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Pharmacokinetics and pharmacodynamics of topotecan given on a daily-times-five schedule in phase II clinical trials using a limited-sampling procedure

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Abstract Topotecan is a novel semisynthetic derivative of the anticancer agent camptothecin and inhibits the intranuclear enzyme topoisomerase I. The lactone structure of topotecan, which is in equilibrium with the inactive ring-opened hydroxy acid, is essential for this activity. We performed a pharmacokinetics study as part of phase II clinical trials in patients with various types of solid tumors, giving topotecan at 1.5 mg/m^2 per day by 30-min infusion for 5 consecutive days, with courses being repeated every 3 weeks. Previously validated limited-sampling models, using concentration measurements in samples obtained 2 h after infusion, were used to calculate the area under the plasma concentration-time curves (AUCs) for both chemical forms. Samples were obtained from a total of 36 patients over 136 treatment days. The mean AUC of the closed-ring form (AUC_{closed}) was 8.74 (range 2.3–16.3) μM min per day, and the mean AUC of the ring-opened form (AUC_{open}) was 11.5 (range 3.2–46.0) μ*M* min per day (interpatient variability 34–61%). In each patient the AUC values achieved on the 1st day of administration were similar to and, thus, predictive for those achieved during the following days, with a day-to-day variation of 7.39% being recorded for the AUC_{closed} and that of 12.6%, for the AUC_{open}. There was no drug accumulation during the 5 consecutive treatment days of each cycle. However, despite the large interpatient pharmacokinetic variability, the importance of regular drug monitoring on this schedule can be questioned, as the pharmacodynamic variability was relatively small.

Key words Limited-sampling model · Pharmacodynamics · Pharmacokinetics · Phase II · Topotecan

On behalf of the EORTC Pharmacology and Molecular Mechanisms group and the Early Clinical Trials Group

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Introduction

Topotecan ([S]-9-dimethylaminomethyl-10-hydroxy-camptothecin, SK&F 104864, NSC 609699, Hycamtin) is a semisynthetic derivative of camptothecin, an anticancer drug derived from the Asian tree *Camptotheca acuminata*. Due to camptothecin's serious and unpredictable gastrointestinal, urothelial, and myelosuppressive toxicities, clinical evaluation had to be discontinued in the early 1970s [12, 13]. As compared with camptothecin, topotecan as the hydrochloride salt is better water-soluble, has a reduced capacity for protein binding, and shows promising preclinical and clinical efficacy with a strongly reduced toxicity profile [7, 9, 15, 25]. The dose-limiting toxicity of topotecan in phase I trials is reversible myelotoxicity, particularly granulocytopenia [15, 16, 18, 24, 25].

The cytotoxicity of topotecan and other camptothecin analogues is ascribed to inhibition of the intranuclear enzyme topoisomerase I [1, 8, 19]. The lactone structure, which is in equilibrium with the open-ring

hydroxy acid (SK&F 105992) at constant pH, is essential for this activity (Fig. 1) [7, 26]. The closed lactone ring predominates at acidic pH, but the reverse reaction of the parent into the open-ring form is favored at physiological pH [2, 4, 21]. The hydrolysis of the parent drug into the inactive form may thus have important pharmacokinetic and pharmacodynamic implications.

The results of phase I clinical trials have suggested that pharmacokinetic parameters are well correlated with pharmacodynamic outcome [4, 5, 20, 23, 25]. Especially the area under the plasma concentration-time curve (AUC) of topotecan has been preeminently related to the degree of neutropenia and leukopenia [4, 5, 20, 23, 25]. This relationship might be of value for the optimization of topotecan therapy since by measurement of the AUC, patients at high risk of developing serious toxicity might be identified at an early stage. Furthermore, the dose could in theory be adjusted upward or downward during a daily-times-five treatment to achieve the AUC associated with an optimal clinical outcome. However, since the topotecan dose used in the phase I clinical trials was linearly related to the AUC [4, 23, 25], the escalation of the dose might consequently have defined predominantly the relationships between the AUCs and the toxicities. To find out whether this was true, we felt it important to investigate further the relationships between the AUCs and the toxicities in different subjects treated with a fixed topotecan dose. The Pharmacology and Molecular Mechanisms (PAMM) group and the Early Clinical Trials Group (ECTG) of the EORTC (European Organization for Research and Treatment of Cancer) have recently taken the initiative in coordinating and stimulating the performance of pharmacokinetics studies as a part of phase II clinical trials [14]. The larger and more homogeneous phase II patient population allows more insight into the variability in pharmacokinetics and the relationships of the latter with pharmacodynamics, such as toxicity and tumor response, as compared with phase I studies.

We have previously developed and validated a limited-sampling model for topotecan [22] that can be used to get the necessary pharmacokinetic data with a minimum of samples taken from the patients. This limited-sampling strategy was used for the present study in patients with ovarian, colorectal, or small-cell lung cancer (SCLC). Pharmacokinetic monitoring is also being performed in other ongoing phase II studies coordinated by the EORTC-PAMM and ECTG groups with the investigational anticancer agents irinotecan, docetaxel, EO9, and rhizoxin [14].

Patients and methods

Patient population

The patients participated in three phase II clinical trials in which topotecan was given daily at a dose of 1.5 mg/m^2 for 5 consecutive days every 3 weeks. These phase II trials have recently been completed, and the detailed clinical results will be published elsewhere. Eligible were patients with ovarian cancer failing treatment with a platinum-based chemotherapeutic regimen, non-chemotherapy-pretreated patients with colorectal cancer, or patients with SCLC failing or relapsing after first-line chemotherapy. All patients had adequate bone marrow function [white blood cells count (WBC) $> 3.5 \times 10^9$/l, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l] normal serum bilirubin ($\leq 26\ \mu M$) and serum creatinine ($\leq 140\ \mu M$) values, no prior history of hemorrhagic cystitis, a WHO performance status of ≤ 2, a life expectancy of ≥ 12 weeks, and an age of 18–75 years. All patients gave informed consent.

Treatment plan

Topotecan (SmithKline Beecham, King of Prussia, Pa., USA) was supplied as the freeze-dried product consisting of topotecan as the hydrochloride salt (5 mg as free base) and 100 mg mannitol as the bulking agent (i.e., topotecan AA formulation). These vials are reconstituted before infusion with 2 ml of water for injection. The appropriate daily dose of the drug was diluted in 50 ml of normal saline (NaCl 0.9%) and was given intravenously by a syringe pump over a 30-min period. For assessment of the hematological and non-hematological toxicities, patients were evaluated after each course by clinical history, physical examination, and serum chemistry. A hematology screen was performed twice weekly. The response was assessed every two courses.

Pharmacokinetics studies

Blood samples (5 ml each) were taken by venipuncture from a cubital vein in the arm contralateral to the arm receiving topotecan. The blood samples were collected at one single time point: at exactly

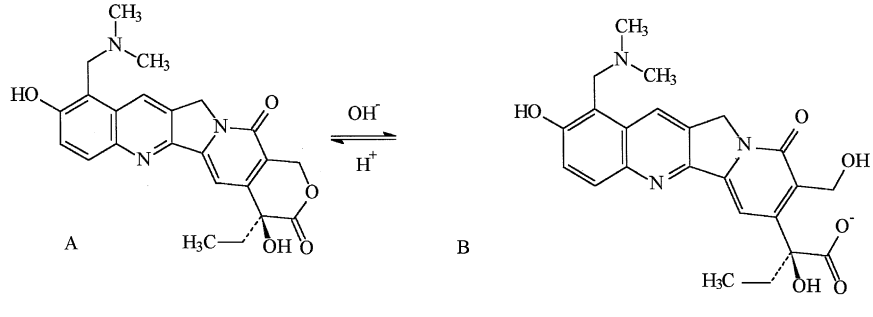

Fig. 1A, B Chemical structures of **A** topotecan and **B** its lactone ring-opened hydroxy acid. Both forms are in equilibrium at constant pH

2.5 h after the start of the 30-min infusion. An error in sample timing of maximally 5 min was allowed. Each sample was collected in a heparinized tube at 1 day and, when possible, at later days of drug administration.

Plasma was obtained by immediate centrifugation (5 min, 1500 g) of the samples, which was followed by protein precipitation with cold methanol (− 30°C); 1.0 ml of plasma was added to 4.0 ml of methanol. Thereafter, the mixture was vortex-mixed and centrifuged (5 min, 1500 g) and the clear supernatant was transferred to a polypropylene tube and stored (− 30°C) until analysis. The closed lactone ring and the lactone ring-opened form of topotecan were determined by a validated high-performance liquid chromatography (HPLC) method using fluorescence detection [2]. The AUCs were calculated using the following validated limited-sampling models [22]:
for the closed-ring form,

$$AUC_{closed}(\mu M \text{ min} = 499(\text{min}) \times C_{2h}(\mu M) + 0.85(\mu M \; min \; m^2 \; mg^{-1} \times dose(mg/m^2),$$

and for the ring-opened form,

$$AUC_{open}(\mu M \; min = 551(min) \times C_{2h}(\mu M) - 0.011(\mu M \; min \; m^2 \; mg^{-1}) \times \text{dose (mg/m}^2),$$

where C_{2h} is the plasma concentration of the closed-ring or the ring-opened form, respectively, at 2 h after the end of the 30-min infusion. The AUC of the lactone plus the ring-opened form (AUC_{total}) was calculated by: $AUC_{closed} + AUC_{open}$. The intrapatient (day-to-day) and interpatient variations in pharmacokinetics were calculated by analysis of variance (ANOVA).

The pharmacodynamics, especially the myelosuppression, were explored using plots of the percentage of decrease (%decr) in ANC, %decr in WBC, and %decr in the platelet count versus the AUC_{closed}/day, the AUC_{open}/day, the AUC_{total}/day, and the total dose (in milligrams). The percentage of decrease (%decr) is defined as:

$$\%\text{decr} = \frac{\text{Pretreatment value} - \text{value of the nadir}}{\text{Pretreatment value}} \times 100\%.$$

The data were fit to the respective sigmoidal maximum-effect ($sigE_{max}$) models derived from the phase I clinical trial [23]. Mathematically, these models are defined as:

$$\%\text{decr} = \frac{100 \times (P)^H}{(P_{50})^H + (P)^H},$$

where P is the value of the pharmacokinetic parameter or the dose, P_{50} is the P that results in a 50% decrease, the H is the Hill constant, which determines the shape of the curve. The following values were obtained for the %decr in ANC versus the dose (in milligrams) : $H = 2.27$, $P_{50} = 1.02$; AUC_{closed}: $H = 1.55$, $P_{50} = 1.55$; AUC_{open}: $H = 1.09$, $P_{50} = 1.97$; and AUC_{total}: $H = 1.30$, $P_{50} = 4.96$ [23]. The performance of these models for the phase II pharmacokinetic data was evaluated using the relative root mean square error (%RMSE) value [17]. The %RMSE is a measure of precision and is defined as:

$$\text{RMSE}\% = \left[N^{-1} \sum_{i=1}^{N} (pe_i)^2 \right]^{1/2} \times 100\%,$$

where N is, e.g., the number of P-pairs (i.e., true with predicted values), the pe is the prediction error $[ln(P_{true\ value}) - ln(P_{predicted})]$. The smaller the %RMSE, the better the relationship is described by the model.

To investigate the determinators of inter- and intraindividual kinetic variability, we correlated continuously scaled patients' characteristics with the pharmacokinetics by linear regression analysis. These characteristics were age, weight, height, creatinine clearance, and the number of topotecan courses received. The investigated pharmacokinetic parameters were the AUC_{closed}/day, the AUC_{open}/day, their ratio (AUC_{closed}/AUC_{open}), and the AUC_{total}/day. These values were calculated per day to account for the missing values during the 5 administration days. This is justified since the intrapatient variability was very small (< 15%) . Discontinuously scaled patients' characteristics, such as gender (male versus female), WHO performance status (0 versus 1 or 2), pretreatment status (prior chemotherapy or not), were also tested (Student's t-test) for differences in the values of the kinetic parameters. In addition, we investigated whether the kinetic parameters and/or patients' characteristics were related to the toxicities by linear regression analysis and Student's t-test, respectively. The computer programs NCSS (Number Cruncher Statistical System, Kaysville, Utah, USA) and Quattro Pro (Borland International, Scotts Valley, Calif., USA) were used for all calculations.

Results

A total of 36 patients were entered in this pharmacokinetic trial, of which 18 patients (8 women, 10 men) had colorectal cancer, 14 had ovarian cancer, and 4 (all women) had SCLC. All patients with ovarian cancer were pretreated with platinum-containing chemotherapy and all patients with SCLC were relapsing after or failing first-line chemotherapy involving a variety of drugs, whereas the colorectal cancer patients had not received prior chemotherapy. The median age was 59 (range 48–75) years, the median performance status was 1 (range 0–2), and the median creatinine clearance was 80 (range 50–112) ml/min.

Toxicity

In all 36 patients the major toxicity was granulocytopenia, with the mean %decr in ANC being 85% (range 48–99%), being of WHO grade IV in 38/61 courses. Thrombocytopenia was much less frequent and less severe, with the mean %decr in platelet count being 68% (range 45–99%), being of WHO grade III in 5/61 courses and of grade IV in 2/61 courses. Mild anemia of grades I and II occurred regularly, with the mean %decr in the hemoglobin (Hb) count being 16% (range 4–34%). The nadirs of both granulocytopenia and thrombocytopenia occurred between day 8 and day 15 and were of short duration (3–5 days). Nonhematologic toxicities were of grade II or less and included nausea, vomiting, diarrhea, alopecia, fatigue, and stomatitis.

Responses

All patients were evaluable for response. Most of the patients (10/18) with colorectal cancer developed progressive disease under topotecan treatment. However, 1 patient had a partial remission, and 7 patients remained stable for at least 2 months. Of the ovarian cancer patients, 1 achieved a complete remission,

2 achieved a partial remission, 7 were stable, and 4 suffered progression. In all, 2 patients with SCLC remained stable, whereas the other 2 developed progressive disease.

Feasibility

It appeared that the requirements for sample acquisition were generally very demanding for the clinical staff; the sample had to be drawn timely at exactly 2 h after the end of infusion, which had to be followed by immediate centrifugation and careful volumetric pipetting into cold and volatile methanol, whereafter centrifugation was required again, followed by refrigeration and, finally, shipment to our laboratory. In addition, it appeared that patients treated on an outpatient basis were frequently not willing to wait for the blood sampling at 2 h after the infusion. For these reasons, although over 200 patients entered the full phase II programs in over 30 institutions, pharmacokinetic samples could be obtained from only 2 institutes in The Netherlands over 136 treatment days and 61 courses.

Pharmacokinetics

Intrapatient data

The AUC values recorded for the 1st day of administration were similar to and, thus, predictive for those achieved in the following days in the same patient ($n = 19$ patients), with the day-to-day variation being 9.7% for the AUC_{total}, 12.6% for the AUC_{open}, and 7.39% for the AUC_{closed}. Thus, no accumulation of topotecan occurred during the consecutive days of administration. Furthermore, the intrapatient variability between courses was also small ($n = 10$ patients, 39 courses), with the course-to-course variation ranging between 9.4% and 10.7%.

Interpatient data

However, a wide interpatient ($n = 36$ patients) variability in the pharmacokinetics of topotecan was found, being 39.3% for the AUC_{total} (Fig. 2), 60.9% for the AUC_{open}, and 34.4% for the AUC_{closed}. The mean AUC of topotecan was 8.71 (range 2.3–15.8) μM min per day, and the mean AUC of the ring-opened form was 11.49 (range 3.2–46.0) μM min per day. The ratios of the AUC_{open} and AUC_{closed} ranged between 0.15 and 1.96 (mean ratio 0.91). The value of this ratio was patient-dependent (interpatient variation 67.2%), with the day-to-day (intrapatient) variation being 10.1%. The patients with ovarian cancer appeared to have higher AUC_{closed} and AUC_{total} levels than did patients with with colorectal cancer ($0.00001 < P < 0.006$). Patients

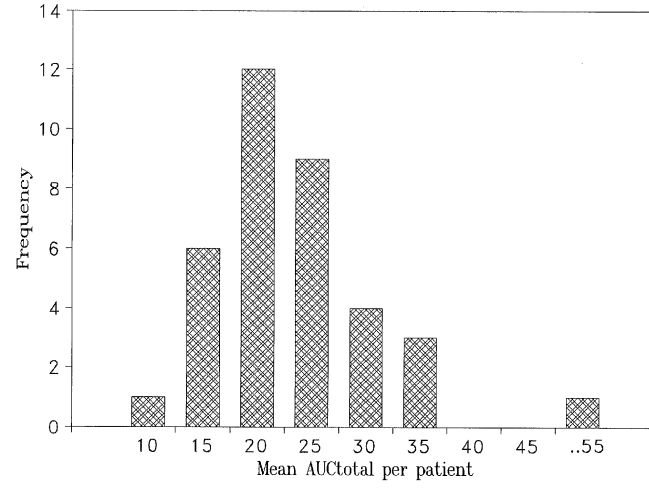

Fig. 2 Frequency plot of the mean AUC_{total} per patient

with SCLC had lower AUC levels than did patients with colorectal cancer, but this difference was not statistically significant ($0.06 < P < 0.35$; $n = 4$). Other parameters such as age, weight, height, gender, creatinine clearance, performance status, or the number of topotecan courses received were not significantly related to the kinetic parameters (Table 1).

Pharmacokinetic-pharmacodynamic relationships

The mean AUC_{closed}/day and AUC_{open}/day, the AUC_{total}/day, and the total dose/day (in milligrams) were plotted against the %decr in WBC, the %decr in ANC, and the %decr in platelets. The sigmoidal E_{max} models previously derived from the phase I clinical trial [23] were used to describe the data and were evaluated for their precision. For example, plots of the toxicity versus the dose (in milligrams) could not adequately be described by the previously defined sigmoidal E_{max} model (RMSE% > 35%), in contrast to plots of the toxicity versus the AUCs of the ring-opened form, the closed-ring form, and the sum of both, which were well described by their respective sigmoidal E_{max} models. Especially plots of the %decr in ANC, which was the most prominent side effect, versus the AUCs fitted adequately to the previously defined sigmoidal models, with RMSE% values ranging from 12.0% to 13.5% (Fig. 3). These values were not significantly different from the RMSE% values found in the phase I study ($P > 0.05$). For the %decr in platelets and %decr in WBC the RMSE% values ranged from 18.3% to 19.1% and from 25.1% to 25.6%, respectively. Besides the AUC values, other predictive parameters for the %decr in ANC were the number of topotecan courses received ($r = 0.42$, $P = 0.001$) and the performance status ($P = 0.022$) . There was no relationship between the grade of the nonhematological toxicities and the investigated patients' characteristics or

Table 1 Relationships between patients' characteristics and pharmacokinetic parameters (AUC area under the concentration-time curve of the lactone form [*closed*], the ring-opened form [*open*], and the sum of both [*total*], respectively; *r* correlation coefficient;–not applicable [Student's *t*-test only])

Patients' characteristic	AUC_{closed}		AUC_{open}		AUC_{total}		AUC_{closed}/AUC_{open}	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Patients with ovarian cancer:								
Age	0.21	0.45	0.19	0.06	0.03	0.04	0.40	0.06
Creatinine clearance	0.03	0.01	0.02	0.07	0.01	0.55	0.04	0.92
Height	0.16	0.26	0.28	0.07	0.27	0.07	0.16	0.41
Number of courses received	0.17	0.45	0.13	0.51	0.01	0.35	0.33	0.35
Weight	0.18	0.68	0.07	0.04	0.03	0.05	0.14	0.30
Performance status	–	0.14	–	0.43	–	0.20	–	0.42
Progression vs no progression	–	0.02	–	0.008	–	0.006	–	0.50
Patients with colorectal cancer:								
Age	0.15	0.88	0.24	0.32	0.21	0.37	0.44	0.18
Creatinine clearance	0.02	0.99	0.16	0.65	0.15	0.67	0.17	0.33
Height	0.10	0.21	0.15	0.73	0.16	0.62	0.03	0.98
Number of courses received	0.08	0.01	0.05	0.01	0.06	0.01	0.08	0.01
Weight	0.17	0.91	0.07	0.67	0.09	0.71	0.06	0.70
Gender	–	0.64	–	0.17		0.56		0.16
Performance status	–	0.87	–	0.47	–	0.48	–	0.78
Progression vs no progression	–	0.48	–	0.47	–	0.41	–	0.99

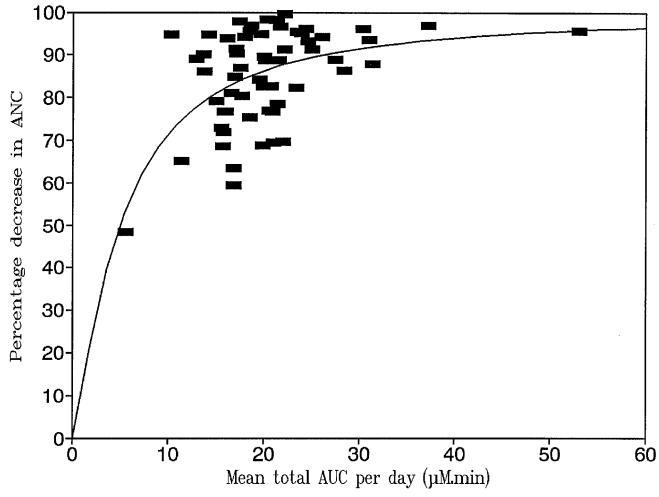

Fig. 3 Relation between the mean total AUC per day (closed form + ring-opened form) and the percentage of decrease in ANC. The *Solid line* represents the fit of the data to the $sigE_{max}$ model as derived from the preceding phase I trial:

$$\%\text{decr} = \frac{100 \times (\text{AUC})^{1.30}}{(4.96)^{1.30} + (\text{AUC})^{1.30}}$$

pharmacokinetic parameters. The quantity of responses was too small to allow a statistically meaningful analysis of relationships between the response and the AUCs or other parameters.

Discussion

The toxicities of topotecan given at 1.5 $mg\,m^{-2}\,day^{-1}$ on this daily-times-five schedule are similar to those reported for the phase I [4, 23, 24] and II [10, 11] clinical trials using this schedule. Myelosuppression, especially granulocytopenia, was most prominent, with 62% of the pharmacokinetically monitored courses resulting in grade IV neutropenia. The pharmacokinetics and their relationships with the pharmacodynamics were also similar, despite the use of a fixed dose in this study. The plots of the %decr in ANC versus the AUCs could adequately be described by the sigmoidal E_{max} models that were originally fitted to the data reported for the preceding phase I clinical trial (Fig. 3) [23]. In that study, we predicted from the fitted models that the administration of a fixed dose of 1.5 $mg\,m^{-2}\,day^{-1}$ in phase II studies would result in an average %decr in ANC of 87%, which is in good agreement with the %decr of 85% found in the present study.

The closed-ring structure is assumed to be essential for cytotoxic activity [6, 7]. Since the ratios of the AUC_{closed} and AUC_{open} varied between 0.15 and 1.96 and were patient-dependent, patients with equal AUC_{total} values were exposed to different concentrations of the lactone form. However, either the $AUCs_{closed}$, the $AUCs_{open}$, or the $AUCs_{total}$ were equally related to the hematological toxicity, which is also in agreement with the results of the phase I clinical trial [23]. Thus, it may seem that the fraction of topotecan present in plasma as the active lactone form is not that important for the toxicity. This may be explained by the reversibility of the conversion of the closed-ring form into the ring-opened form; the open ring might spontaneously close to form the lactone form at the target under the right conditions. This hypothesis is supported by the observation that the parent

compound camptothecin was originally given as the sodium salt of the ring-opened carboxylate form and was also toxic and active [3, 12, 13]. However, it is nonetheless advisable to give topotecan dissolved in an acidic infusion fluid to yield the closed-ring form. The closed-ring form has the largest volume of distribution [4, 23], indicating that this form is better distributed over the body, which may be important for more extensive tumor penetration. Unfortunately, because of the limited numbers involved in the present study a statistically meaningful relationship between the AUCs and the response could not be established. It is, however, noteworthy that patients with progressive ovarian cancer had higher AUC values as compared with the patients who remained stable or the few that responded to therapy. If this finding could be confirmed in larger numbers of patients, it would suggest that the contribution of the drug exposure (AUC) to the tumor response is minimal at the fixed phase II dose. Thus, it is likely that other, tumor-dependent factors such as the tumor type and amount of topoisomerase I levels, the number of cells in the S phase of the cell cycle, and the expression of P-glycoprotein [19] are more important for an antitumor effect.

The variability in the ratio of the AUC_{closed} and AUC_{open} that was found in the present study may be explained by differences in the pH of the infusion fluid. Measurement of the pH in the 0.9% NaCl-containing infusion fluid of several patients yielded pH values ranging between 3.5 and 6.1, indicating that different fractions of the drug present as the lactone form were delivered to patients. Similar results have been reported by Grochow et al. [4] for topotecan added to 5% dextrose infusions. For future studies with topotecan, however, it is expected that the variability in the AUC_{closed} and AUC_{open} will be much lower, since the AA formulation as used in the present study has now been replaced by the AC/AF formulation containing tartaric acid to increase the stability of the lactone form. Measurements of the pH of these infusions indicated that 100 % of the drug is present in the lactone form during infusion (pH < 3.5), which we confirmed by high-performance liquid chromatography (HPLC).

In general, therapeutic drug monitoring is beneficial for toxic drugs that display a high degree of pharmacokinetic variability and a high degree of pharmacodynamic variability in combination with a good relationship between the two. For topotecan, the difference in AUCs varied by up to a factor of 10 between patients but resulted in only a small interindividual difference in toxicity. This can be explained by the use of the maximum tolerable dose of topotecan in this phase II study producing AUCs that generally exceeded 15 μM min per day which is associated with maximal toxicity (%decr in ANC around 85%) and, therefore, low variability. As the pharmacodynamic variability was relatively low, it seems questionable whether regular drug monitoring of topotecan given on this schedule will be valuable in accounting for differences in toxicity or response.

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