ABSTRACT

Topotecan, a water-soluble semisynthetic analogue of camptothecin, is the first topoisomerase I inhibitor to undergo evaluation in pediatric patients with refractory malignancies. A phase I and pharmacokinetic study was performed to determine the maximum tolerated dose (MTD) and dose-limiting toxicities, the incidence and severity of other toxicities, and the pharmacokinetics of topotecan in children. Twenty-nine patients received 42 courses of i.v. topotecan administered as a 24-h continuous infusion every 21 days at doses ranging from 2.0 to 7.5 mg/m². Dose-related hematological toxicity was the dose-limiting toxicity. Leukopenia, neutropenia, and thrombocytopenia occurred sporadically at the 3.0- to 5.5-mg/m² dose levels, but at 7.5 mg/m², 4 of 5 patients experienced dose-limiting thrombocytopenia (grade 4) and 2 of 5 had dose-limiting neutropenia (grade 4). No other dose-limiting toxicities were observed. Nausea and vomiting were mild and occurred in <20 and 10% of patients, respectively. Grade 2 hematuria occurred in one patient. No objective responses were observed. Pharmacokinetic studies revealed a linear relationship between the steady-state topotecan concentration and dose. The mean steady-state concentration at the MTD was 18.2 ± 3.7 nmol/liter and the total body clearance was 28.3 ± 6.5 liters/h/m². Elimination was biexponential with a t½α of 14.4 ± 1.8 min and a t½β of 2.9 ± 1.1 h. The recommended starting dose for phase II pediatric trials is 5.5 mg/m².

INTRODUCTION

Topotecan [(S)-9-dimethylaminoethyl-10-hydroxycamptothecin hydrochloride, SK&F 104864-A, NSC 609699; M, 457.9; Fig. 1], a water-soluble analogue of camptothecin, inhibits topoisomerase I, the enzyme that relaxes supercoiled DNA by creating transient single-strand breaks through which another DNA strand can pass during DNA replication, RNA transcription, and other DNA functions. These enzyme-bridge breaks are then resealed by the topoisomerase I enzyme. Topoisomerase I inhibitors, like topotecan, stabilize the covalent complex between topoisomerase I and DNA, resulting in enzyme-linked DNA single-strand breaks that cannot be rejoined in the presence of drug, leading to cytotoxicity (1, 2).

During the late 1960s, phase I trials of the parent drug, sodium camptothecin, demonstrated objective antineoplastic activity against gastrointestinal adenocarcinoma, melanoma, non-small cell lung cancer, and acute myelogenous leukemia (3, 4). However, further clinical development of sodium camptothecin was limited because of unpredictable and severe myelosuppression, gastrointestinal toxicity, and hemorrhagic cystitis (5, 6). The subsequent elucidation of the novel mechanism of action of camptothecin (7) and the development of water-soluble analogues, such as topotecan, rekindled clinical interest in this class of compounds.

Topotecan differs from the parent compound, camptothecin, by the presence of a basic side chain at the 9-position of the A-ring of hydroxycamptothecin (Fig. 1) which results in greater water solubility. It has been postulated that this increased water solubility may reduce the incidence of bladder toxicity relative to the parent compound (8). The intact E-ring lactone of topotecan, which is required for binding to the topoisomerase I enzyme, undergoes spontaneous hydrolysis at physiological pH to yield an open-ring carboxylate form (Fig. 1) (9, 10). The hydrolysis is pH dependent with the equilibrium favoring the open-ring form at a pH > 7.0 and the lactone form in acidic conditions. Following bolus administration of topotecan in humans, the lactone form is rapidly hydrolyzed (50% conversion to the open-ring form within 15 min), and as a result topotecan is rapidly cleared from the plasma with a terminal half-life of approximately 3 h (11).

Topotecan has demonstrated a high degree of activity in a broad spectrum of murine tumors that are relatively refractory to most established anticancer drugs, including B16 melanoma, colon carcinomas 38 and 51, mammary adenocarcinoma, Lewis lung carcinoma, HT 29 colon carcinoma, and multidrug-resistant P388 leukemia (8). In addition, Houghton et al. (12) recently reported activity in vivo in their established pediatric xenograft model. Complete regressions were observed in all 6 rhabdomyosarcoma xenografts (with 3 of 6 lines demonstrating no regrowth during a 7-month observation period), and significant growth inhibitory activity was observed in 3 of 3 osteosarcoma xenografts, including a complete regression in one (12).

In this report we present the results of the first phase I trial and pharmacokinetic study of topotecan conducted in pediatric patients with refractory cancer. Topotecan was administered as a 24-h infusion every 3 weeks. This schedule was chosen based on the cell cycle specificity shown for this agent in preclinical studies and the rapid clearance of the lactone form of the drug from plasma. The objectives of this study were to identify the optimal topotecan dose for phase II pediatric trials, to determine the pharmacokinetics of topotecan in children, and to determine the incidence and severity of toxicities associated with topotecan administered as a 24-h continuous infusion.

PATIENTS AND METHODS

Patient Eligibility

Patients, 25 years or younger, with histologically confirmed cancer refractory to standard therapy were eligible for this trial. Other eligibility criteria included: (a) an Eastern Oncology Cooperative Group performance status of ≤2; (b) a life expectancy of >8 weeks; (c) adequate liver function (serum bilirubin < 2.0 mg/dl); (d) adequate renal function (serum creatinine <1.5 mg/dl or creatinine clearance >60 ml/min/1.73 m²); (e) recovery from the toxic effects of prior therapy; (f) no prior chemotherapy within 2 weeks (6 weeks if a nitrosourea) of entering onto this protocol; (g) no prior extensive radiotherapy (e.g., pelvic or craniospinal) or bone marrow transplantation with total body irradiation; and (h) no prior history of grade 2 or greater hemorrhagic cystitis (gastro hemuria, no clots) and fewer than 5 RBCs/high-power field by
ance with individual institutional policies prior to entry on this study.

defined as a peripheral absolute granulocyte count >1500/mm³, a hemoglobin

escalation at 4.0 mg/m²/24 h was added as a result of hematological toxicity (2

dose of 2 mg/m²/24 h was based on data from the ongoing adult trial using the

Dosage and Drug Administration

Topotecan was administered i.v. as a 24-h continuous infusion. The starting
dose of 2 mg/m²/24 h was based on data from the ongoing adult trial using the
same schedule. This dose was <80% of the highest tolerable dose in adult trials
at the time the pediatric trial was ready to open. Subsequent planned dose
escalations were to 3.0, 3.5, and 7.5 mg/m²/24 h; however, an interim dose
escalation at 4.0 mg/m²/24 h was added as a result of hematological toxicity (2

A minimum of three patients evaluable for both hematological and nonhema-
tological toxicity were treated at each dose level. The MTD was defined as the
dose level immediately below the level at which either 2 patients of a cohort of
six patients experienced nonhematological dose-limiting toxicity (grade 3 or
4 from the NCI Common Toxicity Criteria (13)) or 4 patients of a cohort of six
patients experienced dose-limiting hematological toxicity (grade 4 from the
NCI Common Toxicity Criteria). Courses were repeated every 21 days in the
absence of dose-limiting toxicity.

Topotecan (hydrochloride salt, adjusted to pH 3–4) was supplied by the
Division of Cancer Treatment, NCI (Bethesda, MD) in 5-mg vials which were
reconstituted in 2 ml of sterile water. The appropriate dose of the drug was
further diluted with 5% dextrose to a final concentration between 0.02 and
0.1 mg/ml. The drug was administered at a constant rate over 24-h through
either a peripheral venous or central venous catheter.

Pretreatment and Follow-up Studies

Patient histories, physical examinations, and laboratory studies were ob-
tained prior to treatment and then weekly throughout the course of the study.
Laboratory evaluation included complete blood cell counts, electrolytes, blood
urea nitrogen, creatinine, liver function tests, and urine dipsticks for the pres-
ence of blood. Patients with measurable disease had appropriate radiographic
or bone marrow evaluations at baseline and then prior to subsequent cycles of
topotecan for evaluation of tumor response.

Criteria for Assessment of Toxicity and Response

Toxicities were evaluated according to the NCI Common Toxicity Criteria
(13). Patients were removed from study if they experienced unacceptable

toxicity, defined as grade 4 hematological toxicity or grade 3 or greater non-

hematological toxicity (with the exception of grade 3 nausea and vomiting,
grade 3 hepatic toxicity that returned to grade 1 prior to the time for the next
treatment course, or grade 3 fever).

Patients with measurable disease at the time of study enrollment were
considered evaluable for response. A complete response was defined as the
complete resolution of all measurable tumors and no bony disease progression
as measured by new sites of involvement on computed tomographic scan or
metastatic survey and no appearance of new lesions for 4 weeks. A partial
response was defined as a 50% reduction, and a minimal response as a reduc-
tion of >25% but <50% reduction, in the sum of the products of the two
longest perpendicular diameters of all tumors and no appearance of new lesions
for 4 weeks. Progressive disease was defined as the appearance of new areas
of malignant disease or an increase in any previously measurable lesion (ex-
cluding bone) by >25% in the product of the two longest perpendicular
diameters. Patients with progressive disease following one or more courses of

topotecan were removed from study.

Pharmacokinetic Studies

Pharmacokinetic studies of topotecan (lactone and total drug) were per-
formed in a subset of patients because the instability of this agent at physi-
ological pH required immediate sample analysis. Twelve patients from the NCI
and two patients from Mayo Clinic were studied following administration of
their first dose of topotecan. The pharmacokinetic results will be reported by
institution because different analytical methods for quantitation of topotecan
were used.

NCI Sample Analysis. A minimum of two blood samples were obtained
between 8 and 24 h into the infusion to assess steady-state drug concentra-
tion, and postinfusion specimens were obtained at approximately 15, 30, 60, 90,
120, and 150 min and then at 30- to 60-min intervals thereafter until the parent
drug could no longer be quantitated. Elimination (postinfusion) kinetics were
only obtained for patients at the 4.0-, 5.5-, and 7.5-mg/m²/24-h dose levels
because steady-state plasma concentrations at lower doses approached the
lower limits of quantitation for the assay. Blood samples were collected in
heparinized tubes and were immediately centrifuged at 12,000 x g for 2 min
in a rapid acceleration/deceleration centrifuge. Plasma was removed for im-
mediate analysis.

Concentrations of topotecan (lactone and total drug) were measured with a
reverse-phase HPLC assay modified slightly from a recently reported method
(11). Fisher PrepSep-C18 columns were activated by washing with 3 ml of
methanol, followed by 1 ml of 0.01 M NaHPO₄, pH 6.3 (buffer A), and 1 ml of
a solution containing 100 mM NaHPO₄, pH 6.0, and 1 mM dioctylsulfosuc-
cinate (buffer B). Plasma (500 µl) mixed with 1.25 ml of buffer B was loaded
onto the activated extraction column which was subsequently washed with
1.25 ml of buffer B and two 1-ml aliquots of buffer A. The cartridge was
aspirated dry under vacuum, and topotecan and its metabolite were eluted with
0.75 ml of methanol, followed by 0.25 ml of buffer A. After an aliquot of this
combined eluant was injected for quantitation of the lactone on the HPLC
system described below, the remaining cartridge eluant was acidified with 2% phosporic acid in order to quantitate the total drug (lactone and open-ring species) and injected.

The HPLC system included a Beckman 75- x 4.6-mm, 3 µm, ODS Ultras-
phere LX analytical column (Beckman Instruments, Inc., San Ramon, CA)
with a 20- x 2-mm, 10 µm. ODS precolumn (Beckman Instruments) and a
30- x 4.6-mm Brownlee ODS-GU Spher 5 cartridge (Applied Biosystems,
San Jose, CA) guard column. Topotecan was eluted with a mobile phase consisting
of 620 ml of methanol-40 ml of 0.250 mol/liter sodium diocylsulfosuccinate
(in methanol:water, 50:50, v/v)-23 ml of 1.0 mol/liter ammonium phosphate
buffer (pH 6.0)-5.6 ml of triethylamine-380 ml of distilled water. The pH was
adjusted to 6.0 with phosphoric acid. The flow rate was 1.0 ml/min (isocratic).
Topotecan was detected using a fluorescence detector (Applied Biosystems) at
a λex of 375 nm and a λem of 470 nm (cutoff filter). Under these conditions, the
open-ring metabolite eluted with the solvent front, and the lactone eluted at 4
min. Standard curves of the patients plasma were prepared for each experiment
by addition of known amounts of topotecan to plasma. Standard curves were
linear (r² > 0.995) over a range of 2–100 nmol/liter. The lower limit of quantitation was 2 nmol/liter.

Mayo Clinic Sample Analysis. Blood samples were collected at times similar
to above. In addition, urine samples were collected for the duration of the
infusion. The HPLC plasma and urine assays were based on a previously
reported method (9). Plasma isolation and protein precipitation with methanol
were performed immediately after blood samples were obtained. The depro-
teinized extract was stable for at least 7 days at ~70°C. HPLC analysis was
performed on the same day (postinfusion samples) or next day (samples
obtained during infusion) to determine the concentration of the lactone in
plasma. Total drug plasma and urine concentrations were determined after

2 The abbreviations used are: MTD, maximum tolerated dose; NCI, National Cancer
Institute; HPLC, high-performance liquid chromatography; Cmax, steady-state concentra-
tion; CLtot, total body clearance; λmax, excitation wavelength; λem, emission cutoff wave-
length; AGC, absolute granulocyte count.
Hematological Toxicity. Dose-related hematological toxicity (grade 4) was the dose-limiting toxicity on this trial (Table 2). Anemia (hemoglobin < 6.5 g/dl), neutropenia (AGC < 500/mm³), and thrombocytopenia (platelet count < 25,000/mm³) occurred sporadically at the 3.0- to 5.5-mg/m² dose levels. However, at 7.5 mg/m², 4 of 5 patients experienced dose-limiting thrombocytopenia and 2 of 5 had dose-limiting neutropenia. Therefore, 5.5 mg/m² was determined to be the MTD. Of the 7 patients treated at the MTD, 5 were evaluable for hematological toxicity. Of these patients, one had grade 4 thrombocytopenia and one had grade 4 neutropenia and thrombocytopenia.

Nadir granulocyte and platelet counts occurred at a median of 10 days, with recovery to an AGC of >1500/mm³ and a platelet count of >150,000/mm³ by a median of 21 and 19 days, respectively. The mean duration of grade 4 neutropenia, which occurred in 16% of evaluable courses, was 8 days, and the mean duration of grade 4 thrombocytopenia, which occurred in 19% of evaluable courses, was 7 days. Drug-related toxicity could not be entirely excluded for one patient who experienced grade 4 anemia at the 3.0-mg/m² dose level.

Nonhematological Toxicity. The primary nonhematological toxicity attributable to topotecan was mild nausea, which occurred in <20% of patients, and vomiting, which occurred in <10% of patients. Other reported toxicities included transient elevations of serum transaminase levels in 3 patients (grade <2), microscopic hematuria (grade 1 in 2 patients and grade 2 in one patient), and headache (grade <2) in 2 patients. One patient developed grade 4 hematocrit which at surgery was found to be secondary to tumor infiltration of bowel wall. Nonhematological toxicities did not appear to be dose related. Two patients died of progressive disease while on the study.

Responses. No complete or partial responses were observed.

Pharmacokinetics

The pharmacokinetics of topotecan were studied in 12 patients treated at the NCI and 2 patients treated at the Mayo Clinic during

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg/m²/24 h)</th>
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<th>Clearance (liters/h/m²)</th>
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<td>7.5</td>
<td>30.7</td>
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* Mean of 2-3 samples obtained between 18 and 24 h after the start of the infusion.

† Lactone + open-ring.

‡ Drug assay for these patients performed at Mayo clinic (see "Patients and Methods").

ND, not done.

<table>
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<tr>
<th>Dose level (mg/m²/24 h)</th>
<th>Grade 3 (Hgb &lt; 6.5 g/dl)</th>
<th>Grade 4 (Hgb &lt; 6.5 g/dl)</th>
<th>Grade 3 (AGC &lt; 500/mm³)</th>
<th>Grade 4 (AGC &lt; 500/mm³)</th>
<th>Grade 3 (Pits &lt; 25,000/mm³)</th>
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</table>

* Hgb, hemoglobin; AGC, absolute granulocyte count; Pits, platelets.

† Number of patients with toxicity/number evaluable for hematological toxicity.

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their first cycle of topotecan. Table 3 shows the \( C_s \) and the \( CL_{TB} \) of topotecan (lactone and total drug) for these patients. The mean lactone steady-state concentrations at each dose level were as follows: 16.3 ± 2.5 nmol/liter at 2.0 mg/m², 11.5 ± 2.2 nmol/liter at 3.0 mg/m², 15.2 ± 4.3 nmol/liter at 4.0 mg/m², 18.2 ± 3.7 nmol/liter at 5.5 mg/m², and 30.7 nmol/liter at 7.5 mg/m². The mean total drug steady-state concentrations at each dose level were as follows: 6.4 ± 2.2 nmol/liter at 2.0 mg/m², 11.5 ± 2.2 nmol/liter at 3.0 mg/m², 15.2 ± 4.3 nmol/liter at 4.0 mg/m², 18.2 ± 3.7 nmol/liter at 5.5 mg/m², and 30.7 nmol/liter at 7.5 mg/m². The mean CL\(_{TB}\) for the lactone and total drug at all dose levels was 28.3 ± 6.5 and 9.8 ± 3.9 liters/h/m², respectively. There appeared to be a linear relationship between the \( C_s \) and dose for both the lactone and total drug (Fig. 2). Concentration-time curves for patients treated at the MTD (5.5 mg/m²) are shown in Fig. 3. The postinfusion elimination of topotecan (lactone) at the MTD was biexponential with an \( t_{\alpha} \) and \( t_{\beta} \) of 14.4 ± 1.8 min and 2.9 ± 1.1 h, respectively. The elimination of the total drug at this dose was monexponential with a \( t_{\beta} \) of 2.3 ± 0.5 h.

The urinary recoveries of topotecan (lactone plus open-ring) measured in the two patients treated at Mayo Clinic were 87% and 99%.

There was no apparent relationship between steady-state levels of either the lactone or total drug and hematological or nonhematological toxicity in the limited number of patients for whom pharmacokinetic studies were performed.

**DISCUSSION**

Topotecan, a water-soluble analogue of camptothecin, is the first topoisomerase I inhibitor to be evaluated in pediatric patients with refractory malignancies. The dose-limiting toxicity of this agent was thrombocytopenia; however, sporadic grade 4 myelosuppression, including neutropenia, occurred at all dose levels >3.0 mg/m². There were no drug-related nonhematological dose-limiting toxicities observed in this study. The other most common drug-related toxicities were mild nausea and vomiting experienced by <20% of patients. The recommended starting dose for phase II pediatric trials of topotecan administered as a 24-h continuous i.v. infusion is 5.5 mg/m².

There was a linear relationship between the steady-state plasma concentration of topotecan and the dose, suggesting linear pharmacokinetics over the dosage range studied. The pharmacokinetic parameters defined in this pediatric trial are very similar to those reported in adult trials (11, 16–19). The plasma clearance of the lactone from one representative adult phase I trial was 27.9 liters/h/m² (19), which is almost identical with the mean plasma clearance of 27.3 ± 6.5 liters/h/m² observed in this phase I pediatric trial.

The 2.5-fold range in the ratio of the open-ring to lactone form of topotecan in plasma suggests that it may be inadequate to only quantitate the concentration of total drug (lactone plus open-ring) since patients with the same steady-state concentrations of total drug may be exposed to significantly different concentrations of the more active lactone species. Future studies that evaluate pharmacodynamic correlations between steady-state concentration of drug and either response or toxicity should, therefore, incorporate measurement of both the lactone and total drug.

The MTD defined in the children enrolled on this study (5.5 mg/m²/24 h) is similar to the MTD for heavily pretreated adult patients who received topotecan as a 24-h infusion (4.0–6.25 mg/m²) (19, 20). However, the MTD for minimally pretreated adult patients (8.4–12.5 mg/m²) is severalfold higher than the MTD defined for heavily pretreated adult patients on the same schedule (16, 21, 22). Adjuvant use of currently available cytokines is unlikely to permit significant topotecan dose intensification in children since the dose-limiting toxicity in this trial was thrombocytopenia. However, a dose escalation (e.g., to 7.5 mg/m²) in individual patients who do not experience toxicity at the 5.5 mg/m² may be a safe and feasible strategy to increase drug exposure for the less heavily pretreated patients who will be enrolled on the pediatric phase II topotecan trials.

There are several compelling reasons for proceeding with phase II studies of topotecan in patients with recurrent or refractory solid tumors. As an inhibitor of topoisomerase I, topotecan has a novel mechanism of action. Unlike its parent compound, camptothecin, which caused severe and unpredictable myelosuppression, the primary toxicity associated with topotecan in both adult and pediatric patients has been dose-related myelosuppression. In addition, hemorrhagic cystitis, a significant toxicity observed with camptothecin has not been observed with topotecan. Topotecan has been shown to have significant preclinical activity against a wide variety of murine tumors, multidrug-resistant P388 leukemia cell lines, and of particular
interest, xenografts derived from childhood tumors. Finally, although responses were not observed in this phase I trial, clinical antineoplastic activity (complete and partial responses) has been observed in patients with non-small cell lung cancer, cisplatin-resistant ovarian carcinoma, small cell lung cancer, and metastatic colorectal cancer in phase I topotecan studies in adults (16, 17, 23, 24). Phase II trials to evaluate the clinical antitumor activity of topotecan against pediatric malignancies are currently in progress.

ACKNOWLEDGMENTS

We are grateful to Leslie Aronson, R.N., for her assistance in obtaining samples for pharmacokinetic studies. We thank the following collaborators for enrolling patients on this study: Children's Hospital and Medical Center, Cincinnati, OH; Children's Hospital of Columbus, Columbus, OH; Children's National Medical Center, Washington, DC; Harbor/UCLA Medical Center, Long Beach, CA; Mayo Clinic, Rochester, MN; M. D. Anderson Cancer Center, Houston, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Medicine and Dentistry, New Brunswick, NJ; and University Hospital, Minneapolis, MN.

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