Cancer Therapy: Clinical

Therapeutic Drug Monitoring for the Individualization of Docetaxel Dosing: A Randomized Pharmacokinetic Study

Frederike K. Engels1,2, Walter J. Loos1, Jessica M. van der Bol1, Peter de Bruijn1, Ron H.J. Mathijssen1, Jaap Verweij1, and Ron A.A. Mathot2

Abstract

**Purpose:** Docetaxel pharmacokinetic (PK) parameters, notably clearance and exposure (AUC), are characterized by large interindividual variability. The purpose of this study was to evaluate the effect of PK-guided [area under the plasma concentration versus time curve (AUC) targeted], individualized docetaxel dosing on interindividual variability in exposure.

**Experimental Design:** A limited sampling strategy in combination with a validated population PK model, Bayesian analysis, and a predefined target AUC was used. Fifteen patients were treated for at least 2 courses with body surface area–based docetaxel and 15 with at least 1 course of PK-guided docetaxel dosing.

**Results:** Interindividual variability (SD of ln AUC) was decreased by 35% (N = 15) after 1 PK-guided course; when all courses were evaluated, variability was decreased by 39% (P = 0.055). PK-guided dosing also decreased the interindividual variability of percentage decrease in white blood cell and absolute neutrophil counts by approximately 50%.

**Conclusions:** Further research is required to determine whether the decrease in PK variability can contribute to a reduction in interindividual variability in efficacy and toxicity. Clin Cancer Res; 17(2); 353–62.

Introduction

The anticancer drug docetaxel (Taxotere) is approved for the adjuvant treatment of patients with breast cancer, locally advanced or metastatic breast cancer, non–small cell lung cancer (NSCLC), hormone refractory prostate cancer, and gastric cancer (www.taxotere.com). The docetaxel dose recommended for treating cancer patients ranges from 60 to 100 mg/m² as a 1-hour intravenous infusion once every 3 weeks.

An important limitation associated with docetaxel use is the substantial and unpredictable interindividual variability in toxicity (notably severe haematologic toxicity) and efficacy. This interindividual variability in both toxicity and efficacy is thought to be partly related to large interindividual variability in docetaxel pharmacokinetics, notably in the primary pharmacokinetic (PK) parameter clearance (coefficient of variation 30%–40%, incidentally up to more than 50%; refs. 1–4) and, consequently in drug exposure, i.e. area under the plasma-concentration versus time curve (AUC). The large interpatient PK variability may result in undertreatment of some patients or overtreatment with unacceptable severe toxicities in others. To date, there is no way to adequately predict a priori in which patient severe toxicities will occur and which patient may be undertreated with the recommended dose. Bruno and colleagues demonstrated that exposure to docetaxel was a significant predictor of time to progression and death in NSCLC patients (2). In addition, a 50% decrease in docetaxel clearance increased the odds of developing grade 4 neutropenia and febrile neutropenia 4-fold and 3-fold, respectively. Reducing the interindividual variability in docetaxel exposure may therefore largely assist in reducing the occurrence of severe toxicity and thereby help optimize the individual risk–benefit ratio for docetaxel therapy.

Given the fact that docetaxel is extensively and predominantly metabolized by hepatic and intestinal cytochrome P450 isoform 3A (CYP3A; refs 5, 6) and that (hepatic) CYP3A activity has also been identified as a strong predictor of docetaxel clearance (3), attempts have been made to individualize (i.e., optimize) docetaxel dosing through CYP3A phenotyping strategies. Several probes, including erythromycin (ERMBT), midazolam, exogenous cortisol, and dexamethasone (1, 3, 7, 8), have been used. Earlier (conventional) docetaxel dosing based on body surface area (BSA) was compared with individualized docetaxel dosing based on a predefined target AUC value and an individual’s estimated docetaxel clearance (9). The latter
PK parameter was derived upon assessment of the patient’s CYP3A activity, using the 24-hour urinary metabolite (6-β-hydroxycortisol) of exogenous cortisol (300 mg hydrocortisone i.v.). A significant decrease in interindividual variability in exposure was demonstrated upon application of this CYP3A phenotyping method. However, despite the availability and applicability of phenotypic probes, all phenotyping techniques are more or less associated with practical and logistical disadvantages (10, 11); that is, administration of a radioisotope (ERMBT), administration of pharmacologically active doses of a drug (midazolam, dexamethasone), and 24-hour urine collection (exogenous cortisol). These drawbacks have limited their use in the average outpatient setting. Other attempts to individualize docetaxel dosing through pretreatment knowledge of an individual’s CYP3A catalytic function include CYP3A genotyping strategies. However, to date, CYP3A genotyping strategies have yielded controversial results in part due to underpowered studies (12, 13).

Although widely practiced in other areas of medicine, routine application of therapeutic drug monitoring (TDM) is limited in oncology (14). The development of limited sampling strategies, in combination with population PK models, Bayesian analysis, and improved analytical procedures that allow for sensitive, specific, and rapid assay of docetaxel samples (15), largely facilitate TDM, making this an interesting strategy for docetaxel dosage individualization. However, up to now, no applicable TDM strategy has been developed for this drug. Here, we present an easy to implement TDM strategy based on a validated limited sampling model and Bayesian analysis to obtain individual estimates of docetaxel clearance.

Translational Relevance

As a result of its narrow therapeutic window, docetaxel therapy may result in serious toxicity. This creates a major clinical problem, with increased morbidity for the patient and higher costs for society due to extra hospitalization periods for the patients. The interindividual variability in the pharmacokinetics of this drug is relatively large after making traditional dose calculations based on body surface area. Currently, there is no generally accepted alternative dosing strategy available for docetaxel. Therapeutic drug monitoring (TDM) may be a promising alternative when it leads to a clinically relevant reduction in pharmacokinetic variability. However, up to now, no applicable TDM strategy has been developed for this drug. Here, we present an easy to implement TDM strategy based on a validated limited sampling model and Bayesian analysis to obtain individual estimates of docetaxel clearance.

Based on a previous PK study. In the above-mentioned study, the feasibility of an elaborate CYP3A phenotypically based dosing procedure was evaluated, an approach that differs conceptually from (AUC-targeted) TDM (16).

We describe here the results of a prospective, randomized, controlled trial conducted to evaluate the feasibility and performance of PK-guided (i.e., AUC-targeted) individualized docetaxel dosing in cancer patients treated with docetaxel once every 3 weeks. Docetaxel clearance was estimated by Bayesian analysis after each course and doses were adjusted iteratively to obtain the target AUC in subsequent courses.

Materials and Methods

Patient selection

Eligible patients had a histologically or cytologically confirmed diagnosis of cancer for which treatment with docetaxel once every 3 weeks was initiated. Additional eligibility criteria included the following: life expectancy of 12 weeks or greater; age 18 years or older; adequate bone marrow function (absolute neutrophil count (ANC) >1.5 x 10^9/L; platelet count >100 x 10^9/L), and renal function [serum creatinine ≤ 2 x the institutional upper limit of normal (ULN); total bilirubin level <1.5 x ULN]. Patients with moderate to severe liver impairment, that is, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >1.5 x ULN, concurrent with alkaline phosphatase levels >2.5 x ULN or greater, were not included in the study (16). Simultaneous (chronic) use of any medication, dietary supplements, or other compounds known to inhibit or induce CYP3A (http://www.medicine.iupui.edu/flockhart/) was not allowed. This single-center study was approved by the Erasmus Medical Center Ethical Review Board, and all patients gave written informed consent before study entry.

Study design, treatment, and treatment evaluation

At study entry, patients were randomized to either BSA-based docetaxel dosing or PK-guided docetaxel dosing. Irrespective of randomization outcome, all patients were treated with BSA-based docetaxel during course 1 after study entry. For patients randomized to BSA-based treatment, the docetaxel dose during all subsequent courses (minimum 1) was calculated according to actual BSA. For patients randomized to PK-guided treatment, the docetaxel dose for all subsequent courses (minimum 1, i.e., at least 1 individualized dose was given to patients) was calculated on the basis of PK data analysis performed after the previous courses. For safety reasons, the dose in the PK-guided study arm was never increased by more than 30% compared with the previous dose. Docetaxel (Taxotere concentrate for infusion 20 mg = 0.5 mL + solvents and 80 mg = 2 mL + solvents; Sanofi-Aventis) was diluted in 250 or 500 mL of 0.9% NaCl (depending on dose) and given as a 1-hour intravenous infusion during all courses. Patients were able to participate in the study for a maximum of 6 courses. Treatment evaluation was according to
standard hospital procedures. In addition, hematologic

toxicity was quantified by expressing docetaxel-induced
toxicity by the percentage decrease in white blood cell
(WBC) and ANC [i.e., (pretreatment value − nadir
value)/pretreatment value × 100%].

Development of a limited sampling strategy

To characterize docetaxel pharmacokinetics, tradition-
ally, dense sampling strategies are used, allowing for the
most accurate estimation of PK parameters (e.g., AUC and
clearance). However, this also implies a substantial burden
and inconvenience for the patient. Application of a limited
sampling strategy in combination with Bayesian analysis
allows individual PK parameters to be estimated using only
a minimal number of blood samples. Thus, patient burden
is reduced and it is possible to collect samples on an
outpatient basis. In a retrospective study, Baille and col-
leagues validated several optimal sampling strategies by
using Bayesian analysis (19). In the referred study, PK
parameters were used from a large (N = 640) cohort of
patients who had received docetaxel as a 1-hour infusion at
doses ranging from 50 to 100 mg/m² (20). Baille et al.
showed that clearance was well estimated when at least 2
samples were taken. For our study, we successfully vali-
dated several limited sampling strategies by using retro-
spective data from our own center (46 densely sampled
courses) based on a population PK model reported by
Bruno et al. (20). The model incorporated BSA, α₁-acid
glycoprotein (AAG), albumin, hepatic function [i.e., ele-
vated levels of alkaline phosphatase and transaminases
(ALT, AST)], and age, as the main predictors of docetaxel
clearance (20). Bayesian analysis was performed to obtain
individual estimates of docetaxel clearance (for procedure,
see the following text). Clearance obtained by the limited
sampling strategy was compared with the value obtained
on PK analysis by using all (average N = 11) blood samples
(i.e., dense sampling). The following limited sampling
strategy was chosen for the current study: sampling time
points at T = 0 hour (i.e., prior to the start of docetaxel
infusion), T = 30 minutes after the start of infusion, T =
50–55 minutes after the start of infusion (i.e., just prior to
end of infusion), and T = 3–6 hours (i.e., 2–5 hours after
the end of infusion). In addition, when possible (for in-
patients), a late PK sample at 24 hours postinfusion was
taken. The predictive performance of the chosen limited
sampling strategy was as follows: bias, that is, mean relative
prediction error (95% CI) of clearance was −0.2% (95%
CI: −2.1 to 1.7%; last sample T = 5 hours), −0.5% (95%
CI: −2.6 to 1.5%; last sample T = 3 hours), and −0.1% (95%
CI: −1.8 to 1.5%; last sample T = 24 hours) with respective
values for precision of 6.5%, 6.1%, and 5.4% (Note: max-
imum accepted value for precision is generally 20%).

As already mentioned, a well-established target AUC
value for which the balance between efficacy and toxicity
is optimal is lacking. In the current study, we chose to use a
weighted mean for the target AUC that was based on several
representative docetaxel PK studies (2, 4, 7, 9, 21), in-
cluding a total of 806 patients treated with docetaxel
100 mg/m². The target AUC was set at 4.90 mg/L h. As
docetaxel pharmacokinetics are linear and independent of
schedule (21, 22), the target AUC for reduced doses of
docetaxel was adjusted accordingly (i.e., if a patient was
treated with a docetaxel dose of 75 mg/m², the target AUC
was set at 0.75 × 4.90 = 3.68 mg/L h. PK sampling
according to this validated limited sampling strategy was
performed during each course for both treatment groups.

Bayesian analysis

Bayesian analysis was performed using the NONMEM
software program (double precision, Version VI; level 1.0;
ref 23). The population PK parameters are given in Table 1.
On the basis of the population PK model (20) and the
observed individual plasma concentrations, individual PK
parameter estimates were obtained by Bayesian (post hoc)
analysis. The plasma concentrations of all previous courses
were used to calculate individual clearance values. The
Bayesian estimation for individual clearance was used to
calculate the individualized dose based on the target AUC
value [i.e., individualized dose (mg) = Bayesian estimated
clearance (L/h) × target AUC (mg/L h)].

Docetaxel analysis

For docetaxel PK analysis, blood samples (approximately
7 ml in lithium-heparinized tubes) were collected accord-
ing to the described limited sampling strategy. All samples
were processed to plasma by centrifugation for 10 minutes
at 3,000 × g (4°C) and stored at −80°C until analysis. Total
docetaxel plasma concentrations were determined using
liquid chromatography coupled to tandem mass spectro-
metry (15, 24).

Sample size calculation

Large interindividual variability in docetaxel PK analysis,
notably in the primary PK parameters clearance and expo-
sure [coefficient of variation (CV): 30%–40%, incidentally
up to more than 50%], has been reported (1–4). The sample
size was based on the hypothesis that the inter-
individual variability (expressed as the SD) in the PK
parameter AUC (i.e., exposure) could be reduced by
50%, given a normal distribution of this (log-transformed)
parameter. The SD of ln AUC is a 1-parameter estimate that
approximates the CV of AUC. To detect a 50% difference
with a 2-sided F test at α = 0.05 and a power of 80%,
sample size was set at 15 patients per treatment arm.

Statistical analysis

The interpatient variability of AUC for each arm was thus
evaluated by determining SD of ln AUC and was compared
by the F test (Levene’s test). PK parameter means and biases
from the target AUC (i.e., mean AUC value in each arm
minus the target AUC) were compared using Student’s
t test. Hematologic toxicity was evaluated by t test for
equality of means and Levene’s test for equality of var-
iances. A 2-sided P < 0.05 was considered to be statistically
significant. Statistical calculations were performed with
SPSS, Version 16.0.
Results

Patient accrual

Nineteen patients were randomized to the BSA-based dosing group and 22 to the PK-guided dosing group (i.e., a total of 41 patients enrolled in the study). Four patients did not continue treatment in the BSA-based dosing group after course 1; 2 upon their own request, 1 due to febrile neutropenia upon which treatment was discontinued, and for 1 patient, PK sampling failed during the first course. Treatment was discontinued after course 2 due to progressive disease. Thus, a total of 15 patients completed at least 2 courses according to the BSA-based dosing strategy and were evaluable for PK data analysis. In the study, 2, 2, and 1 patient(s) completed a total of 3, 4, and 5 courses, respectively, and 1 patient completed the maximum of 6 courses as defined in the protocol. Hence, a total number of 43 courses were evaluated in the BSA-based dosing group, of which 36 were AUC-targeted courses. For both dosing strategy groups, none of the patients used comedication and/or dietary supplements known to modulate CYP3A4-function. Table 2 lists a summary of the baseline characteristics of the patients in both dosing strategy groups.

PK analysis

The primary objective of the study was to evaluate whether the interindividual variability in docetaxel exposure (expressed by the PK parameter AUC) could be reduced by 50% when TDM is applied to individualize the dose in at least 1 subsequent course and whether this approach is technically feasible. Table 3 summarizes the docetaxel PK parameters clearance and AUC (i.e., exposure) for both dosing groups. Mean clearance values (using the Bayesian estimation for individual clearance based on all evaluated courses) did not differ between the 2 dosing strategies. Moreover, interpatient variability (CV) of the clearance was within previously reported ranges for both dosing groups (7, 25). Respective values for the BSA-based and PK-guided group were 39.1 ± 9.7 L/h (25%) and 39.7 ± 11.4 L/h [29%; mean ± SD (CV%), N = 15]. To evaluate the effect of the individualized dosing strategy on exposure (AUC), the AUC values obtained for course 2 in the BSA-based group were compared with the AUC values obtained for course 2 for the PK-guided group. Mean (SD) exposure values for the 2 dosing groups were 5.01 mg/L h (SD = 1.21) and 5.49 mg/L h (SD = 0.78) for the BSA-based group (N = 15) and PK-guided group (N = 15), respectively (P = 0.21). PK-guided dosing affected the interindividual variability in exposure (SD of ln AUC), albeit not statistically significantly (P = 0.16); interindividual variability in exposure was decreased by 35% upon PK-guided dosing. On a linear scale, CV decreased from 24.1% (N = 15) to 14.2% (N = 15) and on a logarithmic scale (i.e., SD of ln AUC) from 0.23 to 0.15. In the BSA-based dosing group, total docetaxel doses received for courses 1 and 2 ranged from 100 to 230 mg and from 85 to 200 mg, respectively. For the PK-guided dosing group, total docetaxel doses for courses 1 and 2 ranged from 130 to 190 mg and from 135 to 246 mg, respectively. Absolute dose adjustments (i.e., dose course 2 minus dose course 1) ranged from +56 to −24 mg (median = 15 mg). In addition, the effect of the individualized dosing strategy on AUC was also evaluated by comparing all AUC values obtained for the BSA-based group (N = 43) with all AUC values obtained from course 2 and further for the PK-guided group (N = 36). Mean exposure values did not differ between both dosing groups; respective values were 4.93 (SD = 1.29) mg/L h and 5.09 (SD = 0.74) mg/L h for the BSA-based group (N = 43) and PK-guided group (N = 36), respectively (P = 0.50). Again PK-guided dosing affected the interindividual variability in exposure; the interindividual variability in exposure (SD of ln AUC) was decreased by 39% upon PK-guided dosing, reaching borderline significance (P = 0.055). On a linear scale, CV was decreased from 26.2% (N = 43) to 14.5% (N = 36).
and on a logarithmic scale (i.e., SD of ln AUC) from 0.23 to 0.14. In 1 patient, the individualized dose was capped at a maximum increase of 30% as defined in the protocol for the 2 PK-guided courses. Of note, the calculated individualized doses for this patient differed only marginally for courses 2 and 3 (absolute difference 12 mg).

The average biases from the target AUC in the BSA-based arm and in the individualized arm were 0.032 and 0.189 mg/L h, respectively, with no significant difference (P = 0.50). Figures 1 and 2 illustrate the AUC values for each evaluated course for all patients in the BSA-based dosing and PK-guided dosing group, respectively. Because of close cooperation and adequate planning, analysis of all blood samples was always feasible in time for calculation of the next individualized dose (i.e., within 3 weeks) and communication with the prescribing physician. The same was applicable for the analysis of the blood samples for AAG, which is not a routine chemistry determination in our institution. Overall, technical feasibility of the individualized dosing approach was considered more than adequate.

### Pharmacodynamic analysis/hematologic toxicity analysis

In both arms, neutropenia was the predominant toxicity related to docetaxel treatment. In the BSA-based dosing group, 1 patient developed febrile neutropenia (ANC < 1.0 × 10⁹/L and fever ≥ 38.5°C) in course 1 and also 1 patient in course 2; in the PK-guided dosing group, 4 patients developed febrile neutropenia in course 1 and 1 patient in course 2. Nonhematologic toxicities were as expected. As hematologic toxicity of docetaxel is correlated to exposure (2), we also evaluated the effect of AUC-targeted docetaxel therapy both on the degree of docetaxel-induced hematologic toxicity and on the interindividual variability in docetaxel-induced hematologic toxicity. Hematologic toxicity for course 2 was expressed by the percentage decrease in WBC and ANC (i.e., [pretreatment value – nadir value]/pretreatment value × 100%). In the BSA-based group, 1 patient was prescribed the granulocyte colony-stimulating factor filgrastim (Neupogen) during the 2 evaluated courses and was excluded from the pharmacodynamic (PD) analysis. Furthermore, for 3 patients, no laboratory

### Table 2. Baseline patient characteristics (N = 15 per treatment arm)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BSA-based dosing</th>
<th>PK-guided dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Age, y</td>
<td>54 (25–74)</td>
<td>59 (44–69)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.96 (1.54–2.40)</td>
<td>1.85 (1.71–2.20)</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, × 10⁹/L</td>
<td>10.64 (6.9–19.7)</td>
<td>10.0 (5.5–17.9)</td>
</tr>
<tr>
<td>ANC, × 10⁹/L</td>
<td>9.8 (4.2–18.3)</td>
<td>8.9 (4.3–17.0)</td>
</tr>
<tr>
<td>Platelets, × 10⁹/L</td>
<td>314 (158–517)</td>
<td>285 (214–581)</td>
</tr>
<tr>
<td>Hemoglobin, mmol/L</td>
<td>7.7 (7.1–9.8)</td>
<td>7.6 (6.6–9.6)</td>
</tr>
<tr>
<td>Clinical chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, U/L</td>
<td>22 (13–196)</td>
<td>23 (11–91)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>27 (11–398)</td>
<td>18 (8–62)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>93 (36–675)</td>
<td>88 (55–514)</td>
</tr>
<tr>
<td>Total protein, g/L</td>
<td>79 (69–89)</td>
<td>73 (65–88)</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L</td>
<td>7 (4–19)</td>
<td>7 (5–15)</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>43 (36–46)</td>
<td>41 (34–45)</td>
</tr>
<tr>
<td>Serum AAG, g/L</td>
<td>1.24 (0.28–2.36)</td>
<td>1.11 (0.76–1.99)</td>
</tr>
</tbody>
</table>

NOTE: Values are given as median with range in parentheses (except for sex and tumor type).
Table 3. Docetaxel PK parameters for the BSA-based dosing group and the PK-guided dosing group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BSA-based dosing</th>
<th>PK-guided dosing</th>
<th>Differencea</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLb (all courses), L/h</td>
<td>39.11</td>
<td>39.65</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>9.68</td>
<td>11.35</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CV%</td>
<td>24.8</td>
<td>28.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLc (course 2 only), L/h</td>
<td>40.09</td>
<td>37.68</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>9.10</td>
<td>10.07</td>
<td>+11%</td>
<td></td>
</tr>
<tr>
<td>CV%</td>
<td>22.7</td>
<td>26.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln CLc</td>
<td>3.67</td>
<td>3.60</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.23</td>
<td>0.24</td>
<td>+4%</td>
<td>0.82</td>
</tr>
<tr>
<td>ln AUCc (course 2 only), mg/L h</td>
<td>5.01</td>
<td>5.49</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1.21</td>
<td>0.78</td>
<td>−35%</td>
<td>0.24</td>
</tr>
<tr>
<td>CV%</td>
<td>24.1</td>
<td>14.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln AUCc</td>
<td>1.59</td>
<td>1.69</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.23</td>
<td>0.15</td>
<td>−35%</td>
<td>0.16</td>
</tr>
<tr>
<td>AUCc (all courses), mg/L h</td>
<td>4.93</td>
<td>5.09</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1.29</td>
<td>0.74</td>
<td>−43%</td>
<td>0.045</td>
</tr>
<tr>
<td>CV%</td>
<td>26.2</td>
<td>14.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln AUCd</td>
<td>1.57</td>
<td>1.62</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>0.23</td>
<td>0.14</td>
<td>−39%</td>
<td>0.055</td>
</tr>
</tbody>
</table>

NOTE: For all courses, the AUC was extrapolated to a dose of 100 mg/m² for reasons of comparison; target AUC for dose 100 mg/m² is 4.90 mg/L h.

Abbreviations: CL, clearance; ln CL, log-transformed clearance; ln AUC, log-transformed AUC; NA not applicable.

aPercent difference between the value for the PK-guided group compared with the BSA-based dosing group calculated as follows: \[ \frac{1- (\text{PK value}/\text{BSA value})}{\text{BSA value}} \times 100. \]

bValue is reported as mean (N = 15 patients); the Bayesian estimation for individual clearance on the basis of all evaluated courses was used for the calculation.

cValues are reported as mean for the BSA-based course 2 (N = 15) and as mean for the first PK-guided course (N = 15; i.e., course 2).
dValues are reported as mean for all BSA-based courses (N = 43) for the BSA-dosing group (i.e., course 1, 2, and optional subsequent courses) and as mean for all PK-guided courses (N = 36) for the PK-dosing group (i.e., course 2 and optional subsequent courses).

Figure 1. AUC values (mg/L h) for all evaluated courses in the BSA-based dosing group (course 1 and subsequent courses; N = 43), specified per course number and extrapolated to a dose of 100 mg/m² for reasons of comparison.

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values were available for the nadir values (day 8). Of the remaining 11 patients, 7 were prescribed a dose of 75 mg/m² and were included in the toxicity analysis. In the PK-guided dosing arm for 2 patients, no data were available for the nadir values. Of the remaining 13 patients, 10 patients were dosed to achieve a target AUC (3.68 mg/L h) corresponding to a dose of 75 mg/m² and were included in the toxicity analysis. In addition, we evaluated overall hematologic toxicity for all patients dosed 75 mg/m² during all courses or targeted to achieve an AUC of 3.68 mg/L h; for the BSA-based dosing group, a total of 19 and 18 courses were evaluable for decrease in both WBC and ANC, respectively. For the PK-guided dosing group, a total of 25 and 23 PK-guided courses (i.e., course 2 and subsequent courses) were evaluable for decrease in both WBC and ANC, respectively. Table 4 summarizes the hematologic toxicity for both dosing groups. There was no statistically significant difference in mean percentage decrease in WBC or ANC.

Figure 2. AUC values (mg/L h) for all evaluated courses in the PK-guided dosing group (course 1 and subsequent courses; N = 51), specified per course number and extrapolated to a dose of 100 mg/m² for reasons of comparison.

Table 4. Summary of docetaxel hematologic toxicity for the BSA-based dosing group and the PK-guided dosing group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BSA-based dosing</th>
<th>PK-guided dosing</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of course 2</td>
<td>7</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease WBC, %</td>
<td>76.1</td>
<td>83.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>15.9</td>
<td>6.9</td>
<td>57%</td>
<td>0.05</td>
</tr>
<tr>
<td>CV%</td>
<td>21.0</td>
<td>8.3</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Decrease ANC, %</td>
<td>85.5</td>
<td>92.8</td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>SD</td>
<td>15.1</td>
<td>7.2</td>
<td>52%</td>
<td>0.04</td>
</tr>
<tr>
<td>CV%</td>
<td>17.7</td>
<td>7.7</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Total evaluated courses</td>
<td>19</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease WBC, %</td>
<td>78.3</td>
<td>82.8</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>SD</td>
<td>15.6</td>
<td>5.6</td>
<td>64%</td>
<td>0.01</td>
</tr>
<tr>
<td>CV%</td>
<td>20.0</td>
<td>6.7</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Total evaluated courses</td>
<td>18</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease ANC, %</td>
<td>90.9</td>
<td>93.3</td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>SD</td>
<td>10.6</td>
<td>5.1</td>
<td>52%</td>
<td>0.07</td>
</tr>
<tr>
<td>CV%</td>
<td>11.7</td>
<td>5.5</td>
<td>53%</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Percent decrease in WBC and ANC defined as [(pretreatment value – nadir value)/(pretreatment value)] × 100.

Values are reported as mean.

Percent difference between the value for the PK-guided group compared to the BSA-based dosing group calculated as follows: [1 – (PK value/BSA value)] × 100.
However, for course 2, interindividual variability for both WBC and ANC was significantly smaller for the PK-guided dosing group, with a reduction in the variability (CV%) of more than 50%. When all courses were evaluated, variability (CV%) was also reduced by more than 50% in the PK-guided dosing group and interindividual variability (expressed as SD) of the decrease in WBC was significantly smaller.

Discussion

An important limitation associated with docetaxel chemotherapy is the substantial and, more important, highly unpredictable interindividual variability in toxicity and efficacy. Moreover, a large population PK-PD analysis has demonstrated that variability in toxicity is strongly associated with wide interindividual variability in docetaxel pharmacokinetics (2). Since clinical introduction, much research has therefore focused on reducing the substantial degree of interindividual variability in docetaxel exposure. Despite all efforts, to date, an individual’s docetaxel dose is (still) calculated on the basis of BSA. Yet, for the average BSA, normalization of docetaxel clearance to BSA results in negligible reduction in PK variability and does not contribute substantially to explaining the interindividual PK variability (26). Presently, approaches to reduce interindividual PK variability through individualized dosing (e.g., CYP3A phenotyping strategies/CYP3A genotyping strategies) are all associated with practical and logistical disadvantages or with controversial results, thus limiting applicability in the average outpatient setting. We therefore conducted a prospective randomized PK study to evaluate whether the simple approach of TDM, based on a limited sampling strategy in combination with a validated population PK model, Bayesian analysis, and a predefined target AUC value, could decrease PK variability compared with BSA-based dosing.

Our study demonstrates that individualized docetaxel dosing based on TDM is feasible in the outpatient setting. Inconvenience for the patient was limited to 4 blood samples and a minimum waiting interval of 2 hours post-infusion. More important, our results demonstrate a decrease in interpatient PK variability by 35% upon AUC-targeted dosing during at least 1 course, and a 39% decrease that reached borderline significance when all AUC-targeted courses were evaluated. However, we were unable to reduce the interindividual variability by 50% as hypothesized. It should be noted that the interindividual variability (CV) in clearance and AUC for the BSA-based dosing group for course 2 was low (23% and 24%, respectively, Table 3) compared to generally reported values of 30% to 40%, incidentally up to more than 50% (1–4).

As such, it is possible that in our study statistical significance regarding the primary outcome (i.e., reduction of variability by 50%) was not reached due to the fact that the study was underpowered. In addition, from our data, it seems that statistical significance in the reduction in interindividual variability in exposure is more likely to be achieved after more than 1 PK-guided course. A possible explanation for the reported low interindividual variability in docetaxel AUC in the BSA-based dosing (i.e., control) group could be poorer characterization of docetaxel PK by the chosen limited sampling strategy in combination with Bayesian analysis compared with characterization by a dense sampling strategy. However, the 35% reduction of the interindividual variability in exposure in the present study is comparable with the reduction achieved upon application of cortisol monitoring as reported by Yamamoto et al. (9). In the referred study, a dense sampling strategy was applied, yet the coefficient of variation was also unexpectedly low for the BSA-based dosing group (CV% = 15). Furthermore, as previously discussed, limited sampling strategies for the estimation of docetaxel dosing have been successfully validated (19, 20). Indeed, for our own study, the predictive performance (bias and precision) of the chosen limited sampling strategy was more than adequate. Another possible explanation for our study results (lack of statistical significance) may be due to a difference in onset in interindividual variability between the 2 dosing groups. Examination of the individual AUC values during course 1 for each dosing group (Figs. 1 and 2) indicates that the interindividual variability is smaller in the PK-based dosing group than the BSA-based dosing group. This was due to 2 patients in the BSA-based dosing group with extreme exposures (7.28 and 9.83 mg/L h).

Although we compared AUC values for BSA-based course 2 and the first PK-based course (i.e., course 2; Table 3), it is possible that the difference at onset seen for course 1 could bias our assessment of variability upon subsequent treatment cycles. In addition, patients with moderate to severe liver impairment, as previously defined by Baker et al. (18), were indeed not included in the study. CYP3A activity has been shown to be reduced by approximately 50% in these patients (18), and Bruno et al. (2, 20) predicted reduced docetaxel clearance by 25%. For this reason, physicians in our clinic are reluctant to prescribe docetaxel to such patients, and so for this feasibility study, we decided to exclude these patients. However, it is possible that the exclusion of these patients limited the extent of variability in the first BSA-based course, which could account for the fact that statistical significance regarding the primary outcome was not reached.

Yamamoto et al. (9) estimated an individual’s clearance from the assessment of the patient’s CYP3A activity by using the 24-hour urinary metabolite of exogenous cortisol (1). In their study, the SD of the AUC for the individualized dosing group (N = 29, mean AUC ± SD: 2.64 ± 0.22 mg/L h) was 46% smaller (P < 0.01) than for the BSA-based group (N = 30; mean AUC ± SD: 2.71 ± 0.40 mg/L h). In our view, the major difference between our study and the previously mentioned one is the clinical applicability: the application of a time- and labor-consuming CYP3A phenotyping method to individualize docetaxel dose limits implementation in a routine clinical outpatient oncology center, whereas our method can be implemented without major adjustments. The only prerequisite is that
bioanalysis of docetaxel samples is done within a period of 3 weeks (i.e., before the next course) and that routine chemistry data can be complemented with AAG measurement, thus allowing for individualized dose calculation before the next course. On the basis of our study, it is not possible to determine how many courses of TDM would be necessary, as participation during only 2 courses was obligatory. In general, patients in the PK-guided dosing group were more motivated to continue in the study after the obligatory first PK-guided course, which explains the difference in the number of patients who completed more than 2 courses in the study compared with the BSA-based dosing group.

Evaluation of docetaxel-induced hematologic toxicity indicated that mean decrease in WBC and ANC did not differ between the 2 dosing groups. Interindividual variability (CV%) in the individualized treatment group was reduced by more than 50% compared with the BSA group. It should be noted, however, that the variable pretreatment characteristics of the patients might have influenced frequency and severity of haematologic toxicity; inclusion criteria did not include a limit to the extent of pretreatment. Furthermore, evaluation of a decrease in hematologic variability was not the primary objective of the study and as such the study was not powered to detect differences in clinical outcome.

In conclusion, individualized dosing of docetaxel based upon a limited sampling strategy in combination with a validated population PK model, Bayesian analysis, and a predefined target AUC value can be used to decrease the interpatient PK variability compared with conventional BSA-based dosing. As borderline significance was reached, further research in a larger population is required to confirm these results. Furthermore, additional research is required to ascertain whether the reduction in PK variability can contribute to a reduction in interindividual variability in toxicity and efficacy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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Therapeutic Drug Monitoring for the Individualization of Docetaxel Dosing: A Randomized Pharmacokinetic Study

Frederike K. Engels, Walter J. Loos, Jessica M. van der Bol, et al.


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