Inter- and Intrapatient Variability in Oral Topotecan Pharmacokinetics: Implications for Body-Surface Area Dosage Regimens

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ABSTRACT

Anticancer drugs still are dosed based on the body-surface area (BSA) of the individual patient, although the BSA is not the main predictor of the clearance for the majority of drugs. The relevance of BSA-based dosing has not been evaluated for topotecan yet. A retrospective pharmacological analysis was performed of kinetic data from four clinical Phase I studies in which topotecan was administered p.o. as a single agent combined with data from a combination study of topotecan and cisplatin. A strong correlation ($r = 0.91$) was found between the area under the plasma concentration time curve of the lactone and carboxylate forms of topotecan by plotting 326 data sets obtained from 112 patients receiving oral topotecan at dose levels ranging from 0.15–2.70 mg/m^2. The intrapatient variability, studied in 47 patients sampled for 3 or more days, for the apparent lactone clearance, ranged from 7.4–69% (mean, 24 ± 13%; median, 20%). The interpatient variabilities in the lactone clearance, calculated with the data of all studied patients, expressed in liter/h/m^2 and in liter/h were 38% and 42%, respectively. In view of the relatively high inter- and intrapatient variabilities in topotecan clearance, in contrast to a variability of only 12% in the BSA of the studied patients, no advantage of BSA-based dosing was found over fixed dose regimens.

INTRODUCTION

Most anticancer drugs are dosed based on the BSA[2] of the individual patient, with the aim of reducing interpatient varia-bility of drug exposure. However, this strategy failed for most drugs (1), except for docetaxel (Taxotere), where BSA has been shown to be a main predictor of the clearance in a pharmacokinetic model (2). The relevance of this concept of BSA-based dosing has not been evaluated for topotecan (Hycamtin), one of the most promising agents that entered the clinical practice in recent years. Topotecan has antitumor activity against various human malignancies, and relationships have clinically been found between systemic exposure of topotecan and hematological toxicity (reviewed in Refs. 3–5) and with antitumor activity in preclinical models (6). The bioavailability of oral topotecan in adult cancer patients ranged from 30–44% with interpatient variabilities of 26–31% (7–9). However, because pharmacokinetic analysis in most patients (10–12) has been carried out for only 2 days, a reliable estimate of the intrapatient variability of p.o. administered topotecan has not yet been established. The recommended dose for single-agent oral topotecan is 2.3 mg/m^2/day for 5 days every 3 weeks. As an alternative, a fixed dose of 4 mg/day for 5 days every 3 weeks was proposed (10). However, thus far, studies on oral topotecan have been performed by dosing patients based on their BSA instead of using fixed dose regimens. Because most patients will take their oral medication in an outpatient setting, it is important to keep dosing regimens as simple as possible, and, because of this, it would be most practical to use fixed dosing regimens (13). The aim of the present analysis of kinetic data from several Phase I studies was to investigate whether dosing of oral topotecan in the treatment of adult cancer patients based on BSA of individual patients has any advantage over fixed dose regimens.

PATIENTS AND METHODS

Patient Selection. The patient selection criteria were fully described elsewhere for the oral Phase I studies in which topotecan was administered as a single agent (3) and for the study in which oral topotecan was combined with i.v. cisplatin (14). In short, patients with a confirmed diagnosis of a malignant solid tumor resistant to standard chemotherapy regimens were eligible for these studies. Age should be between 18 and 75 years, and performance status, defined by the Eastern Cooperative Oncology Group, had to be ≤2. No previous anticancer therapy for at least for 4 weeks was allowed. Adequate hematopoietic and renal functions were required, and patients with mildly impaired liver functions (*i.e.,* total serum bilirubin ≤1.25 × upper normal limit; and aspartate aminotransferase and alanine aminotransferase ≤2 × upper normal limits and, in case of liver metastases, ≤3 × upper normal limits) were allowed to participate in the described studies. A specific exclusion criterion was the existence of any gastrointestinal circumstance, which could alter the absorption of topotecan. All patients signed informed consent.

Table 1 Evaluable pharmacokinetic days in the four single-agent Phase I studies of orally administered topotecan

Dose (mg/m^2)	Twice daily	Once daily	No. of patients	Total number of evaluable kinetic courses				
				Day 1	Day 4	Day 8	Day 21	Total
0.15	21 days		2	2		1		3
0.30	21 days		3	3		3		6
0.40	21 days		2	3		2	2	7
0.50	21 days		4	4		4		8
0.60	21 days		3	3		3		6
0.50	10 days		1	1		1		2
0.60	10 days		4	3		4		7
0.70	10 days		4	4		4		8
0.80	10 days		1	1				1
1.00		10 days	3	3		3		6
1.40		10 days	3	3		3		6
1.60		10 days	4	4		4		8
1.20		5 days	3	3	3			6
1.80		5 days	3	3	3			6
2.30		5 days	6	6	6			12
2.70		5 days	4	4	4			8
1.25[a]		10 days	1	1		1		2
4.00[a]		5 days	6	6	6			12
Total[b]			56	57	22	33	2	114

[a] Fixed dose.
[b] One patient in the twice daily 0.40 mg/m^2 was also sampled during course 2, and one patient in the once daily 1.40 mg/m^2 was also sampled during a course with a fixed dose of 1.25 mg.

Treatment Schedules in the Single-Agent Phase I Studies. Oral administration, using the i.v. formulation, of single-agent topotecan was studied in four Phase I studies (3). The first study involved a twice daily dosing of topotecan at dose levels of 0.15–0.60 mg/m^2 for 21 days, repeated every 28 days (3, 11). In the second study, topotecan was administered twice daily for 10 days, every 21 days, at dose levels of 0.50–0.80 mg/m^2 (3, 12). In the third study, the administration of topotecan was reduced to once a day for 10 days at dose levels ranging from 1.00–1.60 mg/m^2 (3, 12). The final Phase I study of single-agent oral topotecan involved a once daily administration for 5 days, also repeated every 21 days, and included dose levels ranging from 1.20–2.70 mg/m^2 (3, 10). In the daily for 5 days schedule also patients were included who were treated with a fixed dose of 4 mg/day.

Treatment Schedule in the Combination Phase I Study. The latter mentioned regimen of oral topotecan, this time at dose levels ranging from 0.75–2.30 mg/m^2/day for 5 days, using the drug formulated in gelatin capsules, was also studied combined with a fixed dose of 75 mg/m^2 i.v. cisplatin (14). In the present study, we also included pharmacokinetic data of patients treated with oral topotecan daily for 5 days, at dose levels of 1.50 and 1.75 mg/m^2, preceded by a 3-h cisplatin infusion at 50 mg/m^2 on day 1 of each course in an ongoing study, using the same eligibility criteria as reported previously (14).

Pharmacokinetic Sample Collection and Analysis. Blood samples were collected, up to 12 h after dosing (10–12, 14), in 4.5-ml glass tubes containing lithium heparin as anticoagulant and were centrifuged within 10 min to separate the plasma. Subsequently, the plasma was deproteinized by 4-fold dilution in ice-cold (−20°C) methanol, resulting in a stabilized lactone:carboxylate ratio (15), and stored at −80°C upon analysis. Simultaneous determination of the lactone and carboxylate form of topotecan was performed by a reversed-phase high-performance liquid chromatographic method, as described (15), with minor modifications for the analysis of drug levels in the combination Phase I study (14).

On the basis of the best fitted curves, two and three compartmental analysis models after zero-order input were used for the calculation of the $AUC_{0\text{-infinity}}$ of the lactone as well as the carboxylate form of topotecan, as described (14). The apparent CL/F of topotecan lactone was calculated by dividing the dose per m^2 by the observed lactone AUC, expressed in liter/h/m^2. The absolute CL/F, expressed in liter/h, was calculated by dividing the absolute dose by the AUC of topotecan lactone.

Statistical Analysis. Linear regression analysis was performed, using the NCSS package (version 5.X, 1992; J. L. Hintze, East Kaysville, UT), to test potential relationships between evaluated parameters. One-way ANOVA was performed to evaluate statistically significant differences ($P < 0.05$) between groups, using the same program.

RESULTS

In the four Phase I studies on single-agent oral topotecan, 56 patients were evaluable for pharmacokinetic analysis for a total of 114 kinetic days (Table 1). The majority of evaluable days were obtained in the Phase I trial studying the combination of oral topotecan and i.v. cisplatin, in which 56 patients were sampled for a total of 228 days (Table 2).

By plotting 326 data sets (95% of total) of kinetic days for which both the lactone and the carboxylate AUC could be assessed, a strong linear relationship was found between the AUCs of the pharmacological active lactone form of topotecan and its inactive ring-opened carboxylate form ($AUC_{carboxylate} = 1.62 + 1.57*AUC_{lactone}$, $r = 0.91$; Fig. 1). For further estimation of inter- and intrapatient variabilities and their implication

Table 2 Evaluable pharmacokinetic days in the Phase I study in which oral topotecan was combined with i.v. cisplatin

| Dose (mg/m²) | No. of patients | Total number of evaluable kinetic days | | | | | | | | | | |
		C1d1	C1d2	C1d5	C2d1	C2d5	C3d1	C3d5	C6d1	C6d2	C6d5	Total
0.75	6	6		6	6	6	6	6				36
1.00	6	6		6	6	6	6	6				36
1.25	11	10	4	11	5	5	4	4	2	2	1	48
1.50	9	9	5	8	3	3			1	1	1	31
1.75	10	10	6	9	3	3						31
2.00	8	6	3	7	4	4						24
2.30	7	7		7	4	4						22
Total[a]	56	54	18	54	31	31	16	16	3	3	2	228

[a] One patient received 2.30 mg/m² (course 1) and 2.00 mg/m² (course 2).
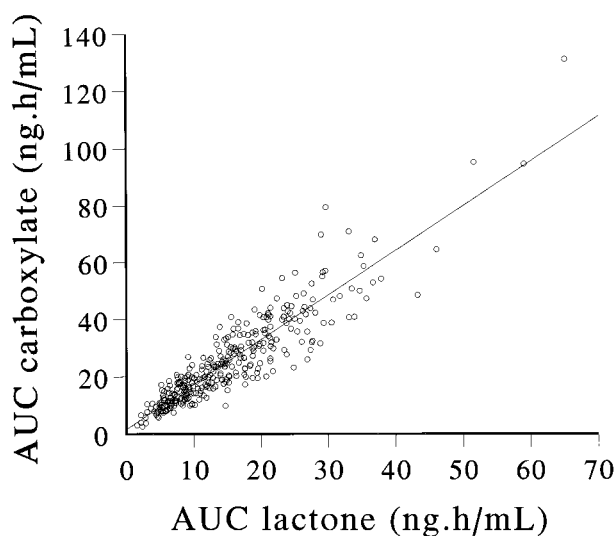

Fig. 1 Relationship between the AUCs of the lactone and carboxylate form of topotecan in 326 evaluable data sets.

for BSA dosage regimens, pharmacokinetic parameters of the lactone form were used in this analysis.

Inter- and Intrapatient Variability. Because the majority of the patients in the single-agent oral Phase I studies were sampled for pharmacokinetic analysis for only 2 days during one cycle, the intrapatient pharmacokinetic parameter variabilities for topotecan lactone were studied using the data obtained in the topotecan/cisplatin combination Phase I study, in which pharmacokinetic sampling was performed during several cycles. As already reported, there was no pharmacokinetic interaction between oral topotecan and i.v. cisplatin (14). In view of this, all kinetic days (with and without cisplatin) were used for the present analysis. The intrapatient variability in AUC and CL/F of topotecan lactone was calculated as the SD divided by the average, using only data from the 47 patients who had at least three evaluable kinetic courses of the AUC of topotecan lactone. The average intrapatient variability in the lactone AUC across all dose levels was 24 ± 13% (median, 20%; range, 7.6–61%). The average intrapatient variability in the CL/F, expressed in liter/h/m² and in liter/h, was 24 ± 13% (median, 20%; range, 7.4–69%).

The interpatient variability in CL/F, expressed in liter/h/m²

as well as in liter/h, was calculated using the data of all of the patients, by using the averaged apparent CL/F of all kinetic days of each patient as single value. The average apparent CL/F was 103 ± 39.0 liters/h/m² (CV = 38%, n = 107; Fig. 2*A*), with no significant difference (*P* = 0.074) in the CL/F over the 19 studied dose levels. The average apparent CL/F, studied over 27 different individual dosages, was 194 ± 80.4 liters/h (CV = 42%, n = 107; Fig. 2*B*) or 195 ± 81.1 liters/h (CV = 42%, n = 114; Fig. 2*B*), by inclusion of the patients treated with a fixed dose.

In addition, no alteration in topotecan lactone kinetics was found (*P* = 0.30) after multiple (up to six) courses (Fig. 3), using the data of patients treated in the combination Phase I study, in which patients were samples for multiple courses.

BSA as Determinant for Dose Calculations. As shown in Figs. 2 and 3, the apparent CL/F was constant over the studied dose ranges and courses. In Fig. 4, the BSA is plotted *versus* absolute apparent CL/F in liters/h (mean ± SD), calculated with the actual dose given to each individual patient. A poor positive relationship was found between BSA and the average apparent CL/F (CL/F = 52.4+75.1*BSA, *r* = 0.29), with large variabilities in the apparent CL/F across all studied BSA values in the 47 patients with three or more pharmacologically evaluable courses.

DISCUSSION

Dosing of most cytotoxic agents is commonly based on the BSA of patients, intending to reduce interpatient pharmacokinetic variabilities of a compound. This, in turn, is based on an assumed relationship between the clearance of a compound and the BSA of the individual patient (1, 13). However, calculation of the exact clearance of topotecan is not feasible because the compound has a reversible conversion from the lactone to the carboxylate form. Moreover, accurate dosing of oral topotecan based on BSA is also not feasible, because for oral use the drug is now only available as gelatin capsules containing 1.0 and 0.25 mg, respectively, resulting in the necessity of rounding of the absolute dose to the nearest quartile mg. Because excretion by the kidneys is a major route of elimination of topotecan (reviewed in Ref. 4) and alterations in the pharmacokinetic parameters for topotecan have only been described in patients with a renal dysfunction (*i.e.*, creatinine clearance <60 ml/min; Ref. 16), in the set of studies we performed an altered topotecan clearance was not expected. The apparent CL/F of oral topote-

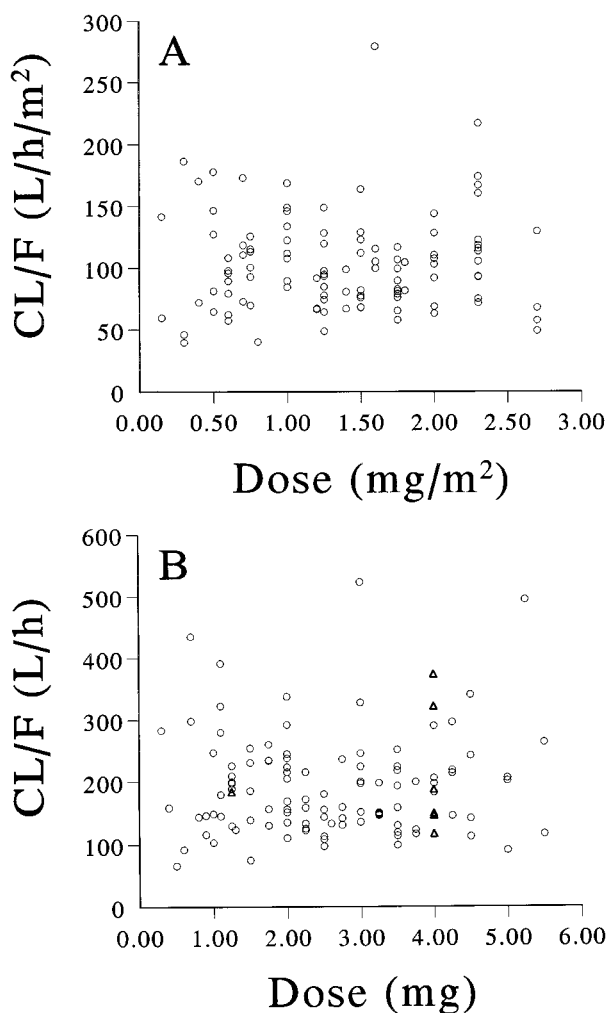Fig. 2 Plot of dose/m² (A) and absolute dose (B) and the averaged apparent CL/F (patients with a fixed dose are indicated by *triangles*).

Fig. 3 Apparent CL/F during multiple courses and days.
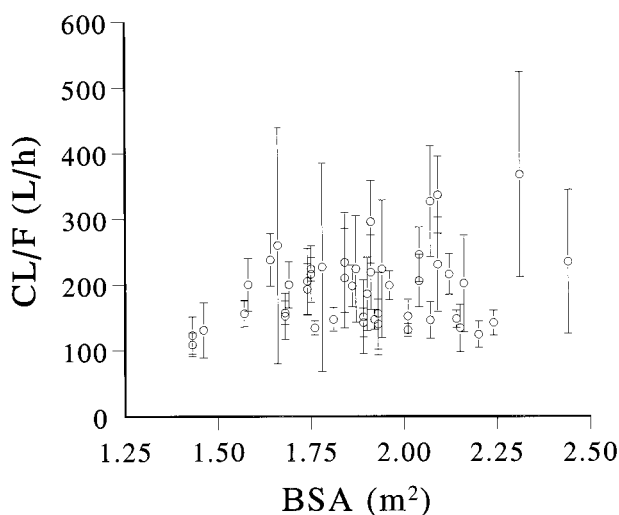
Fig. 4 BSA *versus* absolute apparent CL/F expressed in liter/h (mean ± SD).

can, in patients with a normal renal function, is highly dependent on the absorption of the lactone form from the gastrointestinal tract.

The oral bioavailability of topotecan in adult cancer patients for drinking of the i.v. solution ranged from 30 ± 7.7% (7) to 44% (9) and was found to be 42 ± 13% for the drug formulated in gelatin capsules (8). In these clinical studies, interpatient variabilities in the oral availability in adults ranged from 26–31% (7, 8), which is not dissimilar to the interpatient variability of 38% and 42% for the apparent CL/F expressed in liter/h/m² and in liter/h, respectively, in our studies. Because the interpatient variability was calculated with the average apparent CL/F of topotecan lactone, using the data of patients who were studied up to six times, this variability might even be underestimated.

Only limited information was available on the intrapatient variability of p.o. administered topotecan in adult cancer patients. Gerrits *et al.* (3) reported intrapatient variabilities in AUC of topotecan lactone of 25 ± 31% (*n* = 22) and 35 ± 25%
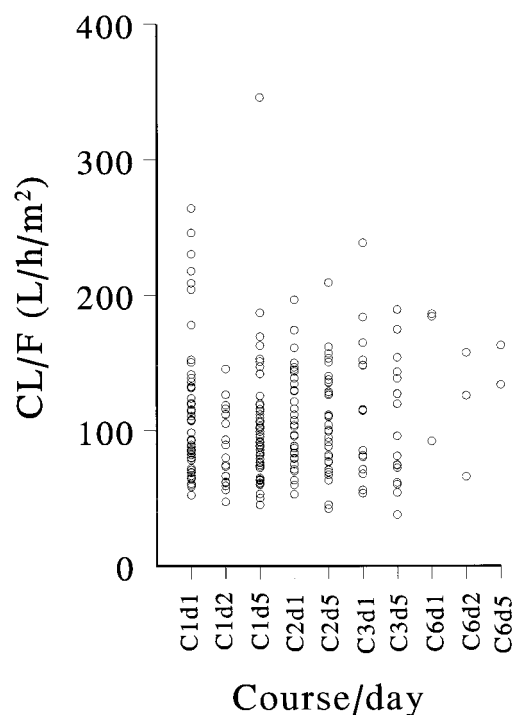
(n = 10) in clinical Phase I studies in which topotecan was administered either once daily for 5 days or 10 days, respectively, and of 97 ± 70% (*n* = 10) and 60 ± 51% (*n* = 13) in the twice daily for 10 days and 21 days schedules, respectively. Because samples were collected only for pharmacokinetic analysis on 2 treatment days during one cycle, an accurate estimation of the intrapatient variability was not possible. In this present analysis, we assessed the intrapatient variability using

data of 47 patients, who were sampled on 3–6 days each, resulting in an average intrapatient variability of the lactone AUC of 24 ± 13% (median 20%), with a range of 7.6- 61%.

The broad range in the intrapatient variability in lactone AUC after oral administration of topotecan is probably related to the fact the carboxylate form is poorly absorbed from the small intestine, whereas the lipophilic pharmacological active lactone form of topotecan is able to pass the membranes of the small intestine (4). Because the pH in the small intestine ranges from pH 5–7 and the rate of interconversion between the lactone and carboxylate form of topotecan is pH dependent, the amount of topotecan that is available for absorption is related to a fluctuation in the pH.

We did not find saturation of the absorption, tissue distribution, or elimination of p.o. administered topotecan over the studied dose range of 0.15–2.70 mg/m^2 apparent from a lack in significant difference in the observed CL/F over the dose range studied. Also, administration of multiple (up to six) courses of p.o. administered topotecan did not alter the apparent topotecan lactone CL/F.

The interpatient variability in the topotecan CL/F of 38% and 42%, expressed in liter/h/m^2 and liter/h respectively, is much larger than the 12% interpatient variability in BSA of our patients (average BSA, 1.9 ± 0.22 m^2, n = 107). In view of the intrapatient variability of 24 ± 13% in the apparent lactone CL/F, with individual variabilities up to 69%, the interpatient variability in the bioavailability of 26–31%, and the poor relationship between the BSA and the average apparent CL/F, we feel that there is no scientific rationale for BSA-based dosing of p.o. administered topotecan in adult patients. This confirms our previous observation of similar pharmacokinetics after oral administration of either 2.3 mg/m^2 topotecan or a fixed dose of 4 mg (10), which was already suggesting that fixed-dose regimens could be applied.

In conclusion, in view of the relatively high intra- and interpatient variabilities in the AUC and CL/F of topotecan lactone and the relatively small range in observed BSA, oral topotecan can be added to the list of agents where BSA-adjusted dosing does not seem definitely better (1). We recommend a fixed dose regimen for future use in clinical trials, which is more convenient for the oncologist and the pharmacist, is more cost-effective, and, last but not least, is less cumbersome for the patients. Further randomized clinical studies in a large population are needed to fully explore the advantages of fixed dose regimens of p.o. administered topotecan, in which simultaneously the need for potential dosage adjustments at extreme BSA values have to be investigated.

A careful study of interpatient variability of topotecan AUC in patients of the same BSA and renal and hepatic function, to look at the effects of factors as age, gender, protein binding, and inherited or acquired metabolic function, in addition to expression of the MDR-1 P-glycoprotein and BCRP drug-transporting proteins (17) in intestinal tissues as an explanation for this variability, is currently being conducted.

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