Combination Metronomic Oral Topotecan and Pazopanib: A Pharmacokinetic Study in Patients with Gynecological Cancer

DAVID C. TURNER[1], TODD D. TILLMANNS[2], K. ELAINE HARSTEAD[1], STACY L. THROM[1] and CLINTON F. STEWART[1*]

[1]*Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, U.S.A.;*
[2]*Department of Obstetrics and Gynecology, Division of Gynecologic Oncology and West Clinic, Memphis, TN U.S.A.*

Abstract. *Background: Combination metronomic topotecan plus pazopanib is active against preclinical models of gynecological cancer. Both agents are substrates for ATP-binding cassette family transporters so there is an increased likelihood for pharmacokinetic (PK) drug-drug interactions. Patients and Methods: PK analyses of topotecan were performed during three cycles of a phase I dose-escalation study of metronomic topotecan and pazopanib in consenting adult patients with gynecological cancer. Concentration time data were analyzed using a population PK approach. Results: Twenty-one patients were evaluable for serial PK studies. Considerable inter- and intra-patient variability was observed in the PK parameters, attributable primarily to highly variable oral bioavailability. No difference in topotecan disposition was detected between administration cycles, nor between the off- versus on-pazopanib studies. Conclusion: The lack of a statistically significant drug-drug interaction agrees with preclinical findings suggesting that pazopanib does not influence the PK of metronomic topotecan. No adjustment of low dose metronomic topotecan dosing is merited when used in conjunction with pazopanib.*

Topotecan (9-dimethylaminomethyl-10-hydroxycamptothecin), a semi-synthetic derivative of camptothecin, has excellent clinical activity against several types of solid malignancies, including small cell lung cancer, colorectal cancer, breast cancer, and ovarian carcinoma (1). Various dosing schedules of oral topotecan have been evaluated in phase I studies, establishing a maximum tolerated dose that ranges from 14 mg/m^2 for a single oral dosage (2) to a 1.0 mg fixed daily dose for a metronomic (once-daily) regimen (3). The efficacy of low-dose metronomic topotecan has been extensively investigated in preclinical animal models (4-6) and early phase clinical trials (7). Merritt and colleagues demonstrated that low-dose, protracted topotecan reduces cell proliferation and angiogenesis in a murine model of advanced ovarian cancer (4), and Soffer *et al*. observed that low-dose topotecan plus antibody to vascular endothelial growth factor (VEGF) suppressed tumor growth and metastases more than either drug alone in an experimental murine xenograft Wilms tumor model (5). Furthermore, topotecan has been noted to elicit an inhibitory effect on hypoxia-driven VEGF induction through suppression of both hypoxia-inducible factor 1-alpha and 2-alpha (HIF-1A and HIF-2A) (8).

Pazopanib, a potent and selective small molecule inhibitor of VEGFR-1, -2, and -3, platelet-derived growth factor alpha (PDGF-α), PDGF-β, and c-KIT tyrosine kinases, has shown encouraging preclinical antitumor results in combination with metronomic topotecan. Hashimoto *et al*. tested several monotherapy and combination metronomic chemotherapy regimens in an ovarian xenograft model and found that low-dose metronomic oral topotecan chemotherapy produced favorable tumor growth inhibition, especially when combined with VEGF pathway-inhibiting drugs such as bevacizumab and pazopanib (9). Kumar and colleagues demonstrated that this combination, compared to other regimens, produced superior survival in an ovarian tumor xenograft model (10), and Merritt *et al*. achieved similar therapeutic results utilizing metronomic oral topotecan plus pazopanib in other models of human ovarian cancer (11).

On the basis of these early promising results, we have implemented a combination of metronomic oral topotecan and oral pazopanib in a phase 1, dose-escalation study in female patients with recurrent or persistent gynecological tumors. An important question yet unanswered is whether

Correspondence to: Dr. Clinton Stewart, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, U.S.A. Tel: +1 9015953665, Fax: +1 9015256869, e-mail: clinton.stewart@stjude.org

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co-administration of pazopanib with topotecan elicits transporter-mediated drug-drug interactions. Earlier work suggests that topotecan is a substrate for ATP-binding cassette protein G2 (ABCG2; BCRP) as well as P-glycoprotein (ABCB1; P-gp), and these drug transporters play a key role in regulating the gastrointestinal uptake and renal/biliary elimination of topotecan (12-16). *In vitro* studies indicate that pazopanib is a substrate for both ABCG2 and P-gp (17). Since the ABCG2/ P-gp transport systems are capacity-limited, it is conceivable that co-medication with pazopanib could impact the disposition of topotecan. A preclinical pharmacokinetic study conducted in mice receiving metronomic topotecan plus pazopanib indicated no apparent drug-drug interactions (10), although the study sample size was limited to three animals per treatment. To our knowledge, only one human pharmacokinetic study has explored interactions of pazopanib and topotecan, but at higher topotecan doses than administered to gynecologic patients on the current trial (18). Thus, a key aim of the present phase I pharmacokinetic study was to investigate potential pharmacokinetic drug-drug interactions of low dose metronomic oral topotecan and oral pazopanib. We also sought to identify covariates predictive of pharmacokinetic disposition of low dose metronomic oral topotecan and establish an adjusted dosing regimen in this patient cohort, if necessary.

Patients and Methods

Patient population and oral formulation administration. Informed consent was obtained from all patients enrolled on this clinical trial (NCT00800345). All patients were required to meet standard laboratory eligibility criteria as defined in the protocol and be at least 18 years of age with recurrent or persistent gynecologic tumors (women of all ethnic groups were eligible). Study participants received topotecan alone as a 0.25 mg daily oral dose or in combination with either 400, 600, or 800 mg of daily oral pazopanib. Oral topotecan was supplied by GlaxoSmithKline as white to pale yellow hard gelatin capsules sealed with a clear gelatin band containing topotecan HCl, equivalent to 0.25 mg of the anhydrous free base. Pazopanib monohydrochloride salt (coded as GW786034B) was was supplied by GlaxoSmithKline as a 400 or 200 mg tablet, containing pazopanib monohydrochloride salt equivalent to 400 or 200 mg of the free base.

Sample collection and processing. Serial venous blood samples were obtained during cycle 1 day 1 (C1D1; without pazopanib) prior to topotecan administration (pre-), and 0.25, 1, 2, 4 (±0.5), and 6 (±0.5) hours after topotecan administration. Serial samples were also collected during cycle 1, day 2 (C1D2; *with* pazopanib), cycle 2 day 1 (C2D1; *with* pazopanib), and cycle 3 day 1 (C3D1; with pazopanib) before both drugs were administered as well as at the timepoints specified above. Metronomic oral topotecan was administered beginning on C1D1. Oral pazopanib was not administered on C1D1 to allow for the characterization of single-agent topotecan pharmacokinetics; oral pazopanib was administered beginning on C1D2.

At each sampling time, 3 ml of venous whole blood was drawn into a heparinized tube. The samples were centrifuged to obtain plasma, which was stored on dry ice or at –80˚C until sent for bioanalysis and pharmacokinetic modeling.

Analytical assay. An isocratic high-performance liquid chromatography (HPLC) assay was used to measure the concentration of total topotecan in the plasma samples as previously described (19). Calibration curves were constructed using blank control plasma, with topotecan concentrations ranging from 0.25 to 10 ng/ml. Topotecan was completely converted to the lactone form by acidification of the plasma extract with 20% *o*-phosphoric acid. Thus, the measured lactone concentration represents the total plasma topotecan (carboxylate and lactone) concentration. The lower limit of quantitation (LLOQ) was 0.25 ng/mL.

Pharmacokinetic analysis. All population pharmacokinetic analyses were performed using nonlinear mixed-effects modeling as implemented in NONMEM (version 7.2) using the total topotecan (topotecan lactone plus topotecan carboxylate) concentration-time data from serial samples collected from 21 patients receiving oral topotecan alone (C1D1) or in combination with oral pazopanib (C1D2, C2D1, and C3D1). The final topotecan nonlinear mixed-effect pharmacokinetic model comprised two elements: (i) a base structural fixed-effect component characterizing the concentration time relationship, and (ii) a random-effects model, including inter-individual/inter-occasion variability in the pharmacokinetic parameters, as well as residual error, which encompasses measurement errors. The distribution of the pharmacokinetic parameters was assumed to be log-normal, thus, inter-individual and inter-occasion variability in parameters were modeled as exponential terms (Eq. 1):

$$\theta_i = \tilde{\theta}\, e^{\eta_i^{\theta} + \sum_{j=1}^{n} \eta_{ij}^{\theta}} \quad \text{(Eq. 1)}$$

where θ_i represents the estimated PK parameter for a given individual i, $\tilde{\theta}$ is the population estimate, η^{θ}_i describes the variation of individual i from the population estimate (*i.e.* between-subject variability) with mean of zero and variance ω^2. When the drug was administered on multiple occasions per individual, the η^{θ}_{ij} term represents the variability of occasion j from individual average i value (*i.e.* between-occasion variability) with mean of zero and variance ϕ^2. An occasion was defined as the set of concentrations obtained after any single topotecan dose.

The residual error was modeled using a mixed proportional and additive error model. The proportional component of the residual error was assumed to have a mean of zero and variance of σ. Fixed-effect relationships between the pharmacokinetic parameters and categorical or continuous covariates was explored using the following model (Eq. 2):

$$\theta = \tilde{\theta} + \sum_{\rho=1}^{m} \text{covariate}_{\rho} \times \theta_{\rho} \quad \text{(Eq. 2)},$$

where $\tilde{\theta}$ is the population estimate, is the population estimate with none of the covariates included, and θ_{ϱ} is the effect of covariate ϱ on the model. Patient weight (kg), body surface area (BSA; m^2), age (years), course number, and pazopanib dose received were examined

as possible sources of variability in pharmacokinetic parameter estimates. Evaluation of potential covariates was performed for topotecan parameters apparent oral clearance (*Cl/F*), apparent volume of distribution (*Vc/F*), as well as absorption rate constant (k_a). A covariate was considered significant in this analysis if the addition of the covariate to the model reduced the –2 log-likelihood by at least 3.84 units ($p<0.05$, based on the χ^2 test for the difference in the –2 log-likelihood between two hierarchical models that differ by one degree of freedom).

Results

Patients' demographics. Pharmacokinetic studies of topotecan were performed for 21 consenting patients. The demographic summary information of these patients is listed in Table I.

Table I. *Summary of patients' demographics*.

	Age (years)	Height (cm)	Weight (kg)	BSA (m^2)
Mean	61.6	165.0	67.5	1.74
SD	14.7	5.0	19.5	0.20
Median	61.6	165.0	67.5	1.74
Min	29.2	154.9	46.8	1.47
Max	92.5	175.3	113.1	2.15
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Pharmacokinetic analysis. A total of 378 samples were analyzed for total topotecan concentrations using the HPLC method stated above. During initial model building, one- and two-compartment structural models both with and without absorption lag time were assessed. Scatter plots of the observed *versus* predicted topotecan concentration were examined for uniformity and closeness to the line of unity, and plots of residuals and weighted residuals *versus* time were examined for randomness about and closeness to zero. This evaluation indicated that a one-compartment model with first-order absorption/ lag-time and linear elimination from the central compartment adequately described the topotecan plasma concentrations *versus* time profiles (ADVAN2 TRANS2 subroutine in NONMEM). Thus, the final structural pharmacokinetic model was parameterized in terms of *Cl/F*, *Vc/F*, absorption lag time (τ), and k_a. The goodness-of-fit plots (Figure 1) indicated good agreement between the observed topotecan concentrations and the empirical *post-hoc* model predictions and the residuals appeared to be well-distributed. A slight negative bias was identified for concentrations at the higher end of the assay, however, several variations of the structural model failed to improve this.

Individual pharmacokinetic parameters for *Cl/F*, *Vc/F*, k_a, and τ were obtained from the final population model by Bayesian *post-hoc* estimation. The median (range) of topotecan *Cl/F, Vc/F,* k_a were 26.7 l/h (11.4-169), 144 l (84.0-1140), and 1.04 h^{-1} (0.25-122), respectively. Population pharmacokinetic parameter estimates and corresponding variability are summarized in Table II. The onset of the absorptive phase was delayed for several patients, and this slight delay in absorption was accounted for by a median τ of 0.24 hours (or about 14 minutes). Figure 2 shows a plot of all concentration time data, illustrating the range of concentrations observed and variability between median population parameter values and the individual observed values. The results in Figure 3 indicate no systematic trends in the distribution of individual *post-hoc Cl/F* estimates in relation to pazopanib dose.

Pazopanib administration was investigated as a potential explanatory variable on topotecan *Cl/F, Vc/F*, and k_a, first graphically using individual parameter estimates, then as a nested covariate model. In the population pharmacokinetic model, pazopanib administration was assessed both as a continuous variable (0, 400, 600, and 800 mg) and as a categorical variable (1 or 0 corresponding to topotecan administration with or without concomitant pazopanib). The graphical analysis (Figure 3) indicated no apparent trend. Other exploratory covariates were tested to reduce the interindividual variability of the population pharmacokinetic model included patient age, weight, BSA, and course number, and no significant trends were identified with any of the covariates investigated.

Discussion

Identifying clinically relevant drug-drug interactions would help mitigate such interactions and the associated clinical toxicities for low-dose metronomic topotecan therapy (*e.g.* myelosuppresion). In the present phase I study, pazopanib influence on topotecan disposition was assessed by comparing topotecan pharmacokinetics when administered as a single agent on C1D1 and when administered in combination with 400, 600, or 800 mg of pazopanib on subsequent days. Our nonlinear mixed effects population pharmacokinetic analysis showed, as expected, wide inter- and intra-patient variability in topotecan pharmacokinetics, and no interaction with pazopanib in our patient population. Given the lack of a statistically significant drug-drug interaction, wide inter-patient variability, and no relation between other patient covariates and topotecan disposition, no alteration in dosing is needed for the low dose topotecan regimen in this patient cohort.

The disposition of single-agent topotecan has been described extensively elsewhere (13, 20-23). Topotecan has a pentacyclic structure with a lactone moiety in the E-ring. This lactone ring undergoes a reversible pH-dependent hydrolysis, with physiologic pH favoring the open ring form,

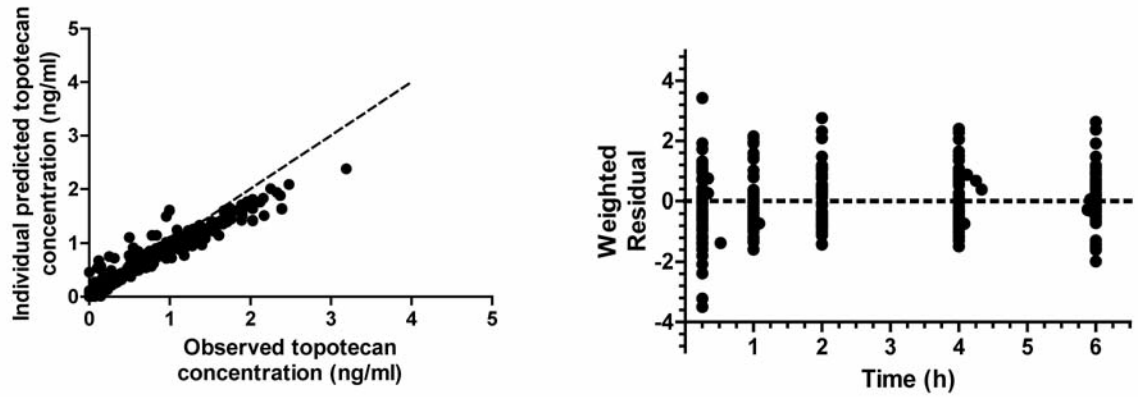

Figure 1. *Diagnostic plots associated with the final population pharmacokinetic model demonstrate acceptable fitting of the model. The observed versus individual post-hoc predicted topotecan concentrations (left) and residuals versus time after dose administration (right panel) are shown. Circles represent individual data points. The dashed line in the left panel represents the line of unity.*

and acidic conditions favoring the active closed ring lactone form. The mean total body clearance of topotecan lactone is typically around 20-30 l/h/m^2 with wide inter-patient variability (24-26). The average elimination half-life ($t_{1/2\beta}$) for topotecan lactone is approximately 3-5 hours, again with a wide inter-patient variability. Topotecan undergoes limited metabolism and three metabolites, *N*-desmethyl-topotecan, topotecan-*O*-glucuronide, and *N*-desmethyl-topotecan-*O*-glucuronide, have been identified in plasma, urine, and bile at low concentrations (27). However, these pathways are not major pathways of drug elimination, as renal clearance accounts for approximately 30 to 60% of the administered dose (with large inter-individual variability).

In the present report, our median topotecan *Cl/F* estimate of 26.7 l/h is consistent with the previously reported value of 20.1 l/h determined in a population pharmacokinetic analysis (23). Substantial inter-individual variability in the parameter estimates of the topotecan base model were observed with a %CV for *Cl/F* and k_a of 71.6% and 58.2%, respectively. The population inter-individual variability for topotecan Cl/F (71.6%) for all dosing occasions (with and without pazopanib) was significantly larger than that previously reported in adult patients with cancer (42%) (20). Although limited information is available on the variability of specific pharmacokinetic parameters of orally administered topotecan in such patients, the large inter-subject variability in topotecan pharmacokinetic parameters coincides with previous estimates of variability in total topotecan oral bioavailability (range from 30-59.1%) (13, 21, 28, 29). The *Cl/F* of oral topotecan is highly dependent on the absorption of the lipophilic lactone form from the gastrointestinal tract, and therefore slight differences in intestinal pH could contribute to the variability in the topotecan *Cl/F* estimate. Inter-occasion variability for *Cl/F,*

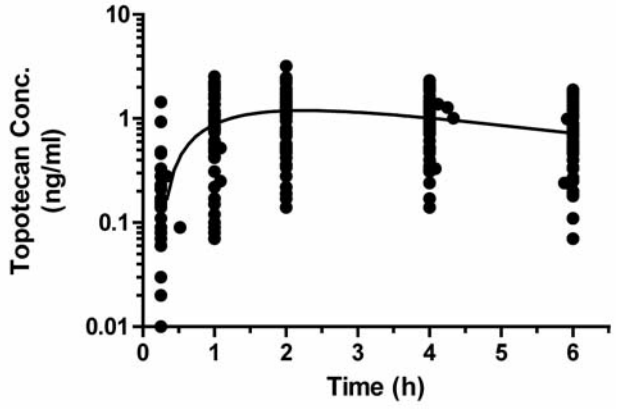

Figure 2. *Total topotecan plasma concentration versus time profile after oral administration of 0.25 mg dose. The solid circles represent the individual concentrations across all observations and the solid line represents the simulated concentration-time curve using the median parameter values.*

Vc/F, and k_a, was also substantial in the population. The inter-occasion variability was 88.8% and 49.0% (CV%) for apparent clearance and volume, respectively.

Among other factors, pazopanib co-administration was examined as a potential explanation for the large variability in topotecan pharmacokinetic parameters. The initial graphical analysis (Figure 3) indicated no apparent trend with regards to pazopanib dose and apparent oral clearance of topotecan. This was statistically confirmed as the nested covariate associated with pazopanib administration did not reduce the –2 log-likelihood for *Cl/F, Vc/F,* or k_a. To our knowledge, only one preclinical study has examined pharmacokinetic interactions of these two agents. Kumar *et al.* compared plasma concentration time profiles of each drug when administered

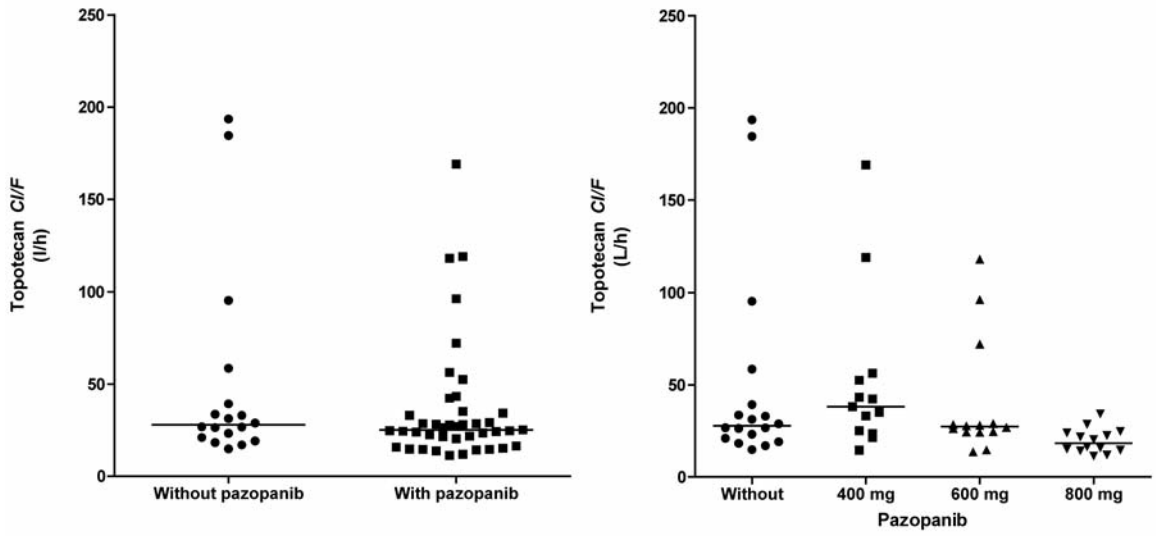

Figure 3. *Topotecan apparent oral clearance (Cl/F) stratified by pazopanib dosage level. Each point represents the Cl/F value of an individual patient. Lines represent the median Cl/F value for each dosage level. The left panel shows topotecan clearance estimates for single-agent topotecan and combination treatment with pazopanib. In the right panel, Cl/F estimates are parsed according to the pazopanib dosing level.*

Table II. *Pharmacokinetic parameter estimates and interindividual and interoccasion variability.*

Parameter	Estimate (95% CI)	Inter-individual variability[a]	Inter-occasion variability[b]
Cl/F (l/h)	11.5 (5.9-17.1)	71.6	88.8
Vc/F (l)	53.6 (35.7-71.5)	7.8	49.0
k_a (h^{-1})	0.306 (0.235-0.541)	58.2	87.6
τ (h)	0.168 (0.144-0.192)	84.2	---

k_a, Absorption rate constant; *CL/F*, apparent oral clearance; *Vc/F*, apparent oral volume of the central compartment; τ, oral absorption lag time; CI, confidence interval of estimate. [a]$\sqrt{(\omega^2)} \times 100\%$ (see Eq. 1); [b]$\sqrt{(\phi^2)} \times 100\%$ (see Eq. 1)

alone and in combination (1 mg/kg topotecan and 150 mg/kg pazopanib), and they showed that the topotecan area under the curve from 0 to 24 h (AUC_{0-24}) in their single-agent group was slightly lower than in the combination group (94 *versus* 122 ng/ml × h); however, inter-animal variability was such that this difference was not statistically significant (10). Although our study sample size is also relatively small considering the observed large inter- and intra-patient variability, our data support these preclinical findings suggesting no statistically significant drug-drug interactions between pazopanib and topotecan. In contrast, results released from a recent human pharmacokinetic phase I study of oral pazopanib and topotecan indicate that topotecan AUC increased 1.58-fold [90% confidence interval (CI)=1.09-1.29] and maximum concentration (C_{max}) increased 1.78-fold (90% CI=1.08-2.92) when administered together with pazopanib (n=7) (18). These data, derived from patients receiving higher topotecan doses,

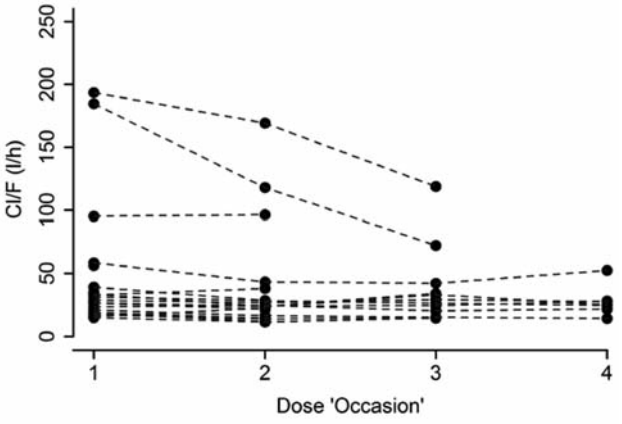

Figure 4. *Individual topotecan apparent oral clearance (Cl/F) across dose occasions after oral administration of 0.25 mg of topotecan. The symbols represent individual estimates of Cl/F and the dashed lines connect Cl/F estimates of individual patients across occasions.*

suggest interactions are possible with this combination and are likely dose-dependent.

The other potential covariates explored to explain the large variability in topotecan pharmacokinetic parameters observed in our population included patient age, weight, BSA, and course number. Although patients of advanced age may have a deterioration of renal function, incorporation of age in our model did not result in a statistically significant reduction in interindividual variability for *Cl/F, Vc/F,* or k_a. Furthermore, patient weight and BSA also ere not prognostic covariates, suggesting that individualized dose scaling on the basis of BSA or weight would not provide an improvement (no reduction in between-subject variability) compared to administering metronomic topotecan as a fixed dose. The two patients with the highest C1D1 clearance (Figure 4) showed a net downward trend in clearance between dose occasions (one to three), but overall, this trend was not statistically significant within the context of the whole population. Out of the potential covariates tested, none were found to account for a significant portion of the pharmacokinetic variability, thus the simpler covariate-free topotecan model was retained.

In summary, a population pharmacokinetic topotecan model was developed using serial concentration time data obtained from 21 patients receiving oral topotecan either alone (C1D1) or in combination with oral pazopanib. Competing nested models (covariate model *versus* no covariate model) were evaluated to determine which covariates were significantly related to topotecan *Cl/F, Vc/F*, or k_a. Several potential covariates were assessed including body-size metrics (patient weight and BSA) as well as patient age, course number, dosing occasion, and pazopanib dose. Although substantial variability was observed in the pharmacokinetic parameter estimates of the base structural model, none of the covariates investigated was identified as a statistically significant source of this variability. We have not ruled out the possibility of observing a significant effect when studying larger sample size, but these data appear to support prior preclinical results suggesting that concomitant pazopanib administration does not produce a statistically significant drug drug interaction with metronomic oral topotecan. While other factors should be considered in refining dosing for future clinical trials with metronomic topotecan (including toxicity and disease response), these data suggest that the pharmacokinetic disposition of low-dose metronomic topotecan is not significantly affected by pazopanib.

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