Optimal Sampling Strategies for Bayesian Estimation of Docetaxel (Taxotere) Clearance

Pascale Baille, René Bruno, Jan H. M. Schellens, Lorraine K. Webster, Michael Millward, Jaap Verweij, and Guy Montay

Department of Drug Metabolism and Pharmacokinetics, Box 58, Rhône Poulenc Rorer, 20 Avenue Raymond Aron, 92165 Antony Cedex, France [P. B., R. B., G. M.]; Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, 3075 EA Rotterdam, the Netherlands [J. H. M. S., J. V.]; and Experimental Chemotherapy and Pharmacology Laboratory, Peter MacCallum Cancer Institute, Melbourne 3000, Australia [L. K. W., M. M.]

ABSTRACT

Docetaxel activity has been documented in many solid tumors, including metastatic breast cancer and non-small cell lung cancer. However, as clinical studies in other tumor types are now being conducted, the validation of an optimal sampling strategy would allow the performance of pharmacokinetics/pharmacodynamics studies with minimum inconvenience for the patient. Six optimal sampling strategies with one to six sampling times were computed, based on the D-optimality theory, using population pharmacokinetic parameters estimated from a large pharmacokinetic database of 547 patients treated in previous Phase II studies. Validation of these sampling strategies was performed on a set of 35 patients, from two Phase I studies, who received docetaxel as a 1-h infusion at doses ranging from 50 to 100 mg/m². Validation consisted of comparing clearance assessed by pharmacokinetic parameters estimated using complete plasma concentration-time data (considered as the reference) and clearance determined by Bayesian estimation with an optimal design. For all of the optimal sampling strategies tested, clearance was found to be well estimated when at least two samples were taken. Bayesian estimation with two measured levels (at the end of infusion and at 6 h after the start of infusion) can be selected, because it allows adequate estimation of clearance with a nonsignificant bias of +1.37% and a precision of 12.3%.

INTRODUCTION

Docetaxel (Taxotere) is a new anticancer agent of the taxoid family, which is active in a wide variety of solid tumors, such as metastatic breast cancer and non-small cell lung cancer (1–3). Docetaxel is currently undergoing further development demonstrating promising activity in many other tumor types either as a single agent or in combination with other cytotoxic drugs. Population PK/PD of single-agent docetaxel were prospectively studied in 547 patients entered in several Phase II studies (4, 5). Typical pharmacokinetic parameter estimates are: clearance, 36.7 liters/h (20.6 liters/h/m²); steady-state distribution volume, 149 liters (83.7 liters/m²); and terminal half-life, 11.4 h (2). Validated optimal sampling would further facilitate PK/PD studies.

Several methods have been developed to estimate individual pharmacokinetic parameters using a limited number of samples. The first approach involving Bayesian estimation is used widely in the area of drug monitoring and particularly for anticancer agents (6, 7). Bayesian estimation has recently been applied in conjunction with population pharmacokinetic methods, as an aid for population pharmacokinetic model building (8–10). Coupled to optimal sampling design (11), Bayesian estimation can be used to estimate individual patient parameters for PK/PD studies in large patient populations. Another approach uses a multiple linear regression procedure to predict a given pharmacokinetic parameter (usually the area under the curve). The latter approach, conceptually simpler, seems to be used more frequently for anticancer agents (7, 12), although Bayesian estimation is more flexible and more general in scope, because it allows full identification of the pharmacokinetic model. Very few papers have performed a direct comparison of the predictive performance of both approaches. In a recent study (13), optimal sampling design coupled to Bayesian estimation performed significantly better than a limited sampling model. The former approach is therefore recommended to perform PK/PD studies (13), whereas the latter might be more convenient for therapeutic monitoring in the routine clinical setting (12).

This article presents the design of optimal sampling strategies based on current population pharmacokinetic parameter estimates and the validation of these sampling strategies to estimate docetaxel pharmacokinetic parameters using Bayesian estimation. The validation has been performed comparing Bayesian estimates to reference maximum likelihood estimates obtained using complete plasma concentration-time data of extensively sampled patients entered in two Phase I studies of docetaxel in combination with cisplatin (14, 15).

MATERIALS AND METHODS

Patients and Treatment

The validation of optimal sampling strategies was performed using pharmacokinetic data from 35 patients entered in two Phase I combination studies of docetaxel and cisplatin (14, 15). Docetaxel was administered as a 1-h infusion at doses ranging from 50 to 100
Optimal Sampling Strategies for Docetaxel

The D-optimality criterion is the most frequently used design criterion. It minimizes total overall variance of parameter estimates. D-optimal designs are sampling designs minimizing the determinant of the inverse Fisher information matrix. D-optimality theory. D-optimal designs are sampling designs minimizing the determinant of the inverse Fisher information matrix.

### Computing of Optimal Sampling Strategies

Assessment of optimal sampling times was based on the D-optimality theory. D-optimal designs are sampling designs minimizing the determinant of the inverse Fisher information matrix. The D-optimality criterion is the most frequently used design criterion. It minimizes total overall variance of parameter estimates. D-optimal designs are sampling designs minimizing the determinant of the inverse Fisher information matrix. D-optimality theory. D-optimal designs are sampling designs minimizing the determinant of the inverse Fisher information matrix.

### Pharmacokinetic Studies

Docetaxel pharmacokinetic profile was assessed using extensive sampling strategies (about 15 samples were collected during and after the infusion, up to 48 h). Docetaxel was assayed in plasma samples by reverse-phase high-performance liquid chromatography and UV detection using a semiautomated method. Determination of Pharmacokinetic Reference Parameters. Reference individual pharmacokinetic parameters were estimated using the complete plasma concentration-time data and MLE with the NONMEM program (version IV, level 2.0; Ref. 18) running on an α-station DEC 2100 5/250. A three-compartment structural model with first-order elimination was used (PRED for Population Pharmacokinetics subroutines ADVAN 5 and TRANS 1). The basic parameters were elimination clearance (CL, liters/h), volume of distribution of the central compartment (Vc, liters) and intercompartmental rate constants (k12, k21, k31, and k32, h⁻¹). The elimination constant (k14) was defined as CL/Vc. Residual variability was modeled as proportional.

### Validation of Optimal Sampling Strategies

Computing of optimal sampling times was performed using population pharmacokinetic parameters. These population parameters were estimated by mixed effects modeling using a database consisting of 2.8 (range, 1-5 over 24 h) samples per patient in a total of 547 patients receiving docetaxel in previous Phase II studies (5). Because the use of covariates was not relevant for the computing of optimal sampling times, the parameters were estimated using the linear three-compartment model without any covariate. The program to determine the optimal times is part of the APIS package version 3.03a (17).

### Table 1: Optimal sampling strategies

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>Sampling times</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>EOI</td>
</tr>
<tr>
<td>4 (over 24 h)</td>
<td>EOI</td>
</tr>
<tr>
<td>4 (over 6 h)</td>
<td>EOI</td>
</tr>
<tr>
<td>3</td>
<td>EOI</td>
</tr>
<tr>
<td>2</td>
<td>EOI</td>
</tr>
<tr>
<td>1</td>
<td>EOI</td>
</tr>
</tbody>
</table>

### Table 2: Predictive performance of Bayesian estimation of docetaxel clearance with the different sampling strategies

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>1 (over 12 h)</th>
<th>3</th>
<th>4 (over 6 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CL, liters/h (SD)</td>
<td>37.7 (13.8)</td>
<td>37.9</td>
<td>37.4</td>
</tr>
<tr>
<td>Bias, me %, (95% CI)a</td>
<td>6.54 (-0.10; 12.97)</td>
<td>3.83 (0.38; 8.49)</td>
<td>1.34 (-3.06; 5.74)</td>
</tr>
<tr>
<td>Precision, rmse %b</td>
<td>20.2</td>
<td>14.4</td>
<td>13.2</td>
</tr>
</tbody>
</table>

a Optimal sampling strategies are classified from the least precise to the most precise.
b me %, mean relative prediction error; CI, confidence interval (α = 5%).
c rmse %, root mean squared relative prediction error.

mg/m². Cisplatin was given after or prior to docetaxel as either a 1- or 3-h infusion at doses ranging from 50 to 100 mg/m². These studies involved either patients with various solid tumor types (14) or patients with non-small cell lung cancer (15).

Detailed clinical and pharmacokinetic results have been published (14, 15). In both studies, no evidence for a pharmacokinetic interaction between cisplatin and docetaxel was found; therefore, docetaxel data are suitable for this validation.

### Computing of Optimal Sampling Strategies

Six optimal sampling strategies were designed as follows: (a) six sampling times with an observation time from the EOI to 24 h after the start of infusion; (b) four sampling times with an observation time up to 24 h after the start of infusion; (c) four sampling times with an observation time up to 6 h after the start of infusion for practical considerations (e.g., outpatient status); (d) three sampling times with an observation time up to 6 h after the start of infusion; (e) two sampling times up to 6 h; and (f) one sampling time.

Computing of optimal sampling times was performed using population pharmacokinetic parameters. These population parameters were estimated by mixed effects modeling using a database consisting of 2.8 (range, 1-5 over 24 h) samples per patient in a total of 547 patients receiving docetaxel in previous Phase II studies (5). Because the use of covariates was not relevant for the computing of optimal sampling times, the parameters were estimated using the linear three-compartment model without any covariate. The program to determine the optimal times is part of the APIS package version 3.03a (17).

### Table 1: Optimal sampling strategies

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>Sampling times</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>EOI</td>
</tr>
<tr>
<td>4 (over 24 h)</td>
<td>EOI</td>
</tr>
<tr>
<td>4 (over 6 h)</td>
<td>EOI</td>
</tr>
<tr>
<td>3</td>
<td>EOI</td>
</tr>
<tr>
<td>2</td>
<td>EOI</td>
</tr>
<tr>
<td>1</td>
<td>EOI</td>
</tr>
</tbody>
</table>

### Table 2: Predictive performance of Bayesian estimation of docetaxel clearance with the different sampling strategies

<table>
<thead>
<tr>
<th>Number of samples</th>
<th>1 (over 12 h)</th>
<th>3</th>
<th>4 (over 6 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CL, liters/h (SD)</td>
<td>37.7 (13.8)</td>
<td>37.9</td>
<td>37.4</td>
</tr>
<tr>
<td>Bias, me %, (95% CI)a</td>
<td>6.54 (-0.10; 12.97)</td>
<td>3.83 (0.38; 8.49)</td>
<td>1.34 (-3.06; 5.74)</td>
</tr>
<tr>
<td>Precision, rmse %b</td>
<td>20.2</td>
<td>14.4</td>
<td>13.2</td>
</tr>
</tbody>
</table>

a Optimal sampling strategies are classified from the least precise to the most precise.
b me %, mean relative prediction error; CI, confidence interval (α = 5%).
c rmse %, root mean squared relative prediction error.
Prediction with MLE
Observed concentrations

Observed concentrations

Fig. 2 Comparison of clearance as determined by MLE and Bayesian estimation using the two sampling times strategy (EOI and 6 h). Regression line: slope = 0.790 ± 0.039; intercept = 7.40 ± 1.57

where $\eta_{CL}$ denotes the (proportional) difference between the true parameter ($CL_j$) of individual $j$ and the typical value ($CL$). Residual variability was modeled as proportional.

Prior information for Bayesian estimation was provided by population pharmacokinetic parameters defined previously (see computation of optimal sampling strategies). Mean (and interpatient variance) population parameters are: $CL = 36.8 (0.226)$ liters/h, $V = 7.83 (0.307)$ liters, $k_{12} = 1.19 (0.599) h^{-1}$, $k_{21} = 1.75 (1.28) h^{-1}$, $k_{13} = 1.22 (0.13) h^{-1}$, and $k_{31} = 0.0879 (0.123) h^{-1}$.

The Bayesian analysis was performed using the NONMEM program (POSTHOC option).

Comparison of Sampling Strategies. On the basis of a large-scale, prospective population PK/PD study involving more than 500 patients, the AUC was a strong predictor of toxicity (e.g., grade 4 neutropenia or febrile neutropenia). Therefore, the present analysis focused on the development of a limited sampling strategy to estimate docetaxel plasma clearance ($CL$), which is related to AUC by the following equation: $CL = \text{dose}/\text{AUC}$. MLE using all of the data points was considered as the reference method, providing the best available estimates of the parameter values.

The population model relative prediction error $pe\%$ for clearance is defined as follows:

RESULTS

Optimal Sampling Strategies. The optimal sampling strategies, described in Table 1, involved six schedules of one to six samples between the EOI and either 6 or 24 h after the start of infusion.

EOI and 6 h after the start of infusion sampling times were found in all of the optimal sampling strategies. EOI samples were obtained immediately prior to the EOI. Additional important sampling times were 15 and 45 min after the EOI, 2–3 h and 24 h after the start of infusion.

Validation of Optimal Sampling Strategies. Because concentrations at 24 h after the start of infusion were missing or were below the limit of quantification for several patients, the 12-h sampling time was always used instead of 24 h. Differences between theoretical and actual sampling times were within 15 min for EOI, EOI + 15 min, and EOI + 45 min samples; within 1 h for 2.5–6.5-h samples; and up to 3 h for the 12-h samples.

Bias and precision of clearance with the different sampling strategies are given in Table 2. Sampling strategies are classified from the least to the most precise strategy.

Reference parameters estimated by MLE were close to those obtained in previous studies as mean (SD): $CL = 37.7 (13.8)$ liters/h. After Bayesian estimation, mean (SD) clearance
ranged from 37.0 (12.2) liters/h with a four sampling times strategy to 38.5 (10.9) liters/h with a one sampling time strategy.

None of the optimal strategies was biased except when only one sample was taken (bias of 6.54% with the confidence interval, which did not include zero). Precision was quite good for all of the strategies, ranging from 12.3% (two samples) to 20.2% (one sample).

The schedule with two sampling times (EOI and 6 h) had a very good performance with a nonsignificant 1.37% overestimation of reference values and a 12.3% precision.

Typical fits for the estimation of reference parameters (considering all of the points) and Bayesian estimation (with the two-point sampling strategy) are illustrated in Fig. 1 for a representative patient.

Comparison of clearance as determined by MLE and Bayesian estimation using the two sampling times strategy is represented in Fig. 2. With this optimal sampling strategy, the relative prediction error of individual patients was less than 20%, except in one case.

**DISCUSSION**

The present analysis focused on the development of a limited sampling strategy to estimate docetaxel plasma clearance (CL), which was a good predictor of several toxicity end points during docetaxel treatment in Phase II studies (4).

Different optimal sampling strategies of one to six sampling times have been computed and tested for investigating docetaxel pharmacokinetics using Bayesian estimation. Optimal sampling strategies and priors for Bayesian estimation have been obtained from the database of 547 patients published previously (5). The EOI and 6 h after the start of infusion were important sampling times, because they were found in all of the strategies to be tested. Differences between theoretical and actual sampling times (within 15 min up to EOI + 45 min samples, within 1 h from the 2.5- to the 6.5-h samples, and up to 3 h for the 12-h samples) demonstrate the flexibility of the optimal design approach versus the stepwise multiple linear regression approach, which assumes that the plasma sample was taken at the specified time.

For all of the optimal limited sampling strategies tested, clearance has been found well estimated by Bayesian estimation when compared with the reference value estimated by maximum likelihood when at least two samples were taken. The performance of Bayesian estimation is illustrated in Fig. 2. Nevertheless, clearance was overestimated slightly for low clearance values and underestimated for high clearance values. This trend, evidenced in Fig. 2 by the regression line, indicates that such Bayesian estimates that were dependent on both the information content of measured levels and that of population priors were somewhat shrunken toward the prior mean. Of note, none of the sampling strategies allowed precise estimation of other model parameters (data not presented).

On the basis of the objective of this study, which was to find an optimal sampling strategy that not only gave both precise and unbiased pharmacokinetic estimates but that was also practical, the two sampling times strategy (EOI and 6 h after the start of infusion) can be selected, because it allows adequate estimation of docetaxel clearance with a nonsignificant bias (+1.37%) and a good precision (12.3%). A single-point sampling strategy would result in biased estimates for clearance.

**REFERENCES**

Optimal sampling strategies for bayesian estimation of docetaxel (Taxotere) clearance.

P Baille, R Bruno, J H Schellens, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/3/9/1535

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.