dose in the 3-h infusion suggested saturable elimination and distribution process. The PK of the 24-h infusion showed linear pharmacokinetic behavior as described previously (14). In the 6-h infusion schedules, decreased CL was reported at the highest dose of 265–275 mg/m², although there were large interpatient variabilities (9, 12, 13). In addition, the findings of another 3-h infusion schedule (11, 30) and a 24-h schedule in children using higher doses than in adults (31) demonstrated that the mean paclitaxel CL and V_{ss} decreased with increasing dose. These findings suggest that at a higher concentration obtained in the shorter infusion or at the higher doses, paclitaxel systemic elimination and tissue distribution will saturate with proportionally greater increase in total drug exposure as related to dose.

Nonhematological toxicities such as peripheral neuropathy, hypotension, and arthralgia/myalgia mainly observed in the 3-h infusion group had no relationship with C_{max} or AUC which are much higher in the 3-h infusion group, although peripheral neuropathy and musculoskeletal toxicity have been suggested to be associated with AUC on a 6- (12) or 24-h (29) schedule. When hematological toxicity was considered, the relationship for % D in granulocytes with the AUC and % D in granulocytes was found as DLT in the 24-h infusion. Each trial was accompanied with precisely performed pharmacokinetic and pharmacodynamic analyses between two Phase I trials have been shown. When the pharmacodynamic models of the two infusion schedules were compared, apparent differences in the relationship between dose, C_{max}, and AUC and % D in granulocytes were observed as shown in Fig. 3. This suggested that these parameters could not be the common parameter predicting granulocytopenia when the data of both schedules were analyzed simultaneously. Longnecker et al. (9)

### Table 3: Sigmoid E\text{max} analysis of duration of paclitaxel concentration greater than threshold levels versus % D in granulocytes on both infusion schedules

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients</th>
<th>P_{50}</th>
<th>CV (%)</th>
<th>H</th>
<th>CV (%)</th>
<th>AIC</th>
<th>r^2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T &gt; 0.04 μM \text{d}</td>
<td>41</td>
<td>14.7</td>
<td>28.40</td>
<td>1.668</td>
<td>32.90</td>
<td>378.54</td>
<td>0.193</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>T &gt; 0.05 μM</td>
<td>41</td>
<td>14.3</td>
<td>20.69</td>
<td>1.883</td>
<td>27.64</td>
<td>375.13</td>
<td>0.257</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>T &gt; 0.06 μM</td>
<td>41</td>
<td>8.39</td>
<td>38.91</td>
<td>1.256</td>
<td>33.59</td>
<td>378.74</td>
<td>0.189</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>T &gt; 0.07 μM</td>
<td>41</td>
<td>5.63</td>
<td>52.06</td>
<td>1.027</td>
<td>36.38</td>
<td>379.89</td>
<td>0.166</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>T &gt; 0.08 μM</td>
<td>41</td>
<td>1.74</td>
<td>118.0</td>
<td>0.604</td>
<td>47.24</td>
<td>382.76</td>
<td>0.107</td>
<td>N.S.</td>
</tr>
<tr>
<td>T &gt; 0.09 μM</td>
<td>41</td>
<td>3.74</td>
<td>75.53</td>
<td>0.874</td>
<td>44.83</td>
<td>404.00</td>
<td>0.023</td>
<td>N.S.</td>
</tr>
<tr>
<td>T &gt; 0.10 μM</td>
<td>41</td>
<td>7.28</td>
<td>39.93</td>
<td>1.440</td>
<td>38.87</td>
<td>414.82</td>
<td>0.056</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

\text{a} Dose, C_{max}, and AUC were not listed because r^2 were too small (<0.001).

\text{b} CV, coefficient of variation; H, hill constant, N.S., not significant.

\text{c} Model predicted parameter to produce a 50% decrease in granulocytes.

\text{d} Values are time (h) of exposure of plasma concentration above a threshold level.

### Fig. 4: % D in granulocyte counts versus the duration of plasma paclitaxel concentration above 0.05 μM in 41 patients treated by the two infusion schedules. The curve has been fitted to the same sigmoid E_{max} model.

### Fig. 5: Dose linearity in the duration of plasma paclitaxel concentration above 0.05 μM in 27 patients of the 3-h infusion and in 18 patients of the 24-h infusion.
demonstrated the relationship between AUC and leukopenia in various infusion schedules of 1–6 h. They showed that scatterplots of % D in leukocytes versus AUC fitted one sigmoidal E_{max} model on different infusion schedules (9, 32). There may be no schedule dependency between AUC and % D in leukocytes for the infusion times ranging from 1 to 6 h. In our study, scatterplots from the 3- and 24-h infusions overlapped only when the duration of concentration above a threshold level was analyzed. In this study T > 0.05 \mu\text{M} seemed the best pharmacokinetic parameter in correlation with % D in granulocytes for all data. The relationship between granulocytopenia and T > 0.1 \mu\text{M} (21) or T > 0.05 \mu\text{M} (30) has been already reported using data from 3- and 24-h infusions. Their available data were from only two or three dose levels for each infusion schedule. In our study using broader dose levels, grade 3 and 4 granulocytopenia were observed at the dose of 49.5 mg/m^2 when the duration of concentration above a threshold level was kept low. The universal parameter for any infusion schedule.

Our findings revealed that paclitaxel is more dependent on schedule than dose concerning hematological toxicity in a clinical setting. If the schedule dependency would be applied also to the drug’s antitumor activity, the longer infusion schedules could produce higher response rates. In spite of the in vitro study that prolongation of drug exposure seemed more important than an increase in concentration for cytotoxicity (18, 19), the clinical study comparing 3- and 24-h infusion could not show the superiority of the 24-h infusion for antitumor effect (20). Etoposide is a typical schedule-dependent drug, which was proven in the clinical setting. Slevin et al. (33) demonstrated that T > 0.1 \mu\text{g/ml} is well correlated with its antitumor activity but not with the hematological toxicity in a clinical study. Likewise, the schedule-dependency of paclitaxel in hematological toxicity may not necessarily mean the schedule-dependency in an antitumor effect. The analysis of the relationship between the pharmacokinetic parameters and antitumor effects of paclitaxel for advanced breast cancer is ongoing (data not shown).

Our results have shown that apparent differences in PK and PD were observed with the 3- and 24-h infusion schedules and that T > 0.05 \mu\text{M} was described as the common pharmacokinetic parameter predicting granulocytopenia in either schedule. To determine the pharmacokinetic parameter predicting antitumor effects, further pharmacokinetic and pharmacodynamic studies will be needed in the Phase II or III settings. Future studies comparing the equitoxic doses of the 3- or 24-h infusion are required to determine which schedule would be better.

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