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Clinical paper

Continuous infusion of low-dose topotecan: pharmacokinetics and pharmacodynamics during a phase II study in patients with small cell lung cancer

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Preclinical schedule dependency suggests that prolonged maintenance of low plasma levels of topotecan, a specific inhibitor of the nuclear enzyme topoisomerase I, results in optimal antitumor activity. The pharmacokinetics and pharmacodynamics of topotecan, administered as single agent in second-line therapy as a continuous low-dose infusion for 21 days, were evaluated in nine patients with small cell lung cancer (SCLC). Topotecan was administered i.v. as a 21 day continuous infusion every 28 days via an ambulatory pump. Dosages ranged from 0.4 to 0.6 mg/m^2/day. Plasma levels of topotecan, the sum of topotecan, and its hydroxy acid congener and the *N*-desmethyl metabolite were determined at 1, 7, 14 and 21 days during infusion, using a validated high-performance liquid chromatography method with fluorescence detection. Myelosuppression was the most important toxicity. All patients experienced anemia, being severe (grade 3/4) in 55% of all courses. Other adverse effects were relatively mild and reversible, and included nausea, vomiting, diarrhea and fatigue. Three patients achieved a partial response. Mean steady-state concentrations of topotecan (C_{ss}) in the first course were 0.46±0.17 and 0.47±0.19 ng/ml after doses of 0.4 and 0.5 mg/m^2/day, respectively. Steady-state levels of the total of topotecan and hydroxy acid ($C_{ss,tot}$) were 1.28±0.25 (range 0.93–1.58) and 1.57±0.19 (range 1.43–1.70) ng/ml at doses of 0.4 and 0.5 mg/m^2/day, respectively. The percentage of the administered topotecan dose excreted in the urine within 24 h was 40±14 and 1.2±1.0% for total topotecan and *N*-desmethyltopotecan, respectively. During the second course, $C_{ss,tot}$ was significantly higher (p=0.032, paired t-test), which suggests altered topotecan disposition. A sigmoidal relationship was found between $C_{ss,tot}$ and the percent decrease in platelets (r=0.76, p=0.018). We conclude that topotecan administered as a 21 day continuous low-dose infusion has activity as single-agent, second-line therapy in patients with SCLC. There was considerable interpatient and intrapatient variability in systemic exposure to topotecan. Differences in organ function might contribute to this variation. Serum aspartate aminotransferase and albumin levels were predictive of topotecan pharmacokinetics. [© 1998 Lippincott-Raven Publishers.]

Key words: Continuous infusion, pharmacokinetics, topotecan.

Introduction

Topotecan (Hycamtin®; 20(*S*)-9-dimethylaminomethyl-10-hydroxycamptothecin; Figure 1) is a semisynthetic water-soluble derivative of camptothecin, an alkaloid extracted from the Chinese tree *Camptotheca acuminata*. Since 1996, topotecan, administered i.v. as five daily doses, has been approved in the USA and different European countries for second-line treatment of metastatic ovarian cancer. Registration for the treatment of recurrent small cell lung cancer (SCLC) is to be expected. Topotecan and other camptothecin analogs exert their cytotoxic activity through inhibition of the nuclear enzyme topoisomerase I.[1,2] Topoisomerase I is intimately involved in DNA replication and transcription. In a cycle of breakage and religation steps it relieves the torsional stress and topological problems that occur during local winding and unwinding of DNA. Topoisomerase I inhibitors stabilize the DNA-topoisomerase I covalent 'cleavable complex' in which one strand of DNA is broken and inhibit the enzyme's ability to religate the cleaved DNA. Free topiosomerase I is depleted when this intermediate is formed. A collision between the stabilized cleavable complex and the advancing replication fork results in irreversible progression fork arrest,

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DNA breakage and finally cell death.[3] Both *in vitro* and *in vivo*, the cytotoxic effects of topotecan are dependent of the administration regimen.[4] Hochster and colleagues demonstrated progressive depletion of free topoisomerase I enzyme in peripheral blood lymphocytes until day 15 of a 21 day continuous infusion of topotecan.[5] These data suggested a biologic rationale for continuous administration of topotecan and analogs. A phase I clinical trial showed that 21 day topotecan infusion was effective with dose intensity exceeding other administration schedules.[6] A multicenter phase II trial with the 21 day continuous infusion regimen was initiated to determine if improved treatment results could be achieved with this schedule in chemotherapy relapsed or refractory SCLC patients.[7]

The importance of mode of administration in the efficacy of topotecan indicates that it is important to fully understand the pharmacokinetics of the drug after different infusion regimens. Topotecan possesses a chemically unstable E-ring lactone, which is subject to non-enzymatic pH-dependent reversible hydrolysis yielding a ring-opened hydroxy carboxylate form (Figure 1). At pH < 4 the lactone form predominates, but at physiological pH equilibrium processes favor the formation of the ring-opened species. An intact lactone ring is essential for topoisomerase I inhibitory activity. The instability of the active lactone greatly complicates the pharmacokinetics monitoring of the drug. Numerous phase I/II studies have explored topotecan pharmacokinetics but this primarily involved short infusion schedules. As part of the phase II clinical trial in SCLC patients, we investigated the pharmacokinetics and pharmacodynamics of topotecan administered as a 21 day continuous low-dose infusion.

Patients and methods

Patient population

Patients were eligible if they had a histologically confirmed diagnosis of SCLC or unequivocally positive cytologic evidence (sputum or aspirate biopsy). All patients had received one prior chemotherapy which had contained cyclophosphamide, doxorubicin and etoposide. Other eligibility criteria included a Zubrod-ECOG-WHO[8] performance status $\leqslant 2$, anticipated life expectancy of $\geqslant 3$ months and age $\geqslant 18$ years.

Previous anticancer chemotherapy, radiotherapy or immunotherapy had to be discontinued for at least 4 weeks before entry into the study. All patients had at least one measurable bidimensional lesion and were suitable and willing to have insertion of a portable device and indwelling catheter (Port-a-Cath®). All patients had acceptable bone marrow function [white blood cells (WBC) $\geqslant 4 \times 10^9$/l and platelets $\geqslant 100 \times 10^9$/l], normal hepatic function [serum bilirubin $\leqslant 35$ μM; alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and alkaline phosphatase (AP) $\leqslant 2$ times the upper limit of normal, or $\leqslant 5$ times the upper limit of normal if liver metastases are present; prothrombin or thrombtest within normal limits] and normal renal function (serum creatinine $\leqslant 135$ μM). The protocol was approved by the Medical Ethics Committee of the hospital. Before treatment, patients provided written informed consent according to institutional guidelines.

Treatment schedule

Topotecan (Hycamtin®) was administered as a con-

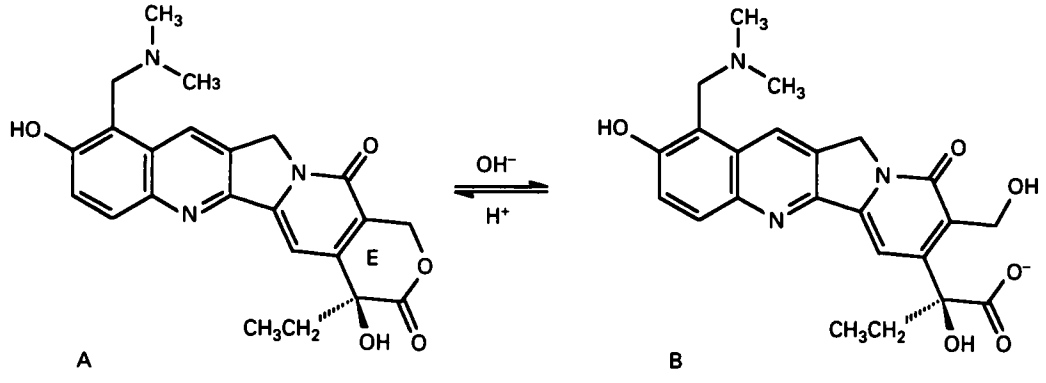

Figure 1. Chemical structures of topotecan (A) and its lactone ring-opened hydroxy acid species (SK&F 105992) (B). Both forms achieve a dynamic equilibrium at constant pH.

tinuous 21 day infusion every 28 days at a dose of 0.4 mg/m^2/day. Topotecan (SmithKline Beecham Pharmaceuticals, King of Prussia, PA) was supplied in vials as a lyophilized light yellow powder. Each vial contained 5 mg topotecan (as the free base), 60 mg mannitol, 25 mg tartaric acid and 2 M hydrochloric acid and/or 0.05 M sodium hydroxide for pH adjustment to 3.0. The content of each vial was reconstituted with 2 ml sterile water for injection, yielding a 2.5 mg/ml solution of topotecan. The appropriate volume of topotecan solution was transferred to a 50 ml pump reservoir. Final dilution to a total volume of 40 ml was made with sterile water for injection such that the total daily dose was contained in every 4.8 ml of solution. The reservoir was connected to a CADD-PLUS ambulatory infusion pump (Pharmacia-Deltec, St Paul, MN) set at a flow rate of 0.20 ml/h and connected to the patient's portable device. New solutions were prepared every 7 days in a new reservoir.

Dose modifications

The next treatment course was administered on schedule if there was no evidence of tumor progression, and if granulocytes were $>1.5 \times 10^9$/l, platelets $>100 \times 10^9$/l and hemoglobin >9 g/dl. The topotecan dose was decreased by one increment of 0.1 mg/m^2/day if myelosuppression lasted beyond day 28 of the previous treatment course, if the previous treatment course was discontinued because of grade 3-4 thrombocytopenia or grade 4 neutropenia, or if a patient had other grade 3-4 drug-related toxicity (except nausea or alopecia). The dose was increased by 0.1 mg/m^2/day, if during the previous course there was no toxicity greater than grade 2 and no dosing delay due to toxicity. The minimum infusion dose was 0.2 mg/m^2/day and the maximum infusion dose was 0.8 mg/m^2/day.

Patient evaluation

Pretreatment evaluation included a complete medical history and complete physical examination. Before each course, interim history (concomitant medications taken, toxicities and adverse experiences), physical examination, performance status, urinalysis and ECG (prior to second treatment course only) were performed. Weekly evaluations included complete blood cell counts (WBC, differential and platelets) and blood chemistries. Creatinine clearance was approximated using the formula of Cockcroft and Gault.[9] All toxicities observed were graded according to the Common Toxicity Criteria (CTC).[10] Tumor lesions that were evaluated by physical exam, X-ray or ultrasound were measured at the end of every course. Measurement of indicator lesions by computed tomographic (CT) scan or magnetic resonance imaging (MRI) scan was performed after every second course. Responses were evaluated according to the WHO criteria.

Pharmacokinetic studies

Clinical pharmacokinetic studies of topotecan were performed during the first and second treatment course. In the first course, blood samples (5 ml each) were collected in heparinized tubes pre-infusion, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h after the start of the infusion, and on days 7, 14 and 21 during the infusion prior to cassette changing to assess steady-state plasma levels of topotecan (C_{ss}) and topotecan plus hydroxy acid ($C_{ss,tot}$). During the second course, concentrations of the total of topotecan and hydroxy acid were determined prior to infusion, and on days 7, 14 and 21 during the infusion prior to cassette changing. Plasma was obtained by immediate centrifugation of the samples (5 min; 2500 *g*). To 1000 µl plasma 2.0 ml cold methanol (−20°C) was added. The sample was mixed on a whirl mixer for 10 s and centrifuged for 3 min at 3000 *g*. The clear supernatant was transferred to a polypropylene tube and immediately stored at −30°C until analysis. Urine was collected from the start of infusion as 24 h aliquots for 5 days and samples were frozen until analysis.

Plasma levels of topotecan and the total of topotecan plus hydroxy acid were determined separately on a validated reversed-phase HPLC system with fluorescence detection as developed in our laboratory.[11] For the determination of topotecan, the plasma methanol extracts were diluted with distilled water (1:1) and a 50 µl aliquot was injected onto the HPLC system. Within-run and between-run precision was less than 12.1% for the concentration range studied (0.05-10.0 ng/ml). Accuracy ranged between 87 and 107%. For the estimation of the sum of topotecan and hydroxy acid levels, the plasma methanol extracts were acidified with perchloric acid 2% (1:1) to a pH of 1.0. At this pH all drug was converted into the topotecan lactone form. Within-run and between-run precision was less than 7.8%. Accuracy ranged between 100 and 114%. The lower limit of quantification for topotecan and topotecan as the total of lactone and hydroxy acid was 0.05 ng/ml. Urine was diluted (1:50) with methanol, acidified with perchloric acid and directly injected onto the HPLC column. Within-

run and between-run precision was less than 5.9%. Accuracy ranged between 100 and 103%.

Chromatographic data processing was performed with a DataJet integrator [Thermo Separation Products (TSP), Fremont, CA] coupled to an IBM compatible computer provided with the WINner/286 data system (TSP) and the spreadsheet software package Lotus 1-2-3 (version 3.4: Lotus, Cambridge, MA). Calibration curves were calculated by least-squares linear regression analysis with weight factor $1/x^2$, where x is the analyte concentration. *N*-desmethyltopotecan concentrations in plasma and urine were quantified using the topotecan calibration curve; this is justified by the equivalent extraction recoveries and molar fluorescence of the analytes under our assay conditions.[12] Individual topotecan pharmacokinetic parameters were estimated by non-compartmental methods. C_{ss} and $C_{ss,tot}$ were determined as the mean of plasma levels on days 7, 14 and 21 during the infusion. The areas under the plasma concentration-time curve of topotecan (AUC) and total topotecan (AUC_{tot}) were estimated up to the last measured time point by the linear-logarithmic trapezoid rule. Topotecan clearance (CL) and total drug clearance (CL_{tot}) were calculated using R_0/C_{ss} and $R_0/C_{ss,tot}$, respectively, where R_0 is the infusion rate of topotecan (in mg/min). Renal clearance (CL_R) of total topotecan was calculated using $f_e \times CL_{tot}$, where f_e is the fraction of the dose that is excreted unchanged in the urine. Data are represented as mean ± SD.

Statistical analysis

The difference between courses for the pharmacokinetic parameters was evaluated using the paired Student's *t*-test. Patient's and biochemical characteristics (i.e. age, performance status, presence of liver metastases, ALAT, ASAT, AP, albumin, bilirubin and creatinine clearance) were linearly correlated to pharmacokinetic parameters of topotecan and total drug obtained in the first course using the non-parametric Spearman's rank correlation test to investigate determinants in interpatient pharmacokinetic variability. Statistical analysis was performed with SPSS® (Statistical Package for Social Sciences, version 6.1 for Windows). The level of significance was set at 0.05. All tests for significance were two-tailed.

Pharmacokinetic–pharmacodynamic analysis

Relationships between dose or systemic exposure to topotecan and pharmacodynamics, in particular the dose-limiting toxicities, were explored using scatter plots of the dose or C_{ss} or $C_{ss,tot}$ versus the percentage decrease in WBC, absolute neutrophil count (ANC), platelets (PLT) and Hb. The percentage decrease is defined as:

$$\% \text{ decrease} = \frac{\text{pretreatment value} - \text{value of the nadir}}{\text{pretreatment value}} \times 100\%$$

The data were fit to a sigmoidal maximum effect (E_{max}) model, as described by the modified Hill equation:[13]

$$E = E_{max} \times \frac{(DE)^{\gamma}}{(DE_{50})^{\gamma} + (DE)^{\gamma}}$$

where E represents the observed effect (i.e. percent decrease) produced by drug exposure DE, E_{max} denotes the maximal elicitable effect, DE is a measure of drug exposure (i.e. AUC), DE_{50} represents the drug exposure associated with 50% of E_{max} and γ is the Hill coefficient, which describes the sigmoidity of the curve. Pharmacokinetic-pharmacodynamic analysis was performed with NCSS® (Number Cruncher Statistical System, Kaysville, UT, 1992).

Results

Patients and treatment

A total of nine patients was enroled in the pharmacokinetic part of this multicenter phase II trial. Eight patients were male and one female, with a median age of 51 years (range 38-68). The median performance status at study entry was 1 (range 0-2). Additional patient characteristics are outlined in Table 1. A total of 29 full courses was administered with a median number of 2 (range 1-7) per patient. One patient received only one course. The reason for discontinuation of treatment was rapid progressive disease. The first two patients enroled in the study received a daily dose of 0.5 mg/m^2, the other patients were entered at the 0.4 mg/m^2/day dose level. Three patients had dose escalations to 0.5 mg/m^2/day after the second course. In one patient the dose further increased to 0.6 mg/m^2/day after the fourth course.

Toxicity and response evaluation

The main toxicity was myelosuppression. One episode of grade 4 and two episodes of grade 3 thrombocytopenia (10% of courses) were observed in three patients

and two patients experienced grade 3 leucocytopenia (6% of courses). Three patients had treatment delays of 1 week due to unresolved myelotoxicity. All patients experienced anemia, which was severe (grade 3 and 4) in 55% of all courses. Non-hematologic adverse effects included mild to moderate (grade 1-2) nausea and vomiting (42 and 35% of courses, respectively) which could be attenuated with standard anti-emetics, and diarrhea (26% of courses). Grade 1 and 2 transient elevations in AP and ALAT occurred in six patients (28% of courses) and five patients (21% of courses), respectively. Greater elevations, grade 3, in ASAT were observed in one patient (7% of courses). Grade 3 elevated bilirubin occurred in one patient. Fatigue was the most common complaint. Three patients achieved a partial response (33%), with a response duration of 10, 16 and 18 weeks, respectively.

Pharmacokinetics

At the beginning of the clinical trial, we verified that topotecan remained exclusively in the active lactone form after dilution in the infusion fluid. The mean pH of the solution was 3.8. At this pH no conversion to the hydroxy acid form was to be expected, which was confirmed by HPLC analysis.

Mean plasma concentration versus time curves of topotecan and the total of topotecan and its hydroxy acid form during the first are depicted in Figure 2. C_{ss} could be determined in eight patients during their first treatment course. In one patient, co-medication (triamterene) caused interfering peaks in the topotecan assay and only total drug levels could be determined. The pharmacokinetic parameters obtained during the first and second treatment cycles are shown in Table 2. Individual total plasma levels on days 7, 14 and 21 during the infusion were in the proportion of 1:1.02:1.12. The lactone-to-total concentration ratio in all patient samples obtained in the first course (n=69) ranged from 0.20 to 0.69 (mean 0.34±0.09). There was no correlation between dose and steady-state plasma levels. In two patients topotecan was detected in pleural and pericard fluid, respectively. The simultaneous pleural fluid-to-plasma and pericard fluid-to-plasma ratios were 1.14 and 1.06, respectively. Of the administered topotecan dose, 40±14% was excreted unchanged in the urine. CL_R was 88.2±34.1 ml/min/m^2. *N*-desmethyltopotecan was detectable in urine samples. The urinary recovery was 1.2±0.9% (range 0.4-3.0) of the administered topotecan dose.

Table 1. Patients characteristics

No. of patients	9
Gender M/F	8/1
Median age [years (range)]	51 (38-68)
Performance status	
0	3
1	4
2	2
Prior radiotherapy	4
Liver metastases	4
Median biochemical baseline values (range)	
alkaline phosphatase (IU/l)	90 (62-350)
ALAT (IU/l)	11 (7-61)
ASAT (IU/l)	15 (10-43)
total bilirubin (μM)	7 (4-13)
creatinine clearance (ml/min)	82 (49-141)

Statistical analysis

The possible influence of prior exposure to topotecan on the pharmacokinetics could be examined in eight patients who received a second treatment course. Course two CL_{tot} values were significantly lower (p=0.032, n=8, paired t-test) than corresponding values during the first course. Remarkably, a patient who had a 44% decrease in CL_{tot} (213 and 119 ml/min/m^2, respectively) in the second course had 2- and 8-fold higher ASAT and ALAT levels prior to the second course compared with values at study entry. Likewise, CL_{tot} was decreased by 40% (185 and 110 ml/min/m^2, respectively) in the second course in a patient who

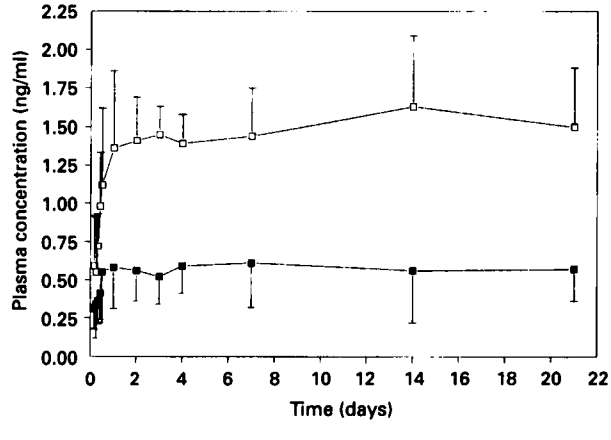

Figure 2. Mean plasma concentration versus time curves of topotecan (■) and topotecan as the the total of the lactone and hydroxy acid forms (□) during the first course in patients who received 0.4 mg/m^2/day by a 21 day continuous infusion.

had a 3- and 2-fold increase in ASAT and ALAT levels prior to the second course compared with pretreatment values.

Nine individual factors were considered in univariate analysis to investigate determinants in interpatient pharmacokinetic variability (Table 3). CL was significantly correlated with ASAT (r=0.71, p=0.05, n=8) and the presence of liver metastases (r=0.85, p=0.008, n=8). A strong relationship was identified between CL_{tot} and serum albumin (r=0.85, p0.004, n=9). Although there was no statistically significant correlation between CL and CL_{CR}, it is worth noticing that a patient with a CL_{CR} of 49 ml/min had the lowest CL (343 ml/min/m^2) in a group of eight patients with normal renal function (CL range 520-926 ml/min/m^2).

Pharmacokinetic–pharmacodynamic analysis

We were unable to find a correlation between dose or systemic exposure to topotecan lactone (i.e. AUC), the active cytotoxic form and hematologic toxicity. A sigmoidal E_{max} model was, however, appropriate to describe the relationship between AUC_{tot} and the percentage decrease in PLT (r=0.76, p=0.018) (Figure 3). No association could be

Table 2. Pharmacokinetic parameters of topotecan lactone and total drug

Patient	First treatment cycle									Second treatment cycle		
	Dose (mg/m^2/day)	Total dose (mg/day)	C_{SS} (ng/ml)		AUC (min.μg/ml)		CL (ml/min/m^2)		f_e (%)	$C_{SS,tot}$ (ng/ml)	AUC_{tot} (min.μg/ml)	CL_{tot} (ml/min/m^2)
			Lactone	Total	Lactone	Total	Lactone	Total				
1	0.50	0.95	0.55	1.77	16.6	53.4	631	196	30			
2	0.50	0.80	0.40	1.43	12.1	43.2	864	243	48	1.75	52.9	199
3	0.40	0.62	0.81	1.58	24.5	47.8	343	176	45	1.66	50.2	168
4	0.40	0.84	0.53	1.30	16.0	39.3	520	213	60	2.33	70.5	119
5	0.40	0.76	0.43	1.35	13.0	40.8	649	206	44	1.45	43.8	192
6	0.40	0.75	0.39	0.94	11.8	28.4	718	297	44	0.96	29.0	290
7	0.40	0.75	0.34	1.50	10.3	45.4	809	185	33	2.52	76.2	110
8	0.40	0.76		1.33		40.2		209		1.40	42.3	199
9	0.40	0.67	0.30	0.93	9.1	28.1	926	300	13	1.49	45.1	187
Mean[a]		0.74	0.47	1.28	14.1	38.6	661	227	40	1.69	51.0	181
SD[a]		0.07	0.19	0.25	4.9	7.7	208	51	11	0.55	16.6	60
% CV		10	40	20	35	20	31	22	28	33	33	33

% CV, coefficient of variation. [a]The mean and SD were calculated using the data from patients 3–8.

Table 1. Influence of patient's pathophysiological parameters on topotecan pharmacokinetics during the first treatment course (Spearman rank order)

Parameter	CL		CL_{tot}	
	r	p value	r	p value
Age	0.38	0.35	−0.17	0.67
Performance status	−0.16	0.70	−0.35	0.36
Liver metastases	0.85	0.008	0.26	0.50
Hepatic function				
ALAT	0.25	0.56	−0.07	0.86
ASAT	0.71	0.05	0.05	0.91
AP	0.05	0.91	−0.40	0.29
albumin	0.26	0.53	0.85	0.004
bilirubin	0.33	0.42	−0.19	0.63
Renal function				
creatinine clearance	−0.17	0.69	0.42	0.27

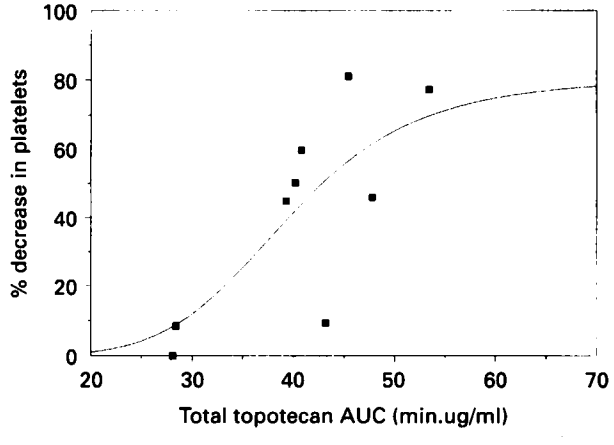

Figure 3. The percentage decrease in PLT versus topotecan AUC_{tot}. The data are fit to a sigmoidal E_{max} model (parameters: E_{max}=80.49; $AUC_{tot,50}$=39.6 ng/ml; γ=6.3).

detected between AUC_{tot} and percentage decrease in WBC or ANC.

Discussion

Promising results have been reported recently with 21 days of continuous low-dose infusion of topotecan. In the heavily pretreated patient population of a phase I study using this infusion schedule, objective responses were observed in seven patients with ovarian, breast, renal and non-small cell lung cancer.[6] Based on these results, a multicenter phase II study was initiated in patients with chemotherapy relapsed or refractory SCLC. We performed a pharmacokinetic study in nine patients participating in this phase II trial.

The individual topotecan plasma levels on days 7, 14 and 21 during the infusion were in the proportion of 1:1.02:1.12, implying that steady-state has been achieved. The small differences in plasma levels on days 7, 14 and 21 can be explained by the fact that the CADD-PLUS ambulatory infusion pump is an intermittent flow device. At a flow rate of 0.2 ml/h, a bolus is delivered every 15 min. Given the short terminal half-life of topotecan, fluctuation at plateau was to be expected. In contrast with our i.v. data, oral administration of topotecan twice daily for 21 days resulted in consistently higher AUC values of topotecan ($p < 0.05$) on day 7 compared with day 1,[14] which indicates accumulation of the drug after oral administration.

Our study revealed moderate interpatient variability in systemic exposure to topotecan (CV of 35 and 20% for AUCs for topotecan and the total of topotecan forms, respectively). *N*-desmethyltopotecan plasma levels were below the detection limit. ASAT and albumin were found to be clinical indicators of interpatient variability in topotecan clearance and this provides preliminary evidence for altered topotecan pharmacokinetics in patients with impaired liver function. To date, only one study by O'Reilly and colleagues[15] has addressed the influence of hepatic function impairement, defined by a serum total bilirubin level between 1.7 and 5.0 mg/dl, on the pharmacokinetics of topotecan. Plasma clearance in patients with hepatic impairment was decreased to about 67% of the value of control patients.

We were unable to demonstrate a statistically significant correlation between CL and CL_{CR}. However, a patient with CL_{CR} of 49 ml/min had the lowest CL in a group of eight patients with normal renal function. Decreased renal clearance is known to be an important determinant of topotecan clearance. In patients with mild renal impairment (CL_{CR} of 40–59 ml/min) receiving 1.5 mg/m^2/day as a daily 30 min infusion, topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function,[16] which agrees with our data.

We demonstrated that during the second treatment course $C_{ss,tot}$ values were significantly higher compared with corresponding course 1 levels, while the administered dosages remained constant, which suggests altered topotecan clearance. This intrapatient variation in pharmacokinetics has not been reported for other administration schedules. The change in clearance of topotecan after the first dose may have arisen from either drug-related effects on the liver and/or the kidney or from declining organ function due to rapid disease progression. The following liver/biliary adverse reactions to topotecan have been reported based on the experience of 452 patients with metastatic ovarian cancer treated with topotecan in the daily 30 min × 5 infusion schedule:[17] grade 1 elevations in ASAT and ALAT occurred in 5% of patients, grade 3/4 elevations in less than 1%. Grade 3/4 hyperbilirubinemia occurred in less than 3% of patients. However, it is impossible to differentiate between cause and effect.

We were unable to relate the AUC of topotecan lactone, the active cytotoxic form, to hematologic toxicity, which may be due to the limited number of data. Moreover, the range of AUCs was small because the dosages were within a tight range. In addition to topotecan plasma levels, we have used the total (lactone plus hydroxy acid) topotecan AUC to explore pharmacokinetic-pharmacodynamic relationships of the drug. Previous studies have demonstrated that the AUC of total topotecan was equally, or even better, related to hematologic toxicity compared with pharmacokinetic parameters of the lactone form (reviewed in Herben *et al.*[18]), indicating that although the hydroxy acid form lacks topoisomerase inhibitory activity, the potential for conversion to the lactone suggests that cytotoxic activity should be possible regardless of what proportion of topotecan is in the open-ring form in the extracellular space.[19] A sigmoidal relationship was found between AUC_{tot} and the percentage decrease in PLT (Figure 3). However, the considerable scatter in the data illustrates that the pharmacokinetic variability is not a major determinant of this toxicity.

We conclude that topotecan administered as a 21 day continuous low-dose infusion has activity as single-agent, second-line therapy in patients with SCLC. Considerable interpatient and intrapatient variability in systemic exposure to topotecan was observed. Differences in organ function might contribute to this variation. Serum ASAT and albumin levels were predictive of topotecan pharmacokinetics.

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