Phase I/Pharmacokinetic Study of Topotecan by 24-Hour Continuous Infusion Weekly

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ABSTRACT

Topotecan (SK&F 104864, hycamptamine, NSC 609699) is believed to exert its cytotoxic effects through inhibition of topoisomerase I, the activity of which recovers rapidly on removal of the drug in vitro. In vivo studies show that the activity of topotecan is schedule dependent, favoring repeated doses. Early human studies showed that topotecan (the active lactone) had a short half-life in plasma. To prolong drug exposure, we administered topotecan as a 24-h i.v. infusion and repeated it weekly. We treated 32 patients with doses of 1.0–2.0 mg/m². Median performance status was 1, and all but four patients had received prior chemotherapy. Dose-limiting neutropenia occurred at doses ≥1.75 mg/m²; nadirs were observed after 1–3 doses. The recommended phase II dose is 1.5 mg/m²/week. One patient with metastatic colon cancer had a partial response. Both plasma topotecan (lactone) and total topotecan (measured by converting the hydroxyacid form to the lactone by acidification of the sample) were measured by high-performance liquid chromatography in 21 patients. During infusion, mean topotecan plasma steady-state concentrations ranged from 4.7–11.4 μM. Plasma elimination was best fit to a one-compartment model with a mean t₁/₂ of 3.5 h. The mean total body clearance was 388 ml/min/m². Concentrations of the inactive form approximated those of the lactone throughout. No evidence for dose-dependent pharmacokinetics was observed in this dose range.

MATERIALS AND METHODS

INTRODUCTION

Camptothecin, a plant alkaloid extracted from Camptotheca acuminata was found to have broad antitumor activity in vitro and in vivo in the early 1970s (1–3). The unacceptable clinical toxicity of camptothecin led to the development of active analogues (4). Topotecan is one of several semisynthetic analogues of camptothecin currently being evaluated in clinical trials (5). The 9-dimethylaminomethyl derivative provides a water-soluble analogue that does not require metabolic activation and that retains the broad activity of the parent compound (6).

This class of drug has been found to exert cytotoxicity through inhibition of topoisomerase I, an enzyme that alters the conformation of DNA through the formation of protein-associated single-strand breaks (7, 8). Camptothecin and its derivatives inhibit the enzyme by forming a covalent complex with the enzyme and DNA that prevents resealing of the DNA breakage (7). Persistence of the DNA strand breaks results in cytotoxicity. In whole cells, dissociation of the complex and recovery of topoisomerase I activity occur rapidly upon removing the camptothecin from the medium (9). Prolonged exposure promotes the accumulation of topoisomerase I-DNA adducts, which are associated with DNA single-strand breaks (10).

In animal tumor models, topotecan shows excellent activity in tumors that are refractory to many anticancer agents, e.g., Lewis lung carcinoma, HT-29 human colon adenocarcinoma, and the murine colon 38 and colon 51 tumors (11–13). In L1210 leukemia and Lewis lung carcinoma, repeated administration of topotecan is superior to a single dose. An infusional schedule has not been tested. In a series of 7 human colon adenocarcinomas and 6 rhabdomyosarcomas carried in immunodeficient mice, Houghton et al. (14) showed that schedules of prolonged dosing (in this case, daily administration) provided efficacy superior to intermittent (every 4 days) dosing. These preclinical data suggested that prolonged exposure to topotecan might optimize the antitumor activity of the drug.

Initial phase I studies suggested that the active lactone form of topotecan has a relatively short half-life (15). An infusional schedule provided a model to study prolonged drug exposure. We wished to treat frequently, to mimic the frequency schedule tested in mice. In consideration of the fact that another camptothecin analogue CPT-11 demonstrated single-agent activity in non-small cell lung cancer on a weekly schedule (16), we performed a phase I/pharmacokinetic study in which 24-h infusions of topotecan were repeated weekly.

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2 To whom requests for reprints should be addressed, at Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111.

3 The abbreviations used are: CPT-11, irinotecan; HPLC, high-performance liquid chromatography; QC, quality control; Vss, steady-state volume of distribution; Cltot, total body clearance; AUC, area under the plasma concentration versus time curve; Cmax, steady-state concentration; ANC, absolute neutrophil count.
sponse criteria were standard (17). The maximum tolerated dose of topotecan was defined as the dose that would produce predictable and reversible toxicity and would not be incapacitating or interfere with the patient’s well-being and general activities. Practically, this was the dose at which fewer than 50% of patients would experience grade 3 or 4 myelosuppression in the face of continuous treatment.

**Treatment Plan.** Patients were admitted to the Mary S. Schinagel Clinical Studies Unit at Fox Chase Cancer Center for 24–48 h for the initial dose of topotecan. Topotecan was obtained from the National Cancer Institute (Bethesda, MD) in glass vials, containing 2.2 ml of either 1 or 5 mg/ml of free topotecan base. The drug was stabilized in n-glucuronic acid, (monopotassium salt) (anhydrous USP), and adjusted to pH 3.0 with either hydrochloric acid or sodium hydroxide. Reconstitution of the material was accomplished by dilution in 0.9% saline at a concentration of 10–500 µg/ml or 5% dextrose (6.7–330 µg/ml) and administered i.v. over 24 h.

The starting dose of topotecan was 2 mg/m², a dose equivalent to 0.025 of the dose producing 10% mortality in mice. Because of granulocytopenia, the next level was decreased to 1 mg/m², and subsequent doses were escalated by 0.25 mg/m². Provision was made to expand accrual to a level on encountering severe or unexpected toxicity. The end point of the study was to describe a dose of topotecan at which fewer than one-third of the patients would experience grade 3 or 4 toxicity and, therefore, to define a regimen suitable for broad phase II testing.

**Pharmacokinetic Studies.** The pharmacokinetics of topotecan were determined in 21 of the 32 patients entered on this study. Blood samples were drawn into heparinized (green-top) Vacutainer tubes and were obtained before treatment; at 3, 6, 9, 12, 15, 18, and 24 h (end infusion); and at 5, 15, and 30 min and 1, 2, 4, 6, 12, and 24 h after infusion. Blood collection times were recorded from the start of the 24-h drug infusion. Blood samples were prepared after collection as described below.

**Sample Preparation.** Patient blood samples were rapidly cooled by immediately placing the collection tube in a dry ice/isopropanol bath. Two 1.5-ml aliquots were transferred to polypropylene microcentrifuge tubes (Marsh Biological Products, Inc., Rochester, NY) and centrifuged at 12,000 x g for 30 s. From each tube 500 µl of plasma were removed and transferred to new microcentrifuge tubes. Extraction was performed by addition of 500 µl of cold acetonitrile (kept in a dry ice/isopropanol bath) and 20 µl of 10% zinc sulfate solution to each tube. After briefly vortex-mixing the samples, the precipitated proteins were removed by centrifugation at 2000 x g for 2 min. The clear supernatant was decanted to a new microcentrifuge tube, labeled, and stored at −80°C until HPLC analysis. Plasma calibration curve samples were prepared by adding varying amounts of one of two topotecan stocks to sufficient control plasma to bring the final volume to 500 µl. These plasma samples were extracted exactly as the patient samples. The supernatant (100 µl) was injected onto the HPLC. To the duplicate of each sample, 20 µl of 20% phosphoric acid were added to convert hydroxyacid topotecan to the lactone, and 100 µl of this mixture were injected onto the HPLC. Topotecan QC samples, made from a separate weighing of topotecan, were prepared on the day of dosing for each subject. QC samples consisted of a low-concentration QC, with nominal values ranging from 6–7.2 nm, and a high-concentration QC, with nominal values ranging from 60–77 nm. Each QC sample was prepared in quadruplicate. Two were used for the topotecan lactone assay and two were acidified and used in the total topotecan assay. All samples from a patient were analyzed the day after the last blood sample was obtained. Groups of 10 samples were removed from the freezer and injected using an autosampler. Because each analytical run takes 5 min, no sample was allowed to remain at room temperature for greater than 50 min. The stability of the extracted sample was sufficient to allow handling in this manner. The half-life of topotecan lactone following acetonitrile zinc sulfate extraction is 28.4 h, thus no more than 2% error is added to the analysis using this procedure.

**HPLC.** Plasma concentrations of topotecan (lactone and total drug) were determined by a modification of the method of Beijnen et al. (18). The chromatographic system consisted of a Hewlett-Packard (Palo Alto, CA) HP-1090 series A liquid chromatograph equipped with an autoinjector/autosampler and an HP-1046A fluorescence detector. The column effluent was monitored for fluorescence with an excitation wavelength of 382 nm and an emission wavelength of 523 nm. The chromatograph was operated with an HP-85B personal computer, and the data were processed with an HP 3393A integrator. Chromatography was performed on a Hewlett-Packard Hypersil ODS C_{18} reverse-phase C_{18} analytical column, 5 µm, 100- x 4.6-mm internal diameter, preceded by a 15- x 3.2-mm, 7-µm Newguard C_{18} guard column (Applied Biosystems, Inc., San Jose, CA). The isocratic mobile phase consisted of 0.005 M diocetyl sodium sulfosuccinate, 0.023 M sodium phosphate, 0.56% triethyamine, 53% methanol, and 40% water, at a flow rate of 1.5 ml/min. Standard curves consisting of eight points (1, 2, 5, 10, 20, 40, 60, and 100 nm) each for acidified and unacidified samples were plotted as the peak area versus concentration of topotecan. The linear regression lines were calculated by the method of least squares and were weighted by 1/y². Concentrations of the inactive hydroxyacid form were calculated by subtracting values for topotecan (lactone) from values for total topotecan.

**Pharmacokinetic Analysis.** Plasma topotecan concentration versus time curves were fitted to the following monoeponential equation

\[ C(t) = Ae^{-\alpha t} \]

where the estimated parameters are the Hill constant (\(A\)) and the pharmacokinetic parameters that produce the half-maximal AUC, \(C_{90}\), and dose effect and (b) a linear relationship (21). Comparisons were made between topotecan dose (mg/m²), and topotecan (both total and lactone) AUC and \(C_{90}\), and neutropenia. Neutropenia was quantified as the percentage decrease in absolute neutrophil count on treatment days 15, 22, and 29 compared to pretreatment values using

\[ \% \text{ decrease in ANC} = \frac{\text{Pretreatment ANC} - \text{ nadir ANC}}{\text{Pretreatment ANC}} \times 100 \]

The data were fit to the above relationship using PCNONLIN (Lexington, KY) a nonlinear curve-fitting program. Selection of best fit between the Hill equation and a linear relationship was made by comparing residual plots, the Akaike Information Criterion, and SE of the parameter estimates.

**RESULTS**

Patients were treated on this study at Fox Chase Cancer Center between February 1991 and April 1992. The demographic characteristics of the patients are summarized in Table 1. The single invaluable patient was registered on study but refused treatment after receiving a single dose without toxicity. All of the patients were of excellent performance status, and the population was not heavily pretreated. The majority of patients had tumors of gastrointestinal origin.

The dose-limiting toxicity of topotecan on this weekly infusional schedule was granulocytopenia (Table 2). At the starting dose of 2.0
mg/m², grade 3 or worse granulocytopenia occurred in 5 of 9 patients; all required interruption of treatment before 4 weeks had elapsed. The dose was reduced to 1.0 mg/m² and escalated in 0.25-mg/m² increments. At 1.75 mg²/m², 2 of 6 patients had grade 4 granulocytopenia. One of these, a 71-year-old man with pancreatic cancer, previously treated with a 5-fluorouracil-containing regimen, became febrile after receiving 2 doses of topotecan. Despite appropriate management, he progressed to develop septic shock and died. At this dose, also, 3 patients experienced grade 2 granulocytopenia after 1, 2, and 2 weeks. One patient discontinued treatment after 1 week without granulocytopenia but with grade 2 leukopenia. Treatment at this dose level could not be sustained. Recovery of counts to ≥2000 granulocytes occurred in a median of 7 days in patients with grade 2 toxicity (range 3–10 days). At 1.5 mg/m², 7 patients were treated. No neutropenia greater than grade 2 was observed. Two patients with extensive prior treatment had grade 4 thrombocytopenia after 1 and 3 doses. Two patients without myelosuppression had decreasing performance status in the face of progressive disease after 2 and 6 doses. Three patients received 5–19 doses without toxicity. We believe that 1.5 mg/m² is an appropriate dose for phase II trials of topotecan on this schedule. The use of this dose will require careful observation of blood counts before each administration of the weekly dose.

In addition to these patients, dose-related thrombocytopenia (Table 3) was observed in this study. The incidence and severity of this complication was considerably less than that of granulocytopenia. Platelet transfusions were not required and no patient experienced bleeding. Other toxicity (grade 2 or more) observed in this trial included moderate nausea and vomiting in 5 patients; symptoms were easily controlled by prochlorperazine. Unexplained fever not attributable to infection occurred in 3 patients. One patient experienced weakness and lethargy that may have been drug associated, and the only evidence for hepatotoxicity was in a single patient who had a grade 2 elevation in alkaline phosphatase that resolved after cessation of the drug.

Analytical Method. The analytical method used in this study was a modification of the method reported by Beijnen et al. (18). Sample extraction was modified by the use of acetonitrile and zinc sulfate as the protein precipitation reagents. The final apparent pH of the supernatant produced using this method is 6.8 and is significantly lower than that produced by methanol precipitation (final apparent pH 9.0; favors conversion to the hydroxyacid form). This modification results in several advantages. Topotecan is relatively stable at neutral pH; thus, it is more stable in an autosampler at room temperature. To illustrate the difference in stability with the 2 methods, the half-life of topotecan at room temperature after acetonitrile/zinc sulfate extraction was 28.4 h compared to 11.6 h after methanol extraction. The second advantage is that the resulting supernatant has a solvent strength similar to the mobile phase used. This allows injection of a 100-µl volume without the problem of peak distortion associated with the injection of large sample volumes (>10–20 µl), when the sample has a solvent strength greater than that of the mobile phase.

The analytical method was linear from 1–500 nm for both lactone and total topotecan (r > 0.999). The quality control samples indicated that total topotecan (samples acidified with 20% phosphoric acid to convert hydroxyacid form to the lactone) could be measured with accuracy and precision. The average deviation from the nominal value was 2.4% (range, −8 to 10%) for the high concentration quality controls (60–77 nm). For the low-concentration quality controls (6–7.2 nm) the average deviation from the nominal value was 1.6% (range, −12 to 22%). If the 22% value was removed as an outlier, the average deviation was −1.8% (range, −12 to 6.7%). For the lactone form, the average deviation from nominal for the low- and high-quality control samples were 3.3 and 10.2%, respectively. However, the range for the low (−14.2 to 21) and high (−10.4 to 27.6) quality controls showed that the assay for the lactone form was somewhat more variable than the total drug assay.

Pharmacokinetics. The plasma pharmacokinetics of both the lactone form and total topotecan were determined following the first drug dose in 21 of 32 patients. The results are given in Table 4 (lactone) and Table 5 (total). Steady-state was reached between 12 and 15 h into the 24-h infusion. From the end of infusion the plasma elimination of both the lactone form and total topotecan was monoeponential and declined in parallel with a half-life of about 3.5 h. A representative time course of total and lactone forms is illustrated in Fig. 1. C₈tot was 350 ml/min/m² for the lactone and 240 ml/min/m² for total topotecan. Linear regression analysis revealed that both C₈ and AUC increased linearly with dose for the total (r = 0.5) and lactone (r = 0.9) forms (P < 0.05), supporting dose linearity of topotecan pharmacokinetics in this dose range. There was excellent agreement between values for C₈ calculated using infusion rate/C₈tot and C₈ calculated by averaging concentrations at 15, 18, and 24 h during infusion. When infusion rate/C₈tot was used, mean ± SD C₈ values were 11.5 ± 2.8 nm for total topotecan and 7.3 ± 2.7 nm for topotecan (lactone). By averaging plasma concentrations at 15, 18, and 24 h, mean ± SD C₈ values of 11.5 ± 3.4 and 7.2 ± 3.0 nm were found for total topotecan and topotecan lactone, respectively, illustrating that similar results are obtained for C₈ values using either method of calculation.

Pharmacodynamics. There were 18, 14, and 12 patients that had pharmacokinetics (performed on day 1) and blood counts determined on days 15, 22, and 29, respectively. For day 15 there were 5 patients at 1.25 mg/m², 5 patients at 1.5 mg/m², 4 patients at 1.75 mg/m², and 4 patients at 2.0 mg/m². For day 22 there were 5 patients at 1.25 mg/m², 5 patients at 1.5 mg/m², and 4 patients at 2.0 mg/m². On day 29 the pharmacodynamic analysis contained 5 patients at 1.25 mg/m², 4 patients at 1.5 mg/m², and 3 patients at 2.0 mg/m². The AUC of topotecan (lactone and total) was predictive of the decrease in neu-
Table 5 Pharmacokinetic parameters of total topotecan (lactone + hydroxyacid forms) following 24-h continuous infusion of topotecan

<table>
<thead>
<tr>
<th>Topotecan dose (mg/m²)</th>
<th>1.25</th>
<th>1.5</th>
<th>1.75</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 5)</td>
<td>(n = 7)</td>
<td>(n = 5)</td>
<td>(n = 4)</td>
<td></td>
</tr>
<tr>
<td>Cmax (nm)</td>
<td>8.7 ± 1.5a</td>
<td>10.7 ± 2.7</td>
<td>15.5 ± 4.0</td>
<td>12.1 ± 2.1</td>
</tr>
<tr>
<td>AUC (nm x h)</td>
<td>210.5 ± 37.5</td>
<td>262.7 ± 65.8</td>
<td>379.6 ± 101.1</td>
<td>304.3 ± 63.9</td>
</tr>
<tr>
<td>Clint (ml/min/m²)</td>
<td>240.6 ± 41.2</td>
<td>239.3 ± 65.2</td>
<td>192.0 ± 46.0</td>
<td>268.9 ± 57.3</td>
</tr>
<tr>
<td>Half-life (h)b</td>
<td>3.0</td>
<td>3.7</td>
<td>3.5</td>
<td>3.7</td>
</tr>
</tbody>
</table>

a Values are means ± SD.
b Values are harmonic means (ranges).

Fig. 1. Concentration-time profile of topotecan (lactone, •; total, ○) in a patient treated with 1.5 mg/m² topotecan.

DISCUSSION

The semisynthetic camptothecin analogues identified to date demonstrate some schedule dependency in preclinical models, in which frequent administration schedules are superior to single doses (10). This phase I clinical trial was designed to provide a schedule of frequent administration of topotecan and to describe drug disposition in that setting. We identified a topotecan dose of 1.5 mg/m² by 24-h infusion repeated weekly as appropriate for phase II trials.

As in phase I trials using 5-day schedules, the dose-limiting toxicity was granulocytopenia (15, 22, 23). A rather sharp dose-response relationship of granulocytopenia was noted: this population, albeit small, tolerated doses up to 1.5 mg/m² weekly by repeated doses but developed myelosuppression within 1–3 weeks at higher doses. Other phase I studies have demonstrated a similarly steep dose-response curve (15). Grade 4 thrombocytopenia occurred in two heavily pretreated patients. Although thrombocytopenia was otherwise mild to moderate, further escalation of this dose is not likely to be practical, especially since the use of colony-stimulating factors with weekly regimens is unhelpful. However, the dose intensity achieved is similar to that on 5-day bolus regimes (phase II dose, 1.5 mg/m²/day for 5 days).

The nonmyelosuppressive toxicity of topotecan was minimal, in contrast to CPT-11, which is associated with substantial gastrointestinal toxicity (mucositis, diarrhea) (24). Rowinsky et al. (15) noted that on a 5-day schedule topotecan is 10-fold more potent than CPT-11 (maximum tolerated dose is 2.0 and 20 mg/m²/day for 5 days, respectively). On this weekly schedule, less than 1/50th of the CPT-11 dose (100 mg/m²) is tolerated. This disparity in dosage and in dose ratio appears to reflect schedule-dependent differences between topotecan and CPT-11. Part of the disparity may be accounted for by pharmacological differences. The half-life of topotecan ranges from 2–4.9 h (5). These values are similar to those for CPT-11 (24). However, CPT-11 is a poor inhibitor of topoisomerase I, and its principal metabolite 7-ethyl-10-dehydroxycamptothecin is the active inhibitor (25, 26). The prolonged half-life of 7-ethyl-10-dehydroxycamptothecin (about 8 h) results in longer exposure of cells to enzyme inhibition on bolus schedules with CPT-11 (26). Therefore, an infusional schedule would be expected to have less of an impact on the toxicity of CPT-11 than that of topotecan. Phase I trials of topotecan support this contention: the recommended phase II dose for a 5-day bolus schedule is 1.5 mg/m², while 0.68 mg/m²/day for 4 days by infusion was excessively toxic (27). Thus, weekly infusion allows the administration of higher total doses, while maintaining a prolonged infusion schedule.

An additional explanation may relate to the susceptibility of various tissues to damage by topoisomerase I inhibitors. The work of several investigators has demonstrated that the level of topoisomerase I activity correlates with sensitivity to topotecan (28–30). Cell lines with high levels of activity are more sensitive than those with little activity. Loss of activity, as with a mutation in the active site of the enzyme, confers resistance. Studies of the relationship of the extent and duration of enzyme inhibition to cytotoxicity may indicate how the schedule of topotecan may be optimized for clinical trials.

The finding of antitumor efficacy in a patient with colorectal cancer is of interest. It supports the further evaluation of this schedule, since this is the only patient with colorectal cancer who has responded to topotecan to date. It also allays some concern that topotecan may be inactive in tumors that express the multiple drug resistance phenotype, based on cross-resistance studies in murine tumors that express the MDR-1 gene product. Hendrick et al. (30) showed that Chinese hamster ovary cells selected for multidrug resistance were 15-fold less...
Fig. 2. Relationship between the percentage of reduction in neutrophils versus the $C_{50}$ of topotecan (lactone) and of total drug (lactone plus carboxylic acid) on days 14, 21, and 29 following the initiation of weekly treatment. The curve represents the fit of the data as described in the text.

Table 7 Pharmacodynamic parameters for sigmoid $E_{max}$ analysis of topotecan (lactone
and total forms) $C_{50}$ versus percentage decrease in neutrophils

<table>
<thead>
<tr>
<th>Day 15</th>
<th>Day 22</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>$C_{50}$</td>
<td>$h$</td>
</tr>
<tr>
<td>18</td>
<td>$7.61 \pm 0.83^c$</td>
<td>$1.38 \pm 0.82$</td>
</tr>
<tr>
<td>14</td>
<td>$6.40 \pm 0.62$</td>
<td>$2.29 \pm 0.69$</td>
</tr>
<tr>
<td>12</td>
<td>$7.57 \pm 1.66$</td>
<td>$1.53 \pm 0.84$</td>
</tr>
</tbody>
</table>

$^a$ $C_{50}$, model predicted $C_{50}$ to produce a 50% decrease in neutrophils.
$^b$ $h$, Hill constant.
$^c$ Values are the PCNONLIN predicted parameter estimate ±SE of the parameter estimate.

Other side effects of topotecan have been unusual and, when present, mild in degree. The pronounced selectivity for the granulocyte series of the bone marrow is unexplained but may relate to elevated topoisomerase I activity in granulocyte precursors. This selectivity is lost in prolonged infusion schedules; thrombocytopenia is pronounced with both the 5- and the 21-day infusion schedules (27, 33). The lack of cumulative toxicity suggests that multipotent stem cells are spared by topotecan. In particular the low incidence of nonmyeloid toxicity makes topotecan an excellent candidate for combination with other drugs with activity in solid tumors.

The modifications in the analytical method allowed the determination of the low concentrations encountered during the course of this study (24-h continuous infusion on a weekly schedule). Unlike previous studies using short infusions (15) or 24-h continuous infusions sensitive to a 1-h topotecan exposure than were parental cells. This ratio was reduced to a 3.2-fold difference when the treatment was prolonged to 24 h. Therefore, prolonged infusions of topotecan may circumvent this mechanism of resistance (31). CPT-11, which appears to be uninfluenced by the MDR phenotype, is reported to have activity in the treatment of colorectal cancer (32). A comparison between the activity of topotecan and CPT-11 in this disease will demonstrate whether these findings in murine models are relevant to the clinical activity of topotecan.

Table 8 Pharmacodynamic parameters for sigmoid $E_{max}$ analysis of topotecan dose
versus percentage decrease in neutrophils

<table>
<thead>
<tr>
<th>Day 15</th>
<th>Day 22</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Dose_{50}^a$</td>
<td>$h^b$</td>
<td>$r$</td>
</tr>
<tr>
<td>$1.66 \pm 0.07^c$</td>
<td>$5.78 \pm 1.64$</td>
<td>$0.732$</td>
</tr>
<tr>
<td>$1.49 \pm 0.07$</td>
<td>$4.71 \pm 1.30$</td>
<td>$0.793$</td>
</tr>
<tr>
<td>$1.58 \pm 0.12$</td>
<td>$3.93 \pm 1.67$</td>
<td>$0.650$</td>
</tr>
</tbody>
</table>

$^a$ $Dose_{50}$, model predicted dose to produce a 50% decrease in neutrophils.
$^b$ $h$, Hill constant.
$^c$ Values are the PCNONLIN predicted parameter estimate ±SE of the parameter estimate.
While the variability in the lactone assay would make the pharmacokinetics of topotecan (mg/m²) on days 14, 21, and 29 following the initiation of weekly treatment.

The use of $C_{\text{ss}}$ as the monitored pharmacokinetic parameter suggests that adaptive dosing could be used during drug infusion to adjust $C_{\text{ss}}$ and thus to achieve tolerable neutropenia while maximizing dose intensity during therapy. While dose in this model is also highly predictive for toxicity, the steep dose-response curve renders it less valuable for adaptive dosing strategies. The data support the further investigation of $C_{\text{ss}}$ for therapeutic drug level monitoring. In summary, this study has defined a phase II dose of topotecan on an infusional schedule. Further optimization of dosing may follow the use of an adaptive dosing strategy.

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