Comparative Pharmacokinetics of Weekly and Every-Three-Weeks Docetaxel

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ABSTRACT

Purpose: Weekly administration of docetaxel has demonstrated comparable efficacy together with a distinct toxicity profile with reduced myelosuppression, although pharmacokinetic data with weekly regimens are lacking. The comparative pharmacokinetics of docetaxel during weekly and once every 3 weeks (3-weekly) administration schedules were evaluated.

Experimental Design: Forty-six patients received weekly docetaxel (35 mg/m²) as a 30-min infusion alone (n = 8) or in combination with irinotecan (n = 12), or in 3-weekly regimens, as a 1-h infusion at 60 mg/m² with doxorubicin (n = 10), 75 mg/m² alone (n = 9), or 100 mg/m² alone (n = 7). Serial blood samples were obtained immediately before and up to 21 days after the infusion. Plasma concentrations were measured by liquid chromatography–mass spectrometry and analyzed by compartmental modeling.

Results: Mean ± SD docetaxel clearance values were similar with weekly and 3-weekly schedules (25.2 ± 7.7 versus 23.7 ± 7.9 liter/h/m²); half-lives were also similar with both schedules of administration (16.5 ± 11.2 versus 17.6 ± 7.4 h). With extended plasma sampling beyond 24 h post-infusion, docetaxel clearance was 18% lower and the terminal half-life was 5-fold longer. At 35 mg/m², the mean ± SD docetaxel concentration on day 8 was 0.00088 ± 0.00041 μg/ml (1.08 ± 0.51 nm) at 75 mg/m², concentrations on day 8, 15, and 22 were 0.0014 ± 0.00043 μg/ml (1.79 ± 0.53 nm), 0.00067 ± 0.00025 μg/ml (0.83 ± 0.31 nm), and 0.00047 ± 0.00008 μg/ml (0.58 ± 0.099 nm), respectively.

Conclusion: Docetaxel pharmacokinetics are similar for the weekly and 3-weekly regimens. Prolonged circulation of low nanomolar concentrations of docetaxel may contribute to the mechanism of action of docetaxel through suppression of microtubule dynamics and tumor angiogenesis and enhanced cell radiosensitivity in combined modality therapy.

INTRODUCTION

The antineoplastic agent docetaxel acts by disrupting the microtubular network, and it is one of the most active agents in the treatment of locally advanced or metastatic breast, non-small cell lung, and ovarian cancer (1–4). The docetaxel dose used for treating cancer patients has ranged from 60 to 100 mg/m² as a 1-h i.v. infusion given once every 3 weeks (hereafter referred to as “3-weekly”). In this regimen, neutropenia occurs in virtually all patients, and grade 4 neutropenia occurs in 75% of patients given 100 mg/m² (n = 2045; febrile neutropenia incidence, 12%), grade 3/4 neutropenia occurs in 65% of patients given 75 mg/m² (n = 176; febrile neutropenia incidence, 6.3%), and grade 4 neutropenia occurs in 75% of patients given 60 mg/m² (n = 174; febrile neutropenia incidence, 0%).3 Other side effects include alopecia, asthenia, dermatological reactions, fluid retention, hypersensitivity reactions, and stomatitis. Drug exposure–toxicity relationships are clearly defined for docetaxel administered as monotherapy at doses of 75–100 mg/m² in 3-weekly regimens where the area under the curve (AUC) of total plasma concentrations during the first cycle of treatment is related to incidence of grade 4 neutropenia and febrile neutropenia (5).

Recent clinical trials have examined single-agent docetaxel administered at doses of 35–40 mg/m² given weekly for 6 consecutive weeks followed by 2 weeks without treatment (6–14) or on other weekly schedules such as 3 consecutive weeks with 1 week of rest (hereafter referred to as “weekly”: Refs. 15–17). Administration of weekly schedules significantly changed the toxicity profile of docetaxel with a reduction in acute toxicity and only mild myelosuppression. Fatigue and asthenia appeared as the dose-limiting side effects, and nail changes and excessive lacrimation became more common. The response rates observed with weekly administration of single-

agent docetaxel in Phase II studies in metastatic breast cancer and advanced non-small cell lung cancer are within the range reported in other studies of 3-weekly docetaxel (18–21), and in general, the planned dose intensity is equivalent to that used in 3-weekly regimens.

At present, the pharmacokinetic profile of docetaxel administered in weekly treatment regimens has not been reported previously. The objectives of the study were to compare the pharmacokinetics of docetaxel during weekly and 3-weekly administrations and to describe plasma drug concentrations during extended periods with both schedules.

PATIENTS AND METHODS

Chemicals and Reagents. Docetaxel powder (batch no. 990720; purity, 99.5%) was supplied by Aventis Pharma (Vitry-sur-Seine Cedex, France). The internal standard, paclitaxel (lot no. 061K1158; purity, 100%) was obtained from Sigma Chemical Co. (St. Louis, MO). Methanol and acetonitrile were purchased from EM Science (Gibbstown, NJ), and formic acid (88%, v/v in water) was from J.T. Baker (Phillipsburg, NJ). All chemicals were of high-performance liquid chromatography grade or better. Purified water was obtained by filtration and deionization using a Milli-Q-UF system (Millipore, Milford, MA) and was used throughout. Drug-free plasma originated from Pittsburgh Blood Plasma, Inc (Pittsburgh, PA).

Patients and Treatment. Docetaxel was administered as part of several clinical study protocols, and pharmacokinetic data were gathered into this study. The clinical docetaxel preparation (Taxotere; Aventis) contained 20 or 80 mg of the drug formulated in 0.5 and 2.0 ml, respectively, of polysorbate 80 and was diluted in ethanol–water (13:87, v/v) to a concentration of 10 mg/ml. This solution was diluted in 250-ml infusion bags with 0.9% (w/v) sodium chloride in water to a concentration of 0.30–0.74 mg/ml. Individual drug doses were normalized to body surface area and administered as part of a clinical study protocol once every week at a dose of 35 mg/m² alone (n = 8) or 30 min before administration of 50 mg/m² irinotecan (n = 12) or once every 3 weeks (3-weekly) at a dose of 60 mg/m²/1 h after administration of 60 mg/m² doxorubicin (n = 10) or as 75 mg/m² alone (n = 9) or 100 mg/m² alone (n = 7). The drug was given as a 0.5-h (35 mg/m²) or 1-h (60, 75, and 100 mg/m²) continuous i.v. infusion by use of an infusion system with an in-line 0.22 µm filter. The clinical protocols were approved by the local Institutional Review Boards (Baltimore, MD and Rotterdam, the Netherlands), and all patients provided written informed consent before enrollment. Patients had adequate renal and hepatic function defined as (a) serum creatinine ≤2.0 times the institutional upper limit of normal (ULN); (b) total bilirubin <1.5 times the ULN; and (c) if alkaline phosphatase was at or below the ULN, any elevations in aspartate aminotransferase and/or alanine aminotransferase, or if aspartate aminotransferase and/or alanine aminotransferase were at or below the ULN, any elevation in alkaline phosphatase. Patients with alanine aminotransferase and/or aspartate aminotransferase >1.5 times the ULN with concomitant alkaline phosphate >2.5 times the ULN were not eligible for treatment with docetaxel on the administration schedules described here because this was considered inadequate hepatic function for docetaxel treatment.

Pharmacokinetic Sampling. Pharmacokinetic studies were part of each study protocol and were performed during the first week of therapy for the weekly regimens and during the first cycle of treatment for the 3-weekly regimens. Pharmacokinetic studies were performed during the second cycle of treatment in three of seven patients receiving 100 mg/m² docetaxel. Blood samples were collected in Vacutainer tubes containing heparin as anticoagulant from a peripheral site contralateral to the infusion site. Blood samples were immediately placed in an ice-water bath, centrifuged within 30 min of collection at 1000 × g for 10 min at 4°C, and were stored at or below –20°C until analysis. The following sampling schemes were used: (a) for docetaxel (35 mg/m²) given alone or followed by irinotecan, sampling was at pretreatment, at 29 min (immediately before the end of the infusion), and post-infusion at 10 and 30 min and at 1, 3, 7.5, 24, and 48 h, and pretreatment on day 8; (b) for 60 mg/m² docetaxel with doxorubicin, sampling was at pretreatment, at 30 min during the infusion, at 59 min (immediately before the end of infusion), and post-infusion at 10 and 30 min and at 1, 2.5, 5, 22, and 46 h, and before cycle 2 on day 22; (c) for 75 mg/m² docetaxel administered alone, sampling was at pretreatment, at 30 min during the infusion, at 59 min (immediately before the end of infusion), and post-infusion at 10 and 30 min; at 1, 3, 7, 24, and 48 h; and on days 8, 15, and 22; and (d) for 100 mg/m² docetaxel administered alone, sampling was at pretreatment, at 30 and 55 min during the infusion, at the end of infusion, and post-infusion at 10, 20, and 30 min; at 1, 1.3, 2, 4, 8.5, 24, 48, and 72 h; and on days 8, 15, and 22.

Analytical Assay. Docetaxel was quantitated in plasma by use of high-performance liquid chromatography with tandem mass spectrometric detection. The method was validated according to the recommendations provided by the United States Food and Drug Administration.4 Briefly, drug was extracted from 1.0 ml of plasma by liquid–liquid extraction with a mixture of acetonitrile–n-butyl chloride (1:4, v/v). The eluate was evaporated under a stream of nitrogen and reconstituted with 200 µl of methanol–water (50:50, v/v). The analytical system consisted of a Model 2690 chromatograph (Waters, Milford, MA) equipped with a model 996 photodiode array detector. Chromatographic separations were achieved on a Waters X-Terra MS column (50 × 2.1 mm internal diameter) packed with an ODS stationary phase with a 3.5-µm particle size, protected by a Phenomenex (Torrance, CA) C18 (4.0 × 3.0 mm internal diameter) guard column. The mobile phase was a mixture of acetonitrile–water (80:20, v/v) containing 0.1% (w/v) formic acid and was delivered isocratically at a flow rate of 0.2 ml/min. Detection was performed with a MicroMass Quattro LC triple-quadrupole mass spectrometer (Cary, NC) in the positive-ion mode. The electrospray ionization operated at 3.6 kV, and the cone voltage was 20 V. The detector was programmed to allow the [M-H]⁺ ion of docetaxel (m/z 808.49) and that of the internal standard paclitaxel (m/z 854.99) to pass through the first

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quadrupole and into the collision cell. The collision energy for collision-induced dissociation was set at 8.0 eV, with argon used as collision gas at a pressure of 0.0027 mbar. The daughter ions of docetaxel (m/z 527.52) and paclitaxel (m/z 509.44) were monitored through the third quadrupole. The dwell time per channel for data collection was set at 0.5 s.

Plasma docetaxel concentrations were quantitated over the range of 0.50–100 nM. The accuracy and precision of quality control samples, which included docetaxel concentrations of 2.0, 20.0, 80.0 nM, and an 80 nM quality control sample that was diluted 100-fold before processing, were <15%. At the assay’s lower limit of quantitation (0.50 nM; 400 pg/ml), accuracy was 103% and between-run precision was 17.5%. This represents a 25–50-fold increase in sensitivity compared with analytical assays based on high-performance liquid chromatography with UV detection (22–28), although an analytical assay based on high-performance liquid chromatography with mass spectrometric detection with an lower limit of quantitation of 0.30 nM has recently been described (29). For quantitation of docetaxel in unknown samples, quality control samples at low, medium, and high concentrations were assayed in duplicate and were distributed among the calibrators and unknown samples in the analytical run; no more than 33% of the quality assurance samples were greater than ±15% of the nominal concentration. Samples with docetaxel concentrations greater than the assay’s upper limit of quantitation (100 nM) were diluted with analyte-free human plasma before extraction and quantitation. Depending on the docetaxel dose, plasma samples were prediluted at volume ratios of 1:10, 1:50, or 1:100.

Pharmacokinetic Data Analysis. Individual docetaxel pharmacokinetic parameters were estimated by model-dependent methods as implemented in Adapt II, release 4 (Biomedical Simulations Resource, Los Angeles, CA; Ref. 30). Pharmacokinetic parameters were estimated twice for each patients by use of (a) data from time 0 to 24 h posttreatment (conventional plasma sampling scheme) for comparison with previously published pharmacokinetic data; and (b) from time 0 to the last measurable concentration on days 8, 15, or 22 (extended plasma sampling scheme). This latter analysis was performed only if patients had measurable docetaxel concentrations on day 8 or later. Data were fit with either a two- or three-compartment model by use of weighted least squares as the estimation procedure and inverse variance of the output error (linear) as the weighting option. Model discrimination was guided by inspection of the weighted sum of squares and the coefficient of variation of the fitted pharmacokinetic parameters and by the Akaike information criterion (31). Maximum plasma concentration (cmax) values were obtained from the model-estimated plasma concentration at the end of the docetaxel infusion. Calculated secondary pharmacokinetic parameters included half-life during the terminal phase of the disposition curve (t1/2,α) and systemic clearance. The area under the plasma concentration–time curve (AUC) was calculated as dose divided by systemic clearance. For weekly regimens, the cumulative AUC during a 3-week treatment period was calculated by multiplying the AUC during week 1 of treatment by 3 with the assumption that docetaxel clearance did not change during weeks 2 and 3 of treatment.

Statistical Considerations. Pharmacokinetic parameters are presented as mean values ± SD, and for all tests the a priori cutoff for statistical significance was taken at P < 0.05. ANOVA was used to compare cmax values and cumulative AUC during a 3-week treatment period at the different dose levels. The Tukey–Kramer HSD method was used to adjust for multiple comparisons of mean values. Differences between pharmacokinetic parameter values, which were calculated with data from sampling to 24 h or extended sampling, were compared by a paired Student’s t test. Statistical calculations were performed with the software package JMP version 3.2.6 (SAS Institute, Cary, NC).

Group sample sizes of 20 were calculated to achieve ~70% power to detect a ratio of 1.50 between the clearance of docetaxel in the respective treatment groups, using a double-sided test with a significance level (α) of 0.05 and assuming equal variances for both groups. This statistical calculation was performed in the SISA Binomial program (D. G. Uitenbroek, Hilversum, the Netherlands, 1997).5

RESULTS

Data from 23 female and 23 male patients were included in this pharmacokinetic study, and the patient demographic data are summarized in Table 1. Docetaxel pharmacokinetic parameters determined from plasma concentrations measured from time 0 to 24 h posttreatment are displayed in Table 2. Docetaxel pharmacokinetic parameters were similar when 35 mg/m2 docetaxel was given alone or with irinotecan (P > 0.50), similar to earlier findings of this combination given in a 3-weekly regimen (32, 33); therefore, data from both schedules were combined,

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and the summary statistics are presented in Table 2. Mean ± SD docetaxel clearance values were similar for weekly and 3-weekly schedules (overall means, 25.2 ± 7.7 versus 23.7 ± 7.9 liter/h/m²; P < 0.5467); half-lives were also similar with both schedules of administration (overall means, 16.5 ± 11.2 and 17.6 ± 7.4 h; P = 0.6990). Docetaxel cₘₐₓ and AUC values at the different dose levels are shown in Fig. 1. Mean ± SD cₘₐₓ values with docetaxel administered at a dose of 35 mg/m² over 30 min (1.93 ± 0.60 µg/ml) were similar to those observed at doses of 60 mg/m² (1.55 ± 0.41 µg/ml) and 75 mg/m² (2.18 ± 0.71 µg/ml) administered over 1 h, but were significantly lower (P < 0.0001) than at 100 mg/m² (4.15 ± 1.35 µg/ml) over 1 h. The difference in cₘₐₓ observed between the weekly and 3-weekly schedules was not related to a pharmacokinetic difference but to the shorter infusion duration in the weekly schedule (30 min versus 1 h) and the different doses administered in the 3-weekly regimens (60, 75, and 100 mg/m²). Because docetaxel clearance is not schedule dependent, exposure–intensity (AUC) comparisons between weekly and 3-weekly schedules are equivalent to dose–intensity comparisons. The AUC during 3 weeks of treatment was larger after the 35 mg/m² weekly dose (4.44 ± 1.24 µg/ml; cumulative 3-week dose of 105 mg/m²) compared with the AUC after 60 mg/m² (2.85 ± 1.40 µg/ml) and 75 mg/m² (3.05 ± 0.85 µg/ml) given 3-weekly but was similar to the AUC for 100 mg/m² (5.62 ± 2.12 µg/ml) given 3-weekly.

Docetaxel pharmacokinetic parameters calculated from data that included extended plasma sampling to days 8–22 posttreatment are listed in Table 3. Observed and model-simulated docetaxel concentration–time profiles from representative patients receiving 35 mg/m² docetaxel as a 30-min infusion and 75 mg/m² as a 1-h infusion are shown in Fig. 2, and mean observed docetaxel concentration–time profiles after single-agent administration at 35 mg/m² (30-min infusion; n = 9), 75 mg/m² (1-h infusion; n = 9), and 100 mg/m² (1-h infusion; n = 7) are illustrated in Fig. 3. With the weekly schedules, clearance values were 19% lower when calculated from concentration–time data from extended sampling to day 8 than versus 24-h data; with the 3-weekly schedules, docetaxel clearance values were 10–34% lower with extended sampling to day 22 (overall paired means, 19.7 ± 5.1 versus 24.0 ± 6.6 liter/h/m²; P < 0.0001). These differences reflect the fact that samples were obtained for longer time periods, thus allowing for a more accurate estimate of the terminal disposition half-life. By measuring docetaxel concentrations over an extended sampling time period of 3 weeks, we found that the calculated terminal disposition half-life of docetaxel was ~5-fold longer than that esti-

### Table 2 Docetaxel pharmacokinetic parameters: sampling to 24 h post-treatment

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Concurrent drug</th>
<th>No. of patients</th>
<th>Infusion time (h)</th>
<th>Parameter*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly</td>
<td></td>
<td></td>
<td></td>
<td>cₘₐₓ b (µg/ml)</td>
</tr>
<tr>
<td>35 mg/m²</td>
<td>None</td>
<td>8</td>
<td>0.50 ± 0.035</td>
<td>1.85 ± 0.73</td>
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<tr>
<td>35 mg/m²</td>
<td>Irinotecan</td>
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<td>0.54 ± 0.053</td>
<td>1.99 ± 0.52</td>
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<tr>
<td>All data</td>
<td></td>
<td>20</td>
<td>0.52 ± 0.044</td>
<td>1.93 ± 0.60</td>
</tr>
<tr>
<td>3-Weekly</td>
<td>Doxorubicin</td>
<td>10</td>
<td>1.01 ± 0.031</td>
<td>1.55 ± 0.41</td>
</tr>
<tr>
<td>60 mg/m²</td>
<td>None</td>
<td>9</td>
<td>1.04 ± 0.036</td>
<td>2.18 ± 0.71</td>
</tr>
<tr>
<td>75 mg/m²</td>
<td>None</td>
<td>7</td>
<td>1.03 ± 0.047</td>
<td>4.15 ± 1.35</td>
</tr>
</tbody>
</table>

*Data represent mean ± SD. Docetaxel plasma concentration–time data from time 0 to 24 h post-infusion were used for calculation of pharmacokinetic parameters.

b cₘₐₓ, maximum concentration; AUC, area under the curve; CL, clearance; t₁/2,ₙₙ, half-life during terminal phase of the disposition curve.

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**Fig. 1** Peak docetaxel plasma concentrations (cₘₐₓ; **panel A**) and area under the plasma concentration–time curve (AUC; **panel B**) values as a function of dose (mg/m²). The difference in cₘₐₓ observed between the weekly and 3-weekly schedules is not related to a pharmacokinetic difference but to the shorter infusion duration in the weekly schedule (30 min versus 1 h) and the different doses administered in the 3-weekly regimens (60, 75, and 100 mg/m²).
Clinical Pharmacokinetics of Weekly Docetaxel

Dis gust, when given at doses used in 3-weekly regimens (36, 37). The influence of polysorbate 80 on docetaxel protein binding is presumably the result of formation of a complex of polysorbate 80 with serum proteins and/or a displacement interaction on the main docetaxel binding protein, α1-acid glycoprotein (38), caused by polysorbate 80 degradation product(s) (39). Regardless of the exact mechanistic basis for this phenomenon, this finding indicates that exposure to the (pharmacologically active) fraction of unbound docetaxel may increase with an increase in dose (from 35 to 75 or 100 mg/m²), which would be expected to result in more severe hematological toxicity. However, docetaxel is often administered as a 30-min infusion with weekly regimens and as a 1-h infusion with 3-weekly regimens, which may achieve similar polysorbate 80 concentrations when given at doses used in 3-weekly regimens (36, 37). The influence of polysorbate 80 on docetaxel protein binding is presumably the result of formation of a complex of polysorbate 80 with serum proteins and/or a displacement interaction on the main docetaxel binding protein, α1-acid glycoprotein (38), caused by polysorbate 80 degradation product(s) (39). Regardless of the exact mechanistic basis for this phenomenon, this finding indicates that exposure to the (pharmacologically active) fraction of unbound docetaxel may increase with an increase in dose (from 35 to 75 or 100 mg/m²), which would be expected to result in more severe hematological toxicity. However, docetaxel is often administered as a 30-min infusion with weekly regimens and as a 1-h infusion with 3-weekly regimens, which may achieve similar polysorbate 80 concentrations at the end of the docetaxel infusion. Measurement of polysorbate 80 concentrations in plasma with weekly and 3-weekly regimens is in progress.

The similar exposure–intensity and dose–intensity (6) relationships for docetaxel is consistent with observations of comparable efficacy of weekly and 3-weekly regimens in Phase II trials in patients with metastatic breast cancer and advanced non-small cell lung cancer (18–21) and with preclinical studies suggesting that the antitumor activity of docetaxel is independent of the dose/schedule of administration (40). Weekly and

DISCUSSION

In the present study, we describe the comparative pharmacokinetics of docetaxel in plasma after weekly and 3-weekly administration schedules. The data complement previous knowledge on the clinical pharmacology of docetaxel and may have practical implications for its clinical use. Previously published studies of docetaxel pharmacokinetics have focused only on 3-weekly schedules in which the drug is administered as a 1-h i.v. infusion (34, 35). There is great current interest in evaluating the administration of docetaxel on weekly schedules. Weekly regimens appear to have antitumor efficacy comparable to that of 3-weekly schedules, together with a distinct toxicity profile with reduced myelosuppression (18–21). Given the known exposure–toxicity relationship that has been defined for 3-weekly regimens with docetaxel monotherapy (AUC during cycle 1 and neutropenia; Ref. 5), we attempted to understand the differences in the toxicity profiles between weekly and 3-weekly docetaxel by evaluating the comparative pharmacokinetics for both schedules. The use of a sensitive analytical method based on liquid chromatography with tandem mass spectrometric detection allowed the determination of docetaxel exposure during the entire week or cycle of therapy.

At doses of 35 mg/m² given weekly and 100 mg/m² given 3-weekly, the predicted AUC over a 3-week period for weekly administration (4.44 μg·h/ml) was similar to that during cycle 1 of the 3-weekly regimen (5.62 μg·h/ml in the present study versus 4.81 μg·h/ml in Ref. 5). Given the difference in the incidence of severe myelosuppression between the two schedules, the pharmacokinetic data suggest that the same exposure–toxicity relationship defined previously for 3-weekly regimens with docetaxel monotherapy (5) may not apply to weekly regimens. It is possible, however, that measurement of unbound drug concentrations is required to understand exposure–toxicity relationships that apply to both regimens. Indeed, it has recently been shown that the plasma protein binding of docetaxel is decreased in the presence of the docetaxel vehicle polysorbate 80 at concentrations that may be achieved at the end of the docetaxel infusion when given at doses used in 3-weekly regimens (36, 37). The influence of polysorbate 80 on docetaxel protein binding is presumably the result of formation of a complex of polysorbate 80 with serum proteins and/or a displacement interaction on the main docetaxel binding protein, α1-acid glycoprotein (38), caused by polysorbate 80 degradation product(s) (39). Regardless of the exact mechanistic basis for this phenomenon, this finding indicates that exposure to the (pharmacologically active) fraction of unbound docetaxel may increase with an increase in dose (from 35 to 75 or 100 mg/m²), which would be expected to result in more severe hematological toxicity. However, docetaxel is often administered as a 30-min infusion with weekly regimens and as a 1-h infusion with 3-weekly regimens, which may achieve similar polysorbate 80 concentrations at the end of the docetaxel infusion. Measurement of polysorbate 80 concentrations in plasma with weekly and 3-weekly regimens is in progress.

The similar exposure–intensity and dose–intensity (6) relationships for docetaxel is consistent with observations of comparable efficacy of weekly and 3-weekly regimens in Phase II trials in patients with metastatic breast cancer and advanced non-small cell lung cancer (18–21) and with preclinical studies suggesting that the antitumor activity of docetaxel is independent of the dose/schedule of administration (40). Weekly and
3-weekly docetaxel regimens are being directly compared in breast cancer in the adjuvant setting. Similar to docetaxel, paclitaxel appears to have comparable efficacy when administered in high-dose or low-dose regimens in patients with metastatic breast cancer (41–43).

When we measured docetaxel concentrations over an extended sampling time period of 3 weeks, docetaxel clearance values were, on average, 10−35% lower than those determined from the 24-h data. Because a 25% decrease in docetaxel clearance has been shown to be associated with a significant increase (150%) in the odds of developing febrile neutropenia (5), when combining data from different studies for pharmacokinetic, pharmacodynamic, and/or pharmacogenetic analysis, it will be important to include data obtained with similar sampling schemes and equally sensitive analytical methods if extended sampling strategies are used.

With the use of prolonged plasma-sampling schemes, the calculated terminal disposition half-life of docetaxel was ~86 h, which is ~5-fold longer than that estimated on the basis of conventional 24-h sampling intervals and almost 9-fold longer than published values (35). Consequently, docetaxel concentrations are maintained above 0.0008 µg/ml (1.0 nM) for 7 days with weekly schedules and above 0.0004 µg/ml (0.5 nM) for 21 days with 3-weekly regimens (Table 3 and Fig. 3). This observation is of particular relevance with regard to potential mechanisms of action of the taxanes; low nanomolar concentrations have been shown to inhibit cell proliferation without arresting cells at mitosis (44, 45), suppress microtubule dynamics (46), inhibit tumor angiogenesis (47–49), or enhance cell radiosensitization (50).

There is current preclinical and clinical interest in the potential antiangiogenic properties of the taxanes. Indeed, docetaxel and paclitaxel have recently been shown to be potent and specific inhibitors of endothelial cell migration in vitro (51), vascular endothelial cell growth factor secretion (52), and angiogenesis in vitro and in vivo at IC_{50} values of approximately ≤1 nM (47–49). It has been suggested that weekly schedules of taxanes possess antiangiogenic properties relative to 3-weekly schedules because a weekly schedule of paclitaxel has been shown to induce responses in some patients with tumors refractory to paclitaxel administered every 21 days (53, 54). However, this has not been demonstrated unequivocally in in vivo preclinical models. Moreover, if maintaining low nanomolar concentrations for prolonged periods contributes to the antiangiogenic properties of docetaxel, then this mechanism of action should apply to both schedules of administration given the similarity in circulating concentrations.

Collectively, these data show that the altered toxicity profiles observed with weekly docetaxel administrations may not

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**Fig. 2** Plasma concentration–time profiles from extended plasma sampling after administration of 35 mg/m^2 docetaxel as a 30-min infusion (A) and 75 mg/m^2 administered as a 1-h infusion (B). Dashed lines are concentrations simulated from fitting a three-compartment model to the observed concentration–time data. The following equation converts docetaxel concentrations in units of µg/ml to nM: concentration (nM) = concentration (µg/ml) / 1237.79.

**Fig. 3** Observed mean docetaxel plasma concentrations after 35 mg/m^2 docetaxel administered as a 30-min infusion (solid line), 75 mg/m^2 administered as a 1-h infusion (dashed line), and 100 mg/m^2 administered as a 1-h infusion (dotted line). Panel A includes concentrations to 24 h post-infusion, and panel B includes concentrations to day 22 (~500 h). The following equation converts docetaxel concentrations in units of µg/ml to nM: concentration (nM) = concentration (µg/ml) / 1237.79.
be explained by a change in plasma pharmacokinetics of total
drug and that previously defined exposure–toxicity relationships
for 3-weekly regimens do not apply to weekly regimens. In
addition, we have shown, by applying an extended sampling
period of 21 days, that until now the circulation time of
docetaxel in cancer patients has been greatly underestimated.
The presently observed prolonged terminal disposition phase of
docetaxel should be taken into consideration when designing
future clinical trials of docetaxel administered in novel drug
combinations and combined modality therapy and when evaluat-
ing alternative schedules of administration.

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