Phase II Trial of Topotecan Administered as a 72-Hour Continuous Infusion in Children with Refractory Solid Tumors: A Collaborative Pediatric Branch, National Cancer Institute, and Children’s Cancer Group Study

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ABSTRACT
The antitumor activity of topotecan administered as a 72-h continuous i.v. infusion was evaluated in children with refractory neuroblastoma and sarcomas of soft tissue and bone. We also attempted to increase the dose intensity of topotecan by including an intrapatient dose escalation in the trial design. Ninety-three children (85 eligible and evaluable for response) with recurrent or refractory neuroblastoma, osteosarcoma, Ewing’s sarcoma/peripheral neuroectodermal tumor, rhabdomyosarcoma, or other soft-tissue sarcomas received topotecan administered as a 72-h i.v. infusion every 21 days. The initial dose was 1.0 mg/m²/day, with subsequent intrapatient dose escalation to 1.3 mg/m²/day for those patients who did not experience dose-limiting toxicity after their first cycle of topotecan. There was one complete response in a patient with neuroblastoma (n = 26) and one partial response in a patient with Ewing’s sarcoma/peripheral neuroectodermal tumor (n = 25). No complete or partial responses were observed in 17 patients with osteosarcoma, 15 patients with rhabdomyosarcoma, or 2 patients with other soft-tissue sarcomas; however, 8 patients had prolonged (15–48 weeks) stable disease while receiving topotecan. Topotecan was well tolerated. The most commonly observed toxicities were myelosuppression (dose-limiting) and nausea and vomiting. Intrapatient dose escalations were performed in 68% of the patients who received more than one cycle of topotecan, and 1.3 mg/m²/day was tolerated by 79% of the patients who received the higher dose and were evaluable for hematological toxicity. In conclusion, topotecan administered as a 72-h continuous infusion every 21 days is inactive (objective response rate, <20%) in children with refractory or recurrent neuroblastoma and sarcomas of soft tissue or bone.

INTRODUCTION
Topotecan, a water-soluble analogue of camptothecin, produces its cytotoxic effect by stabilizing the covalent complex between topoisomerase I and a ligated DNA strand and blocking religation of the DNA (1, 2). In preclinical studies, topotecan was active against a wide variety of murine and human tumors, including human rhabdomyosarcoma and osteosarcoma xenografts (3, 4).

Phase I trials of topotecan have been performed in children and adults on a variety of schedules. The initial pediatric Phase I trials of topotecan evaluated a 24-h continuous infusion every 21 days and a 72-h continuous infusion every 21 days (5, 6).

Because preclinical studies suggested that more prolonged administration schedules were more efficacious, the 72-h infusion schedule was evaluated in this Phase II study. The MTD4 of topotecan in children on the 72-h infusion schedule was 1.0 mg/m²/day (6), and the dose-limiting toxicity was myelosuppression. The pediatric MTD was substantially (38%) lower than the MTD in adults (1.6 mg/m²/day) who were treated on the identical schedule (7). This difference was attributed to the fact that the pediatric patients were more heavily pretreated than the adults. Because response to anticancer agents may be a function of dose intensity (8–10), we attempted to escalate the dose of topotecan in the less heavily pretreated patients who were entered onto our Phase II trial. A similar limited-dose escalation was successfully performed in pediatric patients with central nervous system tumors who were enrolled in a Phase II trial of topotecan administered as a 24-h continuous infusion (11).

4 The abbreviations used are: MTD, maximum tolerated dose; PNET, peripheral neuroectodermal tumor; NCI, National Cancer Institute.
PATIENTS AND METHODS

Patient Eligibility. Patients ≥1 year and ≤21 years of age with a histologically confirmed neuroblastoma, osteosarcoma, Ewing's sarcoma/PNET, rhabdomyosarcoma, or other soft-tissue sarcoma that was recurrent or refractory to standard therapy were eligible for this trial. Patients were also required to have measurable disease and limited prior treatment (≤2 prior chemotherapy regimens). Other eligibility criteria included: (a) an Eastern Cooperative Oncology Group performance status ≤2; (b) a life expectancy >8 weeks; (c) adequate bone marrow function (an absolute neutrophil count >1,000/mm^3, a hemoglobin >9.0 g/dL, and a platelet count >100,000/mm^3); (d) adequate liver function (serum bilirubin <2.0 mg%; alanine aminotransferase <2 times normal); (e) adequate renal function (serum creatinine <1.5 mg% or creatinine clearance >60 ml/min/m^2); (f) recovery from the toxicity of prior therapy; (g) no other chemotherapy within 2 weeks (6 weeks for prior nitrosourea therapy) of entering onto this protocol; and (h) no prior history of NCI grade 2 or greater hemorrhagic cystitis and fewer than five RBCs per high-power field on pretreatment urinalysis. The last eligibility criterion was later removed after clinical experience in children and adults indicated that hemorrhagic cystitis was not associated with topotecan administration. Patients who had received prior Phase I therapy, total body irradiation or bone marrow transplant, or who were pregnant or lactating were excluded from this study. The trial was later amended to add a separate disease strata for patients with neuroblastoma who had previously received an autologous bone marrow transplant.

Informed consent was obtained from the patient or his/her legal guardian prior to entry into this study in accordance with individual institutional policies.

Drug Administration and Study Design. Topotecan (hydrochloride salt, adjusted to pH 3–4) was supplied by the Division of Cancer Treatment, NCI (Bethesda, MD) in 5-mg vials that were reconstituted in 2 ml of sterile water. The appropriate dose of 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 72 h through either a peripheral venous or central venous catheter at a dose of 1.0 mg/m^2/day every 21 days. The dose was escalated on subsequent courses to 1.3 mg/m^2/day if the patient did not experience dose-limiting toxicity on the first cycle. Dose-limiting toxicity was defined as grade 4 hematological toxicity of >7 days duration or any grade 3 or 4 nonhematological toxicity, with the specific exceptions of grade 3 nausea and vomiting, grade 3 hepatic toxicity that returned to grade 1 prior to the next scheduled treatment course, or grade 3 fever. Toxicities were graded according to the NCI Common Toxicity Criteria (12). If five of the first six patients enrolled in the trial tolerated the dose escalation from 1.0 mg/m^2/day on cycle 1 to 1.3 mg/m^2/day on cycle 2, the plan was to increase the starting dose of topotecan to 1.3 mg/m^2/day.

Patient histories, physical examinations, and laboratory studies (complete blood counts, electrolytes, blood urea nitrogen, creatinine, liver function tests, and urine dipsticks for blood) were obtained prior to treatment and at periodic intervals during the course of the study. Complete blood counts were monitored twice weekly. All patients had imaging studies to define the location and extent of the measurable lesion(s). Follow-up imaging studies were repeated after the completion of the second course of treatment and every other subsequent cycle as clinically indicated.

A two-stage design was used to assess efficacy in each stratum defined by disease type. After the first 14 patients were entered, accrual was to be suspended until response was evaluated. If no complete or partial responses were observed in the first cohort, accrual in that stratum was terminated with the conclusion that topotecan was not active. If one or more objective responses were observed in the first 14 patients, additional patients were entered to a maximum of 30 total to obtain a response rate with a 90% two-sided confidence interval of not more than ± 15%.

A complete response was defined as the complete resolution of all clinical evidence of disease for at least 4 weeks. A partial response was defined as a 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions for at least 4 weeks and no appearance of new lesions. Stable disease was defined as a decrease in tumor size less than a partial response but with no disease progression. Progressive disease was defined as the appearance of new lesions or a 25% increase in the product of the two longest perpendicular diameters in any previously measurable lesion (excluding bone). Patients with progressive disease after any treatment course of topotecan were removed from study. Radiographs of the responding patients were reviewed centrally by one of the authors (F. M. B. or S. M. B.).

RESULTS

Ninety-three patients were entered into the trial. Four patients were ineligible because of a prior bone marrow transplant (n = 1), a poor Eastern Cooperative Oncology Group performance score (n = 1), or the absence of measurable disease at study entry (n = 2). Four of the remaining 89 eligible patients were not evaluable for response because follow-up scans to assess response were not performed (n = 1), the parents removed the patient from the trial (n = 1), concurrent radiation therapy was administered (n = 1), or the patient died of disease-related causes 5 days after topotecan administration (n = 1). The ineligible and evaluable patients did not experience any unusual or severe topotecan-related toxicity. Seventy-three patients had all of their protocol-prescribed follow-up laboratory studies performed and were fully evaluable for toxicity. Patient characteristics are shown in Table 1.

Response. Twenty-four patients with neuroblastoma were evaluable for response. One complete response was observed in the first 14 patients. This patient received five cycles of topotecan and was then removed from study while in remission to receive a bone marrow transplant. There were no objective responses in the subsequent 10 patients treated in the second stage of accrual. The overall objective response rate to topotecan in neuroblastoma was 4% in our study population (n = 24), and the true response rate was <18%, with 90% certainty. Only one patient who had previously received an autologous bone marrow transplant for neuroblastoma was treated with topotecan, and this child’s tumor did not respond.
One partial response was observed in the first 14 patients in the Ewing's sarcoma/PNET stratum, but there were no additional objective responses in the next 12 patients (objective response rate, 4%; true response rate, <17% with 90% certainty). Two patients in this disease stratum had stable disease for 11 cycles, one of whom went on to receive a bone marrow transplant. A third patient had stable disease for eight cycles.

No objective responses were observed in the 17 patients enrolled in the osteosarcoma stratum (true response rate, <13% with 90% certainty). However, two patients had stable disease for 11 and 6 cycles, respectively. Likewise, no objective responses were observed in the 15 patients with rhabdomyosarcoma (true response rate, <20%) and the 2 patients with other soft-tissue sarcomas; but 3 patients with rhabdomyosarcoma had prolonged stable disease for 7, 9, and 16 cycles.

**Toxicity.** Myelosuppression was the primary toxicity from the 72-h continuous infusion of topotecan. Of the first six patients who were enrolled on the study, five received a second cycle (the sixth had rapidly progressive disease and was removed from the study). One patient had dose-limiting myelosuppression after the first cycle (at 1.0 mg/m²/day), and two were unable to tolerate escalation of the infusion rate of topotecan from 1.0 to 1.3 mg/m²/day because of dose-limiting myelosuppression at the higher infusion rate. Therefore, the starting dose for the remaining patients was left at 1.0 mg/m²/day, but the protocol was amended to allow intrapatient dose escalation in subsequent patients who did not experience dose-limiting toxicity after their first cycle at 1.0 mg/m²/day. Fifty-seven patients received a second course of topotecan, and 43 patients (75%) met the criteria to dose escalate. Thirty-nine of the 57 patients (68%) actually received the increased infusion rate (1.3 mg/m²/day), and 21% of patients who were evaluable for hematological toxicity during their second cycle experienced dose-limiting myelosuppression.

The primary nonhematological toxicity attributable to topotecan was mild (grade 1 or 2) nausea in 20% of patients and vomiting in 10% of patients. Grade 3 nausea and vomiting was reported in less than 5% of patients. Other infrequently reported non-dose-limiting toxicities included transient elevations of serum transaminases and bilirubin, constipation, mucositis, fever, alopecia, and mild exacerbation of prior sensory neuropathy. One patient had Klebsiella pneumoniae sepsis after the first cycle of topotecan. This patient had an uneventful recovery and subsequently received a second cycle of 1.0 mg/m²/day without problems. There were no toxic deaths from topotecan in patients treated on this trial. There were no apparent cumulative hematological or nonhematological toxicities in the patients who received multiple courses of topotecan.

**DISCUSSION**

Topotecan administered as a 72-h infusion every 21 days is associated with minimal antitumor activity in children with recurrent or refractory neuroblastoma and Ewing's sarcoma/PNET. No antitumor activity was observed in patients with osteosarcoma or rhabdomyosarcoma or other soft-tissue sarcomas. Stabilization of disease was observed in a few patients in all disease strata and was maintained on repeated cycles of topotecan for 15–48 weeks.

The toxicities in this Phase II trial were comparable to the toxicities observed in the pediatric Phase I trials of topotecan and a pediatric Phase II trial of topotecan (24-h infusion) in patients with central nervous system tumors. Topotecan was well tolerated, and a limited intrapatient dose escalation was successfully performed in the majority of patients. In addition, there were no new or unexpected toxicities in the patients who were treated at a dose level that was 33% higher than the MTD defined in the Phase I trial of topotecan administered as a 72-h continuous infusion (6).

Despite the poor objective response rate observed in the present study, consideration should be given to evaluating more prolonged administration schedules, because preclinical studies by Houghton et al. (3, 4) suggest that the antitumor effect of topoisomerase I inhibitors is highly schedule dependent. These studies in a variety of human tumor xenografts have shown that the antitumor effect of topotecan is significantly greater when the drug is administered over a protracted period of time (e.g., daily × 5, every week, for 3 weeks) compared with an intermittent schedule of drug administration (3, 4).

**REFERENCES**


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