A Pilot Study of Protracted Topotecan Dosing Using a Pharmacokinetically Guided Dosing Approach in Children with Solid Tumors

Victor M. Santana, William C. Zamboni, Mark N. Kirstein, Ming Tan, Tiebin Liu, Amar Gajjar, Peter J. Houghton, and Clinton F. Stewart

Departments of Hematology and Oncology [V. M. S., A. G.], Pharmaceutical Sciences [W. C. Z., M. N. K., C. F. S.], Biostatistics [M. T., T. L.], and Molecular Pharmacology [P. J. H.], St. Jude Children’s Research Hospital, and Departments of Pediatrics [V. M. S., A. G.] and Pharmacology [P. J. H.] and The Center for Pediatric Pharmacokinetics and Therapeutics [P. J. H., C. F. S.], University of Tennessee, Memphis, Tennessee 38103

ABSTRACT

Purpose: To assess the use of a pharmacokinetically guided topotecan strategy and evaluate the toxicity of protracted i.v. topotecan in children with recurrent solid tumors.

Experimental design: Fifteen children with measurable relapsed or refractory solid tumors received topotecan i.v. over 30 min 5 days a week for two consecutive weeks. Doses were individualized based on the patient’s topotecan systemic clearance to attain a single day topotecan lactone area under the plasma concentration time curve (AUC) of 120–180 ng/ml h (cohort 1) or 80–120 ng/ml h (cohort 2). Clinical responses and toxicity were assessed by standard criteria.

Results: Twenty-nine courses of topotecan were administered, 11 in cohort 1 and 18 in cohort 2. The median topotecan dosages required to achieve the target AUCs for cohorts 1 and 2 were 4 mg/m² (range, 2.6–6) and 3 mg/m² (range, 2.6–4.2), respectively. The intersubject variance for topotecan clearance exceeded the intrasubject variance by 2-fold. With the pharmacokinetic targeting approach, we observed that 78% (46 of 59) of the measured AUC values were within the target range. The median number of days to an absolute neutrophil count ≥500/mm³ was similar between the two cohorts; however, febrile neutropenia and serious infections limited our ability to deliver drug dosages needed to secure the higher systemic exposure (cohort 1). Five partial responses were observed.

Conclusion: Protracted topotecan dosing using a pharmacokinetic strategy was possible in this heavily pretreated group of children.

INTRODUCTION

Topotecan, a semisynthetic water-soluble camptothecin analogue, has shown promising antitumor activity in preclinical and clinical studies of pediatric solid tumors and leukemia (1–5). The antitumor activity of topotecan, which appears to be S phase specific, is mediated by its interaction with DNA topoisomerase I. We have shown that topotecan is highly active against xenografts derived from childhood rhabdomyosarcoma, neuroblastoma, osteosarcoma, medulloblastoma, and glioblastoma multiforme, whether grown as s.c. tumors on the flank or as intracranial tumors (2, 5). In these models, protracted scheduling of low-dose topotecan given daily for five consecutive days each week for ≥20 courses resulted in greater tumor regression and a higher rate of complete responses than did intermittent higher dose schedules (2). Antitumor effects were clearly related to topotecan lactone systemic exposure, expressed as the AUC (6). Moreover, results from these preclinical studies suggested that the antitumor activity of topotecan follows a steep systemic exposure antitumor response curve, e.g., reduction of the topotecan plasma systemic exposure by as little as 50% led to complete loss of antitumor activity (6).

Results of topotecan pharmacokinetic studies in children have shown marked interpatient variability in topotecan lactone systemic exposure (4). Significant interpatient variability in topotecan CL observed in patients enrolled on Pediatric Oncology Group Study 9275 resulted in a ≥3–5-fold range in topotecan AUC. Similar variability was seen when dosing was based solely on body surface area calculations, which may in part explain the considerable heterogeneity in toxicity and response associated with a given topotecan dose calculated in this manner. In fact, this study demonstrated a predictive relation between topotecan lactone AUC and hematological effects of the drug, such as the percentage of decrease in ANC. This finding is consistent with previous studies showing a more predictive relation between topotecan systemic exposure and pharmacological effect than with dose and effect (7–9).

On the strength of this background, we conducted a pilot clinical trial of i.v. topotecan administered on a protracted
schedule of five consecutive days each week for 2 weeks in children with recurrent or resistant solid tumors. The topotecan lactone systemic exposures in our patients were similar to those in the xenograft model that were associated with antitumor activity. Major objectives were to assess the use of a pharmacokinetically guided dosing strategy to adjust the topotecan dose to achieve a desired target AUC and evaluate the toxicity of a protracted schedule of topotecan administration in children.

PATIENTS AND METHODS

Patient Selection and Monitoring. Patients <21 years of age with histologically documented solid tumors refractory to or relapsing after conventional therapy were eligible for this pilot study. Other requirements included a life expectancy of ≥4 weeks, full recovery from the toxic effects of previous chemotherapy, and an Eastern Cooperative Oncology Group performance status of 0–2, as well as acceptable organ function, defined as a neutrophil count ≥ 1,000/mm³, platelet count ≥ 100,000/mm³, serum bilirubin less than or equal to three times normal, and serum creatinine less than or equal to three times normal adjusted for age. The St. Jude Children’s Research Hospital Institutional Review Board reviewed and approved the study, and informed written consent was obtained from the parent/guardian or patient, as appropriate.

All patients received filgrastim at a dose of 5 μg/kg/day s.c. for a minimum of 10 days starting 24 h after the last topotecan dose (study day 13). Filgrastim was discontinued if the ANC exceeded >1000/mm³ on two consecutive measurements after the expected nadir was reached. All patients were evaluated for toxicity. Among patients given multiple courses of therapy in each dosing cohort, only the first course in a given cohort was considered in the evaluation of dose-limiting toxicity. The toxic effects of topotecan were assessed weekly by National Cancer Institute criteria (Version 1.0) and were considered dose limiting if ≥2 evaluable patients had grade 4 nonhematologic toxicity or grade 4 hematologic toxicity unresolved by day 28 of the treatment course. Complete blood counts with differentials and serum chemistries were obtained at least twice weekly. Tumor responses were assessed after two courses of therapy by standard criteria.

Topotecan Preparation and Administration. For i.v. administration, topotecan (Hycamtin; SmithKline Beecham, Philadelphia, PA) was reconstituted with 2 ml of sterile water, USP, and further dilutions were made in 50 ml of 5% dextrose in water. Each topotecan dose was placed in a syringe set and attached to a controller set for a volume limit of 50 ml and at a rate of 100 ml/h. The drug was administered through either a central or peripheral venous line as a 30-min infusion given daily for five consecutive days each week over 2 weeks, based on results from our xenograft model (6). This course was repeated every 24–28 days.

Systemic Exposure Targets. We evaluated topotecan lactone systemic exposures (AUC) in two cohorts of patients. In cohort 1, the starting dosage for the first 2 patients was 1.4 mg/m², and for the remaining 6 patients, it was 2 mg/m². The systemic exposure target was 120–160 ng/ml × h based on pharmacokinetic and pharmacodynamic studies in which the single-day topotecan lactone AUCs corresponding to antitumor responses were 144 ng/ml × h (mixed tumor xenografts; Ref. 2) and ~120 ng/ml × h (children with recurrent solid tumors; Ref. 4). Although associated with reversible grade 4 myelosuppression, a topotecan lactone AUC of >180 ng/ml × h was not related to dose-limiting nonhematologic toxicity in the latter study. In cohort 2, the starting dosage was selected as 3 mg/m² based on data from cohort 1. The topotecan target AUC was 80–120 ng/ml × h, based on data from the first 8 patients treated in cohort 1, for whom neutropenia and thrombocytopenia were dose-limiting toxicities. Additional studies in five different neuroblastoma xenograft lines suggested that this lower single-day topotecan lactone AUC would not eliminate the possibility of tumor regressions.

Pharmacokinetically Guided Topotecan Dosing. Fig. 1 illustrates our pharmacokinetically guided strategy. During the first course of treatment, plasma samples were obtained after doses 1, 3, 6, 8, and 10, processed immediately, and analyzed. If the single-day topotecan lactone AUC was within the target range after the first dose, then no dose adjustment was required. If not, the topotecan dose was adjusted linearly, based on the patient’s topotecan lactone clearance, to attain the target AUC on day 3. Among the first 8 patients, the increase in topotecan dose was limited to not >100% in any 24-h period; thereafter, it was unrestricted. Regardless of day 1 testing, the same dosing strategy was repeated on days 3, 8, and 10 (third, sixth, and eighth doses). The results of analysis of plasma samples obtained on day 12 (10th dose) were used to guide decisions regarding the starting dose for the next course of therapy.

During all subsequent courses, plasma samples were collected on day 1, with dosage decisions made as described for the first treatment course. Thereafter, samples were taken and analyzed on day 8 (sixth dose). If the single-day AUC was within the target range, a dose adjustment was not required. Otherwise, the topotecan dose was adjusted, and additional plasma samples were taken to determine the adequacy of the modification. As in course 1, the last day of topotecan lactone measurements was used to determine the dosage for any subsequent courses of therapy.
To evaluate our dosing approach, we made a distinction between AUC values resulting from a pharmacokinetically based dosage adjustment and those solely reflecting a predetermined dosage, such as the first dose of course 1. In the latter instance, we refer to the AUC value as a “dose success” or “dose failure,” reserving the terms “pharmacokinetic targeting success” or “pharmacokinetic targeting failure” for situations in which the dosage adjustment did or did not place the patient’s topotecan lactone AUC within the target range. Our pharmacokinetic dosing approach was further assessed in a post hoc comparison with results predicted from use of a fixed dosing approach based on published precedents and current clinical practice for dosing topotecan. AUC values were simulated from the actual clearance data calculated for each patient during the previous studies. Clearances were determined from maximum likelihood parameter estimation of a similar group of 14 pediatric cancer patients. The previous parameter estimates (variances) used for this study were as follows: \( V_c = 16.8 \text{ liters/m}^2 \) (70%), \( k_e = 1.5 \text{ h}^{-1} \) (70%), \( k_p = 1.87 \text{ h}^{-1} \) (85%), and \( k_{pe} = 0.4 \text{ h}^{-1} \) (50%). Standard equations were used to calculate CL and the volume of distribution at steady state \( (V_{dss}) \) from parameter estimates (13). The model parameters for each patient were used to simulate the plasma concentration time profile, from which the area under the plasma concentration time curve from time 0 to infinity was calculated by use of a log-linear trapezoidal method. Because previous studies have shown that topotecan disposition is linear (8, 10), we used the following equation to adjust topotecan dosage:

\[
\text{Adjusted dose (mg/m}^2\text{)} = \text{current topotecan dose (mg/m}^2\text{)/current AUC \times target AUC.}
\]

### Statistical Analysis

Differences in pharmacokinetic parameters between cohorts 1 and 2 were analyzed with a mixed effects model using the robust-variance estimator, which started...
Table 2  Summary of the topotecan lactone pharmacokinetic parameters for each cohort

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cohort (1/2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>$V_t$ (liter/m$^2$)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
<tr>
<td>$K_a$ (h$^{-1}$)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
<tr>
<td>$\beta$ (h$^{-1}$)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
<tr>
<td>$t_{1/2p}$ (h)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
<tr>
<td>CL (liter/h/m$^3$)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
<tr>
<td>$Vd_{ss}$ (liter/m$^2$)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
</tbody>
</table>

* See text for description of statistical test.

![Topotecan lactone concentration versus time plot for a representative patient in cohort 1 receiving a 30-min topotecan infusion. The symbols represent the observed topotecan plasma concentrations, and the lines represent the best-fit curves based on model-fit parameters. The bottom line is from the first day of topotecan therapy and corresponds to a topotecan lactone AUC of 41.4 ng/ml × h (topotecan dose, 2 mg/m$^2$). The middle line is from day 3 and corresponds to a topotecan AUC of 88.3 ng/ml × h (topotecan dose, 4 mg/m$^2$). The top line is from day 8 and corresponds to a topotecan AUC of 132.5 ng/ml × h (topotecan dose, 6 mg/m$^2$).](image)

RESULTS

Characteristics of the Patients. All patients had normal age-adjusted levels of serum creatinine (median, 0.6 mg/dl; range, 0.3–1 mg/dl), total bilirubin (median, 0.4 mg/dl; range, 0.2–0.9 mg/dl), and serum albumin (median, 4 g/dl; range, 2.3–4.7 g/dl). The median age was 12.8 years with a range of 2.1–19 years (Table 1). Tumor diagnoses were predominantly neuroblastoma ($n =$ 5) and brain tumors ($n =$ 5). Most children had received intensive multimodality treatment before study entry. Eight patients in cohort 1 received 11 courses of topotecan in doses intended to produce an AUC of 120–160 ng/ml × h. Although in four courses, the patients were unable to complete the 10-day treatment regimen because of the onset of febrile neutropenia and initiation of empiric antibiotic therapy, all patients were evaluated for toxicity. The AUC target was reduced to 80–120 ng/ml × h in cohort 2 because of unacceptable myelosuppression encountered during attempts to achieve AUCs in the initial target range, as well as preclinical data indicating the possibility of antitumor responses at a lower topotecan lactone AUC. Altogether, 18 courses of lower systemic exposure topotecan were administered to 11 patients, 4 of whom were originally treated as part of cohort 1. Eighteen courses were evaluated for toxicity.

Pharmacokinetic Parameters. Table 2 summarizes the pharmacokinetic parameters derived from the mixed effects model for all patients in each cohort. Comparison of mean and SE values for the two cohorts demonstrated a statistically significant difference in topotecan lactone clearance ($P =$ 0.01), but it was not considered clinically significant (~15%). Thus, further analysis of these parameters was based on courses in which the topotecan dose was either adjusted or unadjusted. None of the resulting intergroup statistical comparisons indicated a significant bias.

We assessed the inter and intrapatient variability using the mixed effects model that allows us to account for possible correlations between topotecan lactone clearance and course with repeated measurements within each subject. However, with the limited data (15 patients total), we have assumed that the correlation among repeated doses across different courses are similar. The estimated inter and intrasubject variance was 53.6 and 27.5, respectively. This reaffirms our findings in previous studies of topotecan pharmacokinetics that the intersubject variability in topotecan clearance is greater than the intrasubject variability (10, 14).

Targeting of Topotecan Systemic Exposure. Presented in Fig. 2 is a representative topotecan lactone plasma concentration time plot for a patient in cohort 1 studied after the initial predetermined topotecan dosage and then after two pharmacokinetically guided dosage adjustments. The initial AUC value
was below the target range (i.e., 41.4 ng/ml × h), and because the topotecan dosage was predetermined, this value was considered a “dosing failure.” The topotecan AUC corresponding to the second concentration time curve was the result of the first dosage adjustment of our pharmacokinetically guided approach and failed to attain the target level (i.e., 88.3 ng/ml × h). This AUC value was inevaluable because of the 100% dose escalation rule in effect for the first few patients in cohort 1. The third AUC value (i.e., 132.5 ng/ml × h) was within the target range and represents a “pharmacokinetic targeting success.” The median (range) topotecan dosages in the courses within the target range for cohorts 1 and 2 were 4 mg/m² (2.6–6) and 3 mg/m² (2.6–4.2), respectively.

We performed a total of 82 pharmacokinetic studies in 15 children, of which 5 studies were inevaluable for technical reasons (problems with venous access or our HPLC) and 4 other studies attributable to the 100% dose escalation ceiling that was initially in place, leaving 73 evaluable studies (Table 3). In cohort 1 of the 32 evaluable studies, 21 AUC determinations were inside the target range, and 11 were outside. None of the studies were considered a “dosing success,” and 7 studies were a “dosing failure.” This is compared with cohort 2 where in 41 evaluable studies, we observed 6 studies that were considered a dosing success and only one dosing failure. We were encouraged to note that our overall pharmacokinetic targeting success rate was 78% (46 AUC determinations in a target of 59 total evaluable determinations). Moreover, this rate was similar between cohorts 1 (~84%) and 2 (~74%).

**Post Hoc Fixed Dosing Analysis.** Fig. 3 compares results of our pharmacokinetic dosing strategy in cohort 1 with those of a “fixed” dosing approach. In this analysis, we excluded AUC values resulting from the first dose of topotecan, because they represented fixed initial doses. Observations after second doses were also excluded for 2 patients, who required a larger single dosage adjustment than was initially permitted in the study. Thus, 27 measured AUC values were retained for analysis. Compared with the fixed dosage group, cohort 1 had a significantly lower percentage of AUC values outside the target range of 120–180 ng/ml × h (22 versus 47%, P = 0.014). Results of the fixed dose analysis were more favorable for patients in cohort 2 (data not shown), for at least two reasons. As reported earlier, the range of topotecan clearance values in cohort 2 was limited (<2-fold), thus restricting the range of systemic exposure values. Moreover, the dosage we selected for the fixed analysis in cohort 2 was influenced by the results we obtained in cohort 1. This learning bias, together with the low interpatient variability in topotecan clearance, led to a relatively high percentage of AUC values within the target range (69 versus 74% for patients receiving pharmacokinetically derived doses).

**Clinical End Points.** The most prominent toxicity associated with topotecan treatment was myelosuppression, regardless of the AUC target range (cohort 1, 120–180 ng/ml × h; cohort 2, 80–120 ng/ml × h). Median times to an ANC ≥ 500/mm³, to resolution of grade 3 or 4 thrombocytopenia, and time to a subsequent course of topotecan in cohort 1 were similar to findings in cohort 2 (Table 4). Diarrhea was more common in cohort 2, whereas skin rashes and documented life-threatening infections were more frequent in cohort 1. The rashes typically occurred during the second week of treatment had an erythematous base, were highly pruritic, and progressed from the trunk to the proximal extremities. Treatment with an antihistamine (diphenhydramine, 0.5 mg/kg, i.v.) and a steroid (hydrocortisone, 100–200 mg, i.v.) produced relief of symptoms and allowed continuation of topotecan therapy.

Only 1 patient died during the study. This was a 16-year-
A Pilot Study of Protracted Topotecan Dosing

Table 4  Toxocities associated with topotecan therapy

<table>
<thead>
<tr>
<th>Hematologic toxicity</th>
<th>Cohort 1 (120–180 ng/ml × h)</th>
<th>Cohort 2 (80–120 ng/ml × h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 11 courses)</td>
<td>(n = 18 courses)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Median (range) days to ANC ≥ 500/mm³</td>
<td>14 (7–21)</td>
<td>13 (6–30)</td>
</tr>
<tr>
<td>Median (range) days to resolution of grades 3 or 4 thrombocytopenia</td>
<td>6 (1–27)</td>
<td>6 (2–34)</td>
</tr>
<tr>
<td>Median (range) days between courses</td>
<td>37 (29–43)</td>
<td>28 (22–43)</td>
</tr>
<tr>
<td>Other toxicities</td>
<td>Grade 2</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Skin rash</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Documented infections</td>
<td>1 sepsis with E. coli</td>
<td>1 C. difficile enteritis</td>
</tr>
<tr>
<td></td>
<td>1 sepsis/death</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 facial cellulites</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

Using a pharmacokinetically guided dosing strategy, we adjusted the topotecan dosage for 15 childhood cancer patients who were within the desired target range in 46 of 59 evaluable AUC determinations or 78%. This approach was possible primarily because the intrapatient variability in topotecan clearance was less than the interpatient variability, a finding consistent with data from studies in adults (15–17). The major form of drug-associated toxicity was reversible myelosuppression. Partial therapeutic responses were observed in 5 of our 15 patients, most of whom had received extensive previous treatment.

Of the six dosage adjustments judged pharmacokinetic-targeting failures, three were attempted in a single patient during one course of therapy. Intermittent administration of several potentially interacting medications, including cotrimoxazole (18) and loperamide, during that course could have likely affected the targeting outcome. Another factor that may have contributed to these failures was the unstable condition of the patient (e.g., fluid changes), possibly leading to variability in the volume of distribution.

It should be emphasized that failures of pharmacokinetic targeting were carefully distinguished from failures resulting from a predetermined topotecan dosage. Although subtle, this distinction is important when evaluating any pharmacokinetic targeting approach, in contrast to the routine clinical practice of using a predetermined fixed drug dosage. However, this advantage did not extend to cohort 2, possibly because of the low interpatient variability in topotecan CL in these patients, ~2-fold compared with the 7–10-fold range observed in larger populations of patients (14). We therefore suggest that the results of the pharmacokinetically guided dosing for cohort 1 are more representative of pediatric solid tumor patients who are

old girl, who had a pontine glioma, had not received any previous chemotherapy, and was treated at the topotecan target AUC of 120–160 ng/ml × h. During her first course of therapy, she required a topotecan dose of 4 mg/m² to attain the target AUC. Although her first course of topotecan was uneventful, during the second week of her second course, she was admitted to an outside hospital with febrile neutropenia and hypotension and died within 24 h. Postmortem examination did not reveal a clear cause of death, although the patient did have culture-negative febrile neutropenia.

It is encouraging to note that 5 patients enrolled in this pilot study achieved a partial response to topotecan. The protocol required a tumor response evaluation after cycle 1 and after every other cycle thereafter. The best response was used as the criterion for response evaluation. An adolescent with metastatic refractory Wilms’ tumor had a large metastatic lesion in the posterior segment of the right lobe of the liver that displaced the remaining kidney (Fig. 4). After one course of topotecan at a target AUC of 120–160 ng/ml × h, the tumor mass was reduced by 75% (Fig. 4, right). This response was maintained for 4 months. In cohort 1, 1 patient each with neuroblastoma, medulloblastoma, and ovarian carcinoma achieved partial responses that persisted for 2, 3, and 6 months, respectively. In cohort 2, 1 patient with neuroblastoma achieved a partial response that lasted for 4 months. All 4 of these patients had been treated extensively with chemotherapy, 2 had received irradiation, and 2 had relapsed after autologous bone marrow transplantation.

Fig. 4  Computerized axial tomography scan of a patient with Wilms’ tumor who had a partial response to pharmacokinetically guided topotecan therapy as noted by a 75% decrease in the size of a metastatic hepatic lesion. Left panel, pretopotecan therapy; right panel, after two courses of pharmacokinetically guided topotecan.
characterized by a high degree of interpatient variability in topotecan clearance. Moreover, because we have shown that pharmacokinetically guided dosing is possible, this approach might be useful to reduce interpatient variability in topotecan systemic exposure in pediatric solid tumor patients.

Our second objective was to evaluate the toxicity of a protracted schedule of topotecan administration in children. At the outset, we were aware of the 7–10-fold range in topotecan clearance, so a pharmacokinetic dosing approach was used to control topotecan systemic exposures during the protracted topotecan therapy. In previous studies of topotecan administered to children in 30-min infusions, myelosuppression was the primary toxicity (4, 19). The topotecan dosages in these studies ranged from 1.7 to 2.4 mg/m²/day for five daily doses repeated every 21 days, and a 7-fold range for topotecan lactone clearance was reported. Clearly, to extend therapy from 5 to 10 days, clinicians must account for patients with slow topotecan clearance, in whom fixed dosing might produce dose-limiting toxicity. In cohort 1, the median (range) topotecan dosage required to attain the targeted AUC was 4 mg/m² (2.6–6 mg/m²). Because the topotecan clearance values in these patients ranged from 19 to 47 liters/h/m², it is unlikely that a fixed dosing would have avoided intolerable myelosuppression or other toxicities. Thus, even in this very heavily pretreated patient population with limited marrow reserves, they were able to tolerate protracted exposures to topotecan.

Although this pilot study was not expected to yield a high rate of antitumor responses, we are encouraged by the five partial responses in patients with histologically diverse tumors, all of whom had received extensive previous treatment. Of our patients that responded to topotecan therapy, 3 of 5 had topotecan clearance values above the median for the study population. The rapid topotecan CL of these patients suggests our pharmacokinetic dosing strategy may have been an important factor in their antitumor responses. A future trial comparing standard topotecan dosing with a pharmacokinetically guided dosing approach appears warranted in children with refractory or relapsed solid tumors, such as neuroblastoma.

An additional application of this dosing strategy would be to identify potential drug–drug interactions, e.g., we reported that topotecan CL was greater in a patient who was receiving concomitant phenytoin (11), a finding that was confirmed in our population pharmacokinetic analysis of this agent (14). Pharmacokinetically guided topotecan dosing in patients receiving combination chemotherapy could be expected to maintain a constant topotecan systemic exposure after other anticancer drugs are added or eliminated. This would assist in determining the therapeutic contribution of the additional anticancer drugs, because the systemic exposure the topotecan would remain relatively constant. Finally, pharmacokinetically guided topotecan dosing could be used to target another tissue or body compartment besides plasma, e.g., Zamboni et al. (20) demonstrated their ability to achieve cytotoxic levels of topotecan in cerebrospinal fluid, based on plasma topotecan concentrations, in a primate model. This approach is currently under evaluation in a clinical trial of topotecan in children with high-risk medulloblastoma.

In conclusion, we have demonstrated both the safety and success of pharmacokinetically guided topotecan dosage adjustments in children with solid tumors. Even though our targeting success rate of 78% in our initial study is promising, more studies are needed to refine the strategy, particularly with regard to protracted dosing in an outpatient setting. If future clinical trials show a therapeutic advantage for maintaining a relatively constant topotecan systemic exposure, it will be important to find ways to simplify the current pharmacokinetic dosing strategy. One avenue might be to develop a dosing nomogram similar to that used with carboplatin. The results of our ongoing population topotecan pharmacokinetic analysis will be helpful in this regard.

ACKNOWLEDGMENTS

We thank Lisa Walters, Terri Kuehner, and Sheri Ring for assistance in obtaining plasma samples, Suzan Hanna and Audrey Smith for their invaluable technical support in the laboratory, Yuri Yanishhevski for his excellent technical support, and Micki Cain for her support with data management.

REFERENCES


A Pilot Study of Protracted Topotecan Dosing Using a Pharmacokinetically Guided Dosing Approach in Children with Solid Tumors
