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Population pharmacokinetics of topotecan: intraindividual variability in total drug

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Abstract The inter- and intraindividual variabilities in topotecan clearance (CL) were explored using a population pharmacokinetic approach. Total (lactone + hydroxy acid) topotecan plasma concentrations were obtained in 31 women with metastatic epithelial ovarian cancer treated by the 30-min intravenous infusion on 5 subsequent days. The data corresponding to three occasions (days 1 and 5 of cycle 1, and day 1 of cycle 2), were analyzed using the nonlinear mixed effect model program. A large interindividual variability was observed, with CL varying from 9.1 to 42.5 l per hour (mean 21.0). Topotecan CL was related to serum creatinine level, and age. A close relationship was also observed between topotecan CL and creatinine clearance. Intraindividual variability both within cycle 1 and between the two first cycles was limited, with a mean variation of $-2 \pm 17\%$, and $+5 \pm 20\%$, respectively. A limited sampling strategy using Bayesian estimation based on two samples (5 min before the end of the 30-min infusion, and 4 h after the end of infusion) was developed. The results of this study combine relationships between topotecan pharmacokinetic parameters and patient covariates that may be useful for a priori dose adjustment, and convenient sampling procedure that can be used for further studies and drug monitoring.

Key words Topotecan · Nonlinear mixed effect model · Population pharmacokinetics · Therapeutic drug monitoring

Abbreviations *AUC* Area under the curve · *CL* Topotecan clearance · *CrCl* Creatinine clearance · *EOI* End of the infusion · *HPLC* High-performance liquid chromatographic · *NONMEM* Nonlinear mixed effect model · *Scr* Serum creatinine

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Introduction

Topotecan (9-dimethylaminomethyl-10-hydroxycamptothecin) is a water-soluble semisynthetic analogue of camptothecin that binds to the topoisomerase I–DNA complex, leading to single-stranded, protein-associated DNA breakage and cellular cytotoxicity. Topotecan (Hycamtin) was approved in 1996 for the treatment of ovarian cancer patients following failure of first-line therapy. The dose-limiting toxicity of topotecan is myelosuppression, predominantly neutropenia [18]. The drug is poorly bound to plasma proteins, but is present under open hydroxy acid and closed lactone forms within the plasma according to a relatively constant ratio determined primarily by pH [11]. Several studies have shown pharmacokinetic-pharmacodynamic relationships for topotecan [9]. For the most used schedule (i.e., 30-min intravenous infusion on 5 subsequent days every 3 weeks), a correlation has been shown between the total (i.e., lactone plus hydroxy acid forms) plasma area under the curve (AUC) observed on day 1 and the percentage decrease in white blood cells [8, 15, 16, 20]. In keeping with these previous reports, we performed a clinical trial with dose individualization of topotecan based on a pharmacokinetic exploration during cycle 1 (days 1 and 5) and cycle 2 (day 1). The methodology of

the study consisted of individual analysis of the topotecan plasma concentrations versus time. The conventional pharmacokinetic parameters (i.e., obtained by individual analysis) and toxicity results will be presented elsewhere. After completion of this trial, we analyzed the data according to a population approach using the nonlinear mixed effect model (NONMEM) program [1] to describe more accurately the inter- and intraindividual pharmacokinetic variabilities, to examine the correlation between pharmacokinetic parameters and patient covariates, and to develop a limited sampling strategy for determining topotecan clearance (CL).

Materials and methods

Patients and treatment

Pharmacokinetic evaluation was performed in 31 women with metastatic epithelial ovarian cancer previously treated with at least one platinum-containing chemotherapy regimen; of these, 26 had been pretreated by cisplatin. Patient characteristics are presented in Table 1. Topotecan (Hycamtin, SmithKline Beecham Laboratories, USA) provided as the hydrochloride salt. This was dissolved in 100 ml 5% dextrose solution and administered intravenously by an automatic infusion pump over 30 min, repeated for 5 consecutive days every 3 weeks. In cycle 1 the daily dose for the 3 first days corresponded to the standard recommendation: 1.5 or 0.75 mg/m^2 per day if the patient creatinine clearance (CrCl calculated according to Cockcroft-Gault equation [5]) was greater than 40 or between 20 and 40 ml/min, respectively. The daily dose for the last 2 days of cycle 1 depended the observed topotecan AUC on day 1; the general objective was to constrain the overall AUC (i.e., from day 1 to day 5) within 37,500–75,000 nM/min (263–527 μg/l per hour). In patients with AUC on day 1 greater than 15,000 nM/min the daily dose for the last 2 days was decreased to achieve an overall AUC of 75,000 nM/min. In patients with AUC on day 1 lower than 7500 nM/min the daily dose for the last 2 days was increased to achieve an overall AUC of 37,500 nM/min. In patients with AUC on day 1 between 7500 and 15,000 nM/min no dose modification was performed during cycle 1. In cycle 2 the daily dose was 75%, 100%, or 125% of the mean daily dose of cycle 1 in patients with dose-limiting toxicity, with minor toxicity, or without toxicity, respectively, during the intercycle period.

Blood sampling and topotecan analysis

A pharmacokinetic exploration was performed on days 1 and 5 (except in three patients for whom the treatment was stopped after 3 days because of high topotecan AUC on day 1) of cycle 1, and day 1 of cycle 2 (except for six patients not retreated because of toxicity or deterioration of their performance status due to the disease progression). Blood samples were taken immediately before, 5 min before the end of the 30-min infusion, and 0.5, 1, 2, 4, 8 h after the end of infusion. Blood samples (3 ml in heparinized tubes) were collected using an indwelling intravenous cannula placed in the opposite arm. After immediate centrifugation at 1500 *g* for 10 min, at 4 °C, the plasma was separated and stored (−20 °C) until analysis. The total (i.e., lactone plus hydroxy acid forms) topotecan levels were determined using high-performance liquid chromatographic (HPLC) method previously described [17]. The limit of quantification was 0.5 μg/l plasma. A cross-validation was performed within the four sites of HPLC analysis (Toulouse, Montpellier, St-Herblain, and St-Cloud) using four seeded plasma control samples with nominal values from 1.15 to 65.5 μg/l: the intercenter coefficients of variation for precision ranged between 6% and 15%. These seeded were used as quality control to validate each HPLC assay; the obtained concentrations should be within ±10% of the nominal values (±15% for the lowest quality control).

Table 1 Characteristics of the 31 patients at inclusion

Characteristics	Mean	Range
Age (year)	61	47–76
Body surface area (m^2)[a]	1.62	1.36–1.86
Weight (kg)	61	46–85
Serum creatinine (μmol/l)	86	45–140
Creatinine clearance (ml/min)[b]	64	35–126
Bilirubin (μmol/l)	9	2–22

[a] Calculated according to the Dubois formula [6]
[b] Calculated according to the Cockcroft-Gault equation [5]

Pharmacokinetic analysis

Total topotecan plasma levels were analyzed according to a two-compartment model with linear elimination from the central compartment using NONMEM [3] (version V, level 1.1) with the first-order conditional estimation method and the PREDPP package [2] running on a personal computer. A proportional error model was used for the interpatient variabilities. A combination model (i.e., additive plus proportional) was used for residual variability.

Intraindividual variabilities

The intraindividual variabilities in CL between days 5 and 1 of cycle 1, and between day 1 of cycle 2 and day 1 of cycle 1 were both evaluated by using the interoccasion variability as described by Karlsson and Sheiner [12]. This model takes accounts of random variability in subject's parameters between study occasions and allows one to obtain a specific value of CL for each occasion. The intrapatient variability in clearance within cycle 1 (data available in 28 patients) was expressed as the percentage variation between day 5 and day 1: $(CL_{d5}–CL_{d1}) \times 100/CL_{d1}$. The percentage variation between the CL on day 1 of cycle 2 (data available in 25 patients) and that on day 1 of cycle 1 was also calculated to evaluate the pharmacokinetic variability between cycles.

Relationships between covariates and pharmacokinetic parameters

Six patient covariates were tested using the data from all patients ($n = 31$) on day 1 of cycle 1: weight, body surface area calculated according to the Dubois formula [6], age, WHO performance status score, serum creatinine (Scr), and CrCl calculated according to the Cockcroft-Gault equation [5]. In fitting the data, NONMEM computed the value of a statistical function and the minimal value of the objective function, which is equal to minus twice the log likelihood. For testing of the covariates the different models were compared using the approximation to the χ^2 distribution of the objective function value of the reduced model (e.g., model without covariate) minus that of the full model (e.g., model with covariate); the number of degrees of freedom was equal to the difference in the number of parameters between two nested models. For example, a difference in the objective function larger than 3.8 (associated with a $P < 0.05$ and 1 degree of freedom) was required to consider the model without covariate more appropriate than the model with the covariate.

Development of a limited sampling strategy to estimate topotecan clearance

The patients were randomized into two groups: 16 in the reference group and 15 in the test group. Bayesian estimation was performed using the NONMEM program to determine the CL of test group patients from a limited number of samples. The data base consisted of the data of the reference group patients. Regarding the previous report showing a close relationship between CL and CrCl [16], for all patients (i.e., both reference and test groups) Cockcroft-Gault

CrCl was taken into account to compute the typical value of CL (TVCL = $\theta \times$ CrCl). For a patient j of the test group, the relative prediction error, pej (%), for CL was defined as follows: pej (%) = (CL_{LSS}–CL) × 100/CL, where CL_{LSS} is the Bayesian estimate of CL for patient j, CL is the actual CL that was obtained using all data points. Predictive performance of Bayesian estimations using the various sampling times was evaluated by computing the mean relative prediction error (me):

$$\text{me } \% = N^{-1} \cdot \sum_{j=1}^{N} (\text{pej})$$

(where N is the number of patients) as a measure of bias and the root mean squared relative prediction error (rmse):

$$\text{rmse } \% = \left[N^{-1} \cdot \sum_{j=1}^{N} (\text{pej}^2)\right]^{1/2}$$

as an assessment of precision. One- (each of the six available samples), two- (ten combinations), and three-sample (5 min before the end of the 30-min infusion (EOI) +2 h post-EOI +4 h post-EOI; 5 min before EOI +4 h post-EOI +8 h post-EOI) schedules were tested. The data from day 1 of cycle 1 of the test group were used to select the optimal sampling schedules which was tested by using the data from day 5 of cycle 1, and from day 1 of cycle 2 of the same group.

Results

The topotecan plasma concentrations versus time were well described by a two-compartment model. There was good agreement between model-predicted and observed concentrations for each database (i.e., data from day 1 of cycle 1, data combining days 1 and 5 of cycle 1, or day 1 of cycle 1 and day 1 of cycle 2); the values of the proportional part and the additive part of the residual variability never exceeded 17.1% and 0.45 μg/l. Figure 1 shows an example of the fit of the topotecan plasma concentrations observed on days 1 and 5 of cycle 1 in two patients.

Inter- and intrapatient variabilities in clearance

Table 2 shows the mean values of CL observed at each pharmacokinetic exploration, and the intrapatient variability within cycle 1 and between the two first cycles of treatment. Interoccasion variability was first considered in all pharmacokinetic parameters, but was finally relevant only for CL and the central volume of distribution. There was no significant difference (paired Student's test) between days 1 and 5 of cycle 1 or between day 1 of cycle 1 and day 1 of cycle 2.

Relationships between covariates and pharmacokinetic parameters

During the individual testing three covariates (i.e., Scr, age, and the Cockcroft-Gault CrCl), were significantly

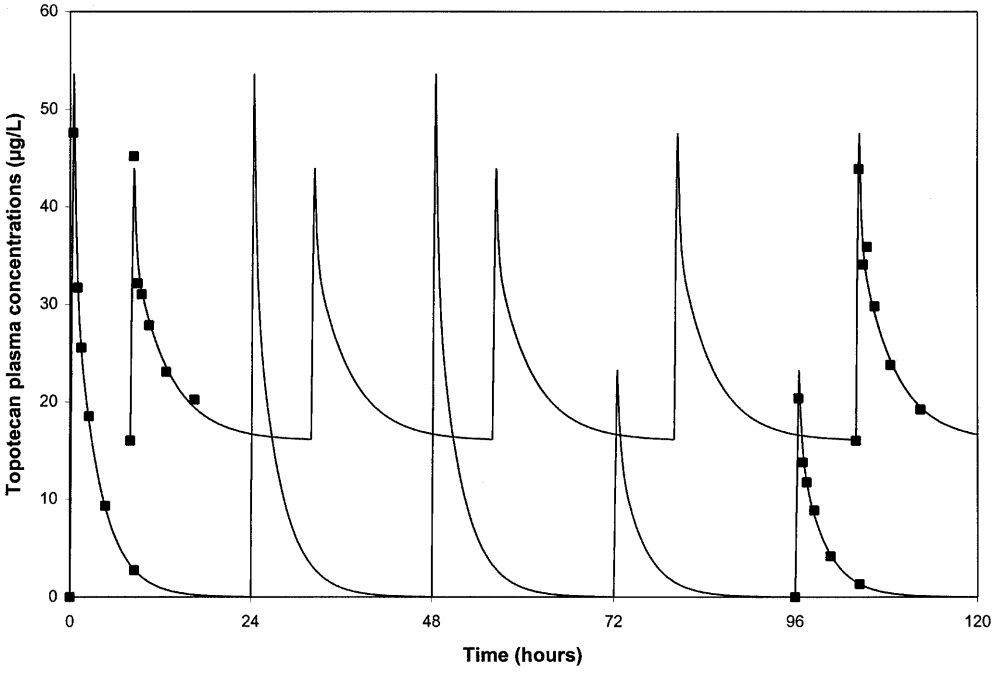

Fig. 1 Observed topotecan concentrations (*data points*) and the model-predicted concentrations using the interoccasion variability option: data from one patient (treated with 2.7 mg on days 1, 2, and 3, and 1.4 mg on days 4 and 5) and from another (curve shifted for both x- and y-axes; treated by a constant dose of 1.1 mg), illustrating a typical and the worst fit, respectively

Table 2 Mean and range of topotecan clearance, and of its percentage of variation by comparison with the clearance observed on day 1 of cycle 1 (*n* number of patients)

	n	Clearance (l/h)		Percentage variation	
		Mean	Range	Mean	Range
Cycle 1, day 1	31	21.0 ± 8.5	9.1–42.5	–	–
Cycle 1, day 5	28	21.4 ± 9.5	8.4–45.2	−2 ± 17	−34 to +29
Cycle 2, day 1	25	24.5 ± 13.8	11.6–74.1	+7 ± 24	−31 to +62

correlated with CL. For the volumes of distribution the only correlation was found between the body weight and the central volume. Testing of intermediate models led to the final models that are presented in Table 3. For CL the final model takes into account (CrCl): $CL = \theta 1 \times CrCl$. This covariate decreased the interindividual variability in CL from 42% (no covariate) to 24%. Figure 2 shows the correlation between CL calculated according to the CrCl (i.e., $CL = 5.47 \times CrCl$) and actual CL on day 1 of cycle 1. It should be noted that the model $CL = \theta 1 \times CrCl + \theta 2$, was tested but led to a value for $\theta 2$ close to zero ($9.36 \cdot 10^{-6} \pm 0.574$), indicating that CL varies proportionally to CrCl. Nevertheless, a model involving the age and the Scr presented similar performance than that of the final model. The attempt to include the patient weight at the numerator of Scr (as proposed for calculation of CrCl [5] or carboplatin clearance [4]) did not improve the objective function.

Performance of limited sampling strategy to estimate clearance

Bias and precision corresponding to the best of each schedule (i.e., one-, two-, and three-sample schedules) are given in Table 4. For the one- and two-sample groups the results of two schedules are shown since they present similar performance. The two-sample schedule (5 min before the end of infusion and 4 h after the end

Table 3 Testing of the covariate models on the topotocan pharmacokinetic parameters: final estimates of the regression coefficients provided by NONMEM analysis

Model investigated	Mean (±95% CI)	Change in OBJ[a]	*P*	%CV[b]
Final model				
CL = $\theta 1 \times$ CrCl, with CrCl for Cockcroft-Gault CrCl (in l/h)	$\theta 1$ = 5.47 ± 0.55			24
Central volume = $\theta 3 \times$ weight	$\theta 3$ = 0.584 ± 0.168 l/kg			50
Peripheral volume = $\theta 4$	$\theta 4$ = 33.9 ± 9.6 l			53
Alternative models				
CL = $\theta 1 \times (1-\theta 2 \times$ age)/Scr, with Scr (in μM)	$\theta 1$ = 3260 ± 1240 l/μM per hour			
	$\theta 2$ = 0.0081 ± 0.0032 per year	−0.7	NS	24
CL = $\theta 1$/Scr	$\theta 1$ = 1640 ± 169 l/μM per hour	+7.2	< 0.01	27
CL = $\theta 1 \times (1-\theta 2 \times$ age)	$\theta 1$ = 54.6 ± 20.4 l per hour			
	$\theta 2$ = 0.010 ± 0.002 per year	+36.0	< 0.0005	36
V1 = $\theta 3$	$\theta 3$ = 35.4 ± 13.7 l	+5.5	< 0.05	59

[a] Change in objective function by comparison with the final model
[b] Coefficient of variation for interindividual variability (not explained by the covariate, if any) of the considered pharmacokinetic parameter

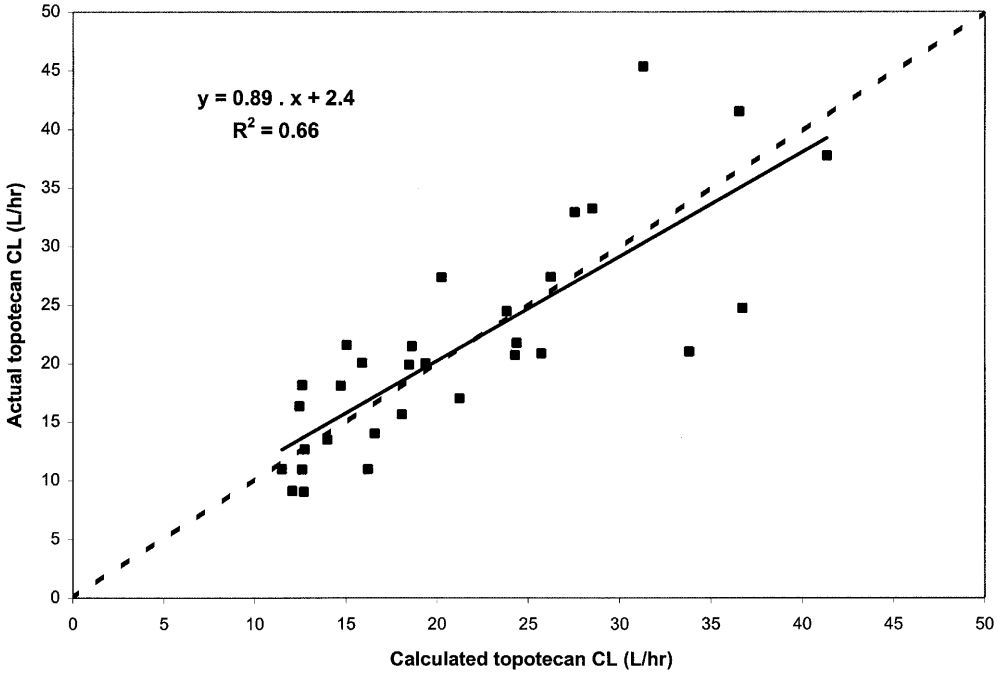

Fig. 2 Relationship between the topotecan clearance (*CL*) calculated according to the covariate model with the Cockcroft-Gault creatinine clearance (i.e., $CL = 5.47 \times CrCl$, with CrCl in liters per hour) and the actual topotecan clearance on day 1 of cycle 1 in 31 patients. *Dashed line* Line of identity; *solid line* linear regression line

of infusion) combines accurate prediction and convenience. This limited sampling schedule was evaluated by using the data from day 5 of cycle 1 (13 patients), and from day 1 of cycle 2 (12 patients) of the test group: me–rmse (range for percentage errors) were −3% to −9% (−18% to +15%) and −4% to −6% (−15% to +3%), respectively. Figure 3 compares CL determined by considering all data concentrations and that obtained from these two samples. Lastly, when the selected sampling schedule was applied to reference group patients (day 1 of cycle 1), me–rmse (range) were −4% to −13% (−31% to +13%).

Retrospective evaluation of drug monitoring

To evaluate whether intrapatient pharmacokinetic variability limits the benefit of performing a drug monitoring on day 1 of cycle 1 we compared the difference in prediction of topotecan CL on day 5 of cycle 1 and on day 1 of cycle 2 given (a) the full sampling schedule (i.e., 6 blood samples on day 1 of cycle 1), (b) the limited sampling schedule (i.e., 5 min before the end of infusion and 4 h after the end of infusion on day 1 of cycle 1), or (c) calculated from CrCl (i.e., CL = 5.47 × CrCl using the Scr level before the corresponding cycle). The root mean squared relative prediction errors (rmse%) as an assessment of precision of these three predictions are shown in Table 5.

Table 4 Predictive performance of Bayesian estimation of topotecan clearance with different limited sampling schedules tested in 15 patients (*me* mean relative prediction error, *rmse* root mean squared relative prediction error, end of 30-min infusion)

Sampling time	Bias, me (%)	Precision, rmse (%)	Range of prediction error (%)
4 h (after EOI)	−3	12	−19 to +27
8 h (after EOI)	−5	13	−25 to +14
5 min before EOI +4 h	0	9	−13 to +13
5 min before EOI +8 h	0	8	−13 to +14
5 min before EOI +4 h +8 h	+2	7	−13 to +12

Discussion

The present study confirms the large interindividual variability in CL, as previously reported during the development of the drug [11, 14]. We observed a ratio of almost 5 between the extreme values (9.1 and 42.5 l/h) on day 1 of cycle 1. It is interesting to note that the body surface area was not a covariate significantly correlated to CL, although body surface area is currently used for topotecan dosing. The results of the covariate analysis showing significant correlation between Cockcroft-Gault CrCl and CL, are consistent with those obtained by O'Reilly et al. [16]. In the later study, however, CrCl was measured rather than estimated from the Scr value. The difference in the extent of the clearance (mean values of 350 and 86 ml/min for CL and CrCl, respectively) indicates that the drug is not eliminated only by glomerular filtration. However, the equation corresponding to the final model (CL = 5.47 × CrCl) or that with age and Scr [CL = 3260 × (1–0.0081 × age)/Scr], may be useful for individual dosing of topotecan. With both equations the interindividual variability in CL, as expressed by the coefficient of variation, decreased from 42% (no covariate) to 24%. Renal tubular secretion

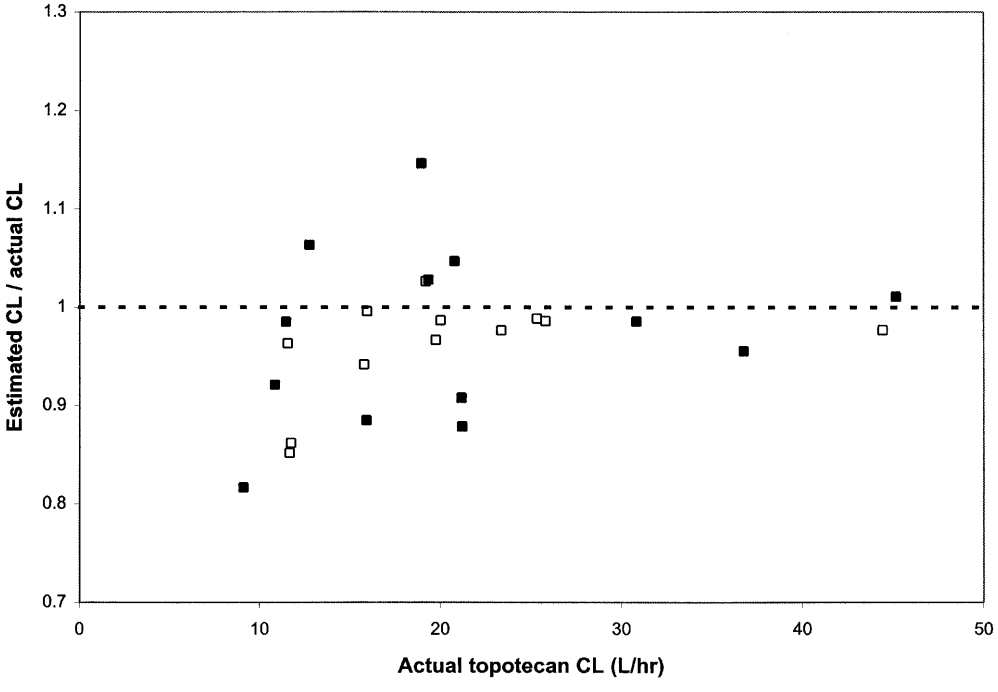

Fig. 3 Ratio plot for evaluation of the limited sampling applied to the data of the test group: *solid squares* day 5 of cycle 1; *open squares* day 1 of cycle 2). Topotecan clearance values were estimated on concentrations at times 5 min before the end of the 30-min infusion and 4 h after the end of infusion using NONMEM

Table 5 Performance of prediction of topotecan clearance (*CL*) on day 5 of cycle 1, and on day 1 of cycle 2 by performing a drug monitoring on day 1 of cycle 1 (full or limited sampling schedule) or using relationship between CL and creatinine clearance (*CrCl*): root mean squared relative prediction error (percentages)

	n	Day 1 cycle 1, full sampling	Day 1 cycle 1, limited sampling	CL = 5.47 × CrCl[a]
Day 5, cycle 1	28	23.0	22.9	29.1
Day 1, cycle 2	25	22.9	23.6	25.1

[a] Calculated from the Cockcroft-Gault equation and creatinine plasma level before the respective cycle

should account for a large part of the remainder interpatient variability in CL. Concomitant medication may influence this secretion, but topotecan was used here as a single agent.

However, if drug exposure needs to be accurately controlled, a pharmacokinetic exploration would be necessary to modulate the topotecan dose during the cycle according to the individual observed CL. However, monitoring of a drug may be considered only if the intrapatient pharmacokinetic variability is low. In addition to the population approach used for analyzing the topotecan data, the originality of the present work consists in the careful evaluation of intraindividual pharmacokinetic variability. Intrapatient variability between day 1 and day 5 of cycle 1 was limited; the absolute percentage of variation was lower than 20% for 21 of 28 patients and never exceeded 34%. Moreover, it is reasonable to speculate that CL did not change significantly during the unstudied days (i.e., days 2, 3, and 4). Therefore a dose adjustment according to the observed CL on day 1 would allow an overall targeted AUC to be achieved. Concerning intrapatient variability between cycle 1 and cycle 2, the absolute percentage of variation was lower than 20% for 14 for 25 patients, displaying a larger change between cycles than that between days of the same cycle. This is not surprising considering the longer lapse of time between the pharmacokinetic explorations. However, the mean percentage of variation was not significantly different from zero ($+7\% \pm 24\%$), showing no systematic change in CL. Thus the decreased platelet toxicity with successive topotecan treatment cycles as shown by Goldwasser et al. [10] cannot be explained by a pharmacokinetic time-dependency phenomenon. We tried to explain this intercycle variability in CL by considering the modifications in CrCl between cycles. However, prediction of CL was not better when CrCl was updated in comparison with analysis with the initial (i.e., before cycle 1) CrCl value assigned to all data (concentrations vs. time on day 1 of both cycles and 2; data not shown). Nevertheless, the correlation between CL in cycle 2 and the predicted value according to the final model with CrCl (i.e., $CL = 5.47 \times CrCl$ with cycle 2 value for CrCl) remained high (regression line: $y = 1.16x + 1.1$, $R^2 = 0.54$).

For determining topotecan AUC in clinical routine with minimal constraints for patients we propose a limited sampling strategy based on Bayesian estimation using the NONMEM program. The two-sample schedule based on times 5 min before the end of the 30-min infusion and 4 h after the end of infusion, combines good precision and convenience. The optimal sampling schedule and prospective evaluation were selected with the data from the same patients but on different days of administration. Two mathematical equations based on stepwise multiple linear regression models have previously been proposed to estimate topotecan AUC administered by 30-min intravenous infusion; these required two samples (0.25 and 6 h after the end of infusion) [13] or one sample (2 h after the end of infusion) [19]. However, the methodology based on Bayesian estimation using NONMEM is more flexible since stepwise multiple linear regression models require accurate control of both the duration of topotecan infusion and the time at which the samples are obtained. Moreover, it should be noted that single-point sampling (either 4 or 8 h after the end of infusion) allows an adequate estimation of CL by using the present Bayesian approach.

Results shown in Table 5 indicate that a pharmacokinetic exploration after the first infusion of cycle 1 using a limited sampling schedule better predicted the CL observed after the last infusion of the same cycle than the relationship between CL and CrCl did. However, the topotecan CL on day 1 of cycle 2 was similarly predicted by using the pharmacokinetic results from the previous cycle or the Scr measured just before the second cycle. However, these comparisons must still be evaluated entirely prospectively.

The clinical results of this trial are promising; the major toxicity of topotecan was limited, with no sign of drug underdosing. Therefore drug monitoring of topotecan is planned to be performed systematically in the cancer centers that participated in this first trial with dose individualization of topotecan. In the future, however, the pharmacokinetic data will be analyzed by NONMEM rather than by individual analysis. The limited number of blood samples would allow generalization of this drug monitoring and identification of other factors influencing the interindividual pharmacodynamic variability of topotecan. This would also make it possible to determine the optimal topotecan plasma exposure when the drug is combined with other cytotoxic drugs. As for carboplatin [7], the target values of topotecan AUC may likely be lower when the drug is administered as combination therapy. Nevertheless, the results of this study cannot be extrapolated to patients such as males or children, who did not compose the present population. They would require complementary pharmacokinetic explorations.

Lastly, the high quality (as indicated by the small residual variability obtained by NONMEM analysis) of the pharmacokinetic data collected under multicenter conditions shows the feasibility of topotecan drug monitoring at a large scale.

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