Phase I Study of Topotecan Administered as a 21-Day Continuous Infusion in Children with Recurrent Solid Tumors: A Report from the Children's Cancer Group

Haydar Frangoul, Matthew M. Ames, Revonda B. Mosher, Joel M. Reid, Mark D. Krailo, Nita L. Seibel, Dennis W. W. Shaw, Peter G. Steinherz, James A. Whitlock, and John S. Holcenberg


ABSTRACT

The purpose of this study was to determine the toxicity, maximum tolerated dose, and pharmacokinetics of a 21-day continuous infusion of topotecan in children with relapsed solid tumors. Fifteen patients received 40 courses of continuous ambulatory infusions of topotecan every 28 days or when there was resolution of hematological toxicity and any grade 2 or greater nonhematological toxicity. The starting dose was 0.4 mg/m²/day. Total topotecan levels were measured on days 1, 7, 14, and 21. Three of four patients who received a starting dose of 0.4 mg/m²/day experienced dose-limiting myelosuppression. At the reduced dose of 0.3 mg/m²/day, only two of the seven patients experienced dose-limiting myelosuppression. Subsequently, four patients with more limited prior therapy were treated with 0.4 mg/m²/day; three had dose-limiting myelosuppression. Two patients with a dose-limiting toxicity at 0.4 mg/m²/day tolerated additional courses at 0.3 mg/m²/day. An equal number of patients had grade 4 neutropenia or thrombocytopenia. Other adverse events were rare. Two patients with ependymoma, one with rhabdomyosarcoma, and one with retinoblastoma metastatic to the brain had objective responses. The steady state plasma concentration and clearance of topotecan (Css) was achieved by day 1. Css in six patients with complete data were 1.44 ± 0.50 and 2.13 ± 0.83 ng/ml at 0.3 and 0.4 mg/m²/day, respectively. Thus, a 21-day topotecan infusion was well-tolerated at 0.3 mg/m²/day. Myelosuppression was the dose-limiting toxicity at 0.4 mg/m²/day. The steady state and clearance of topotecan in this study are similar to those reported in adult patients.

INTRODUCTION

Topotecan is a semisynthetic water-soluble derivative of camptothecin, a plant alkaloid first isolated in 1966 from a Chinese deciduous tree, Camptotheca acuminata (1). Camptothecin demonstrated antineoplastic activity but had unpredictable side effects, including severe myelosuppression, hemorrhagic cystitis, and severe diarrhea (2–4). On the assumption that the undesirable side effects of camptothecin were partly due to its lack of aqueous solubility, topotecan (20(s)-9-dimethylaminomethyl-10-hydroxy-camptothecin) was synthesized (5). Topotecan exerts its cytotoxic activity by inhibiting the enzyme topoisomerase I. Topoisomerase I forms covalent adducts with DNA, which are called covalent topoisomerase I-DNA complexes. This reaction relaxes supercoiled duplex DNA, resulting in single-strand breaks that allow the intact strands to pass. The enzyme-bridged breaks are then re-ligated. Topotecan inhibits topoisomerase I by stabilizing the covalent topoisomerase I-DNA complexes, resulting in single-strand DNA breaks that cannot be re-ligated in the presence of the drug (6–8).

Topotecan has antitumor activity against a variety of adult and pediatric tumors in murine models (9–11). Initial Phase I studies in adult patients have been performed using a range of schedules, including a single 30-min infusion every 3 weeks (12) and 30-min infusions daily for 5 days every 3 weeks (13). Mouse xenograft models derived from human solid tumors indicate that prolonged exposure to topoisomerase I inhibitors produces optimal antitumor activity (10, 11). Consequently, clinical trials have evaluated continuous infusions of 1–21 days duration (14–17) as well as prolonged daily or bid oral dosing (18, 19). Myelosuppression has been dose-limiting in the majority of phase I trials (18, 20–24). Mucositis was dose-limiting at higher doses in patients with acute leukemia where hematological toxicity was not considered dose-limiting (25–27), whereas diarrhea was dose-limiting at some oral dosing schedules (19).

Because prolonged continuous exposure to topotecan might improve its antitumor activity against pediatric solid tumors, we conducted a Phase I trial of 21-day continuous infusion topotecan in children with recurrent solid tumors. In
adult patients, the MTD\textsuperscript{3} for this schedule was 0.53 mg/m\textsuperscript{2}/day in those with a median of two prior regimens, 0.6 mg/m\textsuperscript{2}/day with one prior regimen or minimal radiation therapy, and 0.7 mg/m\textsuperscript{2}/day with no prior therapy (20, 28). The starting dose for this trial of pretreated children was 80% of 0.53 mg/m\textsuperscript{2}/day or 0.4 mg/m\textsuperscript{2}/day.

The objectives of this trial were: (a) to determine the MTD and toxicities of this schedule of topotecan in children; (b) to determine the steady state concentration of topotecan in the plasma and compare it to adult data; and (c) to document any antitumor activity within the confines of a Phase I trial.

**MATERIALS AND METHODS**

**Eligibility Criteria.** Patients between the ages of 1 and 21 years with a histologically confirmed solid tumor refractory to conventional therapy were eligible for this study (Children’s Cancer Group-0956). Brain stem tumors were eligible without a biopsy. Other requirements included a life expectancy of at least 2 months, an Eastern Cooperative Oncology Group performance status of 0–2, and full recovery from the toxic effect of prior therapy. Patients were required to have adequate bone marrow function (absolute neutrophil count >1500/mm\textsuperscript{3}, platelet count >100,000/mm\textsuperscript{3}, and a hemoglobin >10 g/dl), renal function (serum creatinine <1.5 times normal or glomerular filtration rate >70 ml/min/1.73 m\textsuperscript{2}), liver function (total bilirubin <1.5 × normal and aspartate aminotransferase or alanine aminotransferase <2.5 × normal), and central nervous function (central nervous system toxicity < grade 2 and adequate seizure control on anticonvulsants). Patients were required to be off cytokines for at least 2 weeks before the start of the study. All patients were required to have a central venous access device. Patients previously treated with a topoisomerase I inhibitor were excluded from this study. Initially, the study only excluded children with more than three prior chemotherapy regimens, bone marrow invasion with tumor cells, or prior bone marrow transplant. To better define the MTD in less heavily treated patients, we entered a cohort of patients with more limited prior therapy, defined as two or fewer prior myelosuppressive therapies and no radiation therapy to the craniospinal axis or to >50% of the marrow space.

The Institutional Review Board of participating institutions approved this study. Informed consent was obtained from the patient or his/her legal guardian before entry in the study.

**Dosage and Drug Administration.** Topotecan was administered as a 21-day continuous i.v. infusion using a commercially available infusion pump (CADD-plus, CADD-1 Ambulatory Infusion Pump, Pharmacia Deltec, St. Paul, MN, or comparable model) beginning on day 0. The infusion pump was calibrated to deliver each day's dose over 24 h. Cassettes containing a 7-day supply of topotecan were changed weekly. The minimum infusion volume was 49 ml per 7-day period, and the minimum concentration was 10 μg/ml. Some centers used larger volumes by further dilution of the topotecan solution by or piggybacking D5W or normal saline with a dual pump to avoid possible line clotting with low infusion rates. If the pump malfunctioned, the infusion could be stopped for a maximum of 48 h during any 21-day infusion period. Longer delays could lead to termination of protocol therapy.

The infusion was stopped early if the patient experienced grade 4 hematological or grade 3 or 4 nonhematological toxicity (except for nausea and vomiting that could be controlled by supportive care). Once stopped, the infusion could be restarted after 7 days if the toxicity had resolved to grade 2. Nevertheless, the total duration of the infusion from the first dose could not exceed 21 days.

The starting dose of topotecan was 0.4 mg/m\textsuperscript{2}/day. Additional 21-day courses were allowed beginning at least 28 days after the start of the previous course if the patients had recovered from any grade 2 or greater nonhematological toxicity, had an absolute neutrophil count >1500/μl, platelet count >100,000/μl (transfusion independent), hemoglobin >10 g/dl, and no evidence of PD. Patients received the same dose if these treatment criteria were met by day 35. If >35 days were required, the topotecan dose was reduced by 25% for the next course. The patients were taken off the study if these criteria were not met by day 35 at the reduced dose.

Topotecan (NSC-609699) was supplied by the National Cancer Institute (Bethesda, MD). The 4-mg vials were reconstituted with 4 ml of Bacteriostatic Water for Injection, USP. This 1 mg/ml of topotecan solution is stable for 21 days when stored at 2°C-8°C. The reconstituted solution was further diluted in a plastic bag to a concentration of 10–500 μg/ml. These topotecan solutions are stable at room temperature for at least 7 days.

**Pretreatment and Follow-up Studies.** Patient history and physical exam, complete blood count, creatinine, bilirubin, alanine aminotransferase, and urinalysis were obtained before the start of therapy and before each subsequent course. Complete blood count, creatinine, and liver function tests were obtained weekly. Patients with measurable disease had baseline radiographic evaluation and subsequent scans every 1–2 courses of therapy to evaluate response. Complete response was defined as disappearance of all known disease for at least 4 weeks; PR as a decrease of at least 50% in the size of all measurable tumor as quantified by the sum of the products of the two largest diameters of measurable lesions for at least 4 weeks; and STBD as a decrease of <50% or an increase of <25% in the sum of the products of the largest diameters of measurable lesions and no evidence of new lesions. PD was defined as a >25% increase of the measurable lesions or the appearance of new lesions. All patients who had complete response, PR, or STBD that persisted >4 weeks were considered to have experienced an objective response. Duration of response was defined as the interval from the first scan that demonstrated the patient’s maximal response (PR or STBD) and the first scan that demonstrated PD after the best response was determined. An independent neuroradiologist reviewed MRI scans of three patients with central nervous system tumors who were considered responders by the local institution and two who were considered nonresponders. The patient’s identity and response status were not available to this reviewer.

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\textsuperscript{3}The abbreviations used are: MTD, maximum tolerated dose; PR, partial response; STBD, stable disease; PD, progressive disease; MRI, magnetic resonance imaging; DLT, dose-limiting toxicity; G-CSF, granulocyte colony-stimulating factor.
Toxicity and MTD. The National Cancer Institute Common Toxicity Scale was used to grade all adverse events. DLT was defined as any grade 4 hematological toxicity or any grade 3–4 nonhematological toxicity except for grade 3 nausea or vomiting that could be managed with supporting care. The MTD was defined as the dose at which less than one-third of patients experience DLT.

Pharmacokinetics. Topotecan plasma concentrations were determined on days 1, 7, 14, and 21 during the first course of therapy. Blood was collected in heparinized tubes and immediately cooled in ice water. The plasma was separated by centrifugation and immediately frozen. The samples were analyzed for total topotecan according to Beijnen et al. (29). High-performance liquid chromatography separations were performed on a Lichrospher RP-100 cartridge column eluted at a flow rate of 1 ml/min with a mobile phase of methanol:water:0.025 m sodium diocytldisodiumsulfosuccinate:1.0 m sodium phosphate buffer (pH 6.00):triethylamine (325:215:20:11.5:1.5); the apparent pH of the mobile phase was adjusted to 6.0. The fluorescence of the effluent was monitored with extinction and emission wavelengths of 381 nm and 527 nm, respectively. The assay sensitivity limit and linear range were 1.0 ng/ml and 1.0–20.0 ng/ml, respectively. The interday variability was <15% as determined by measuring the coefficient of variation of quality control specimens on 5 separate days over a 2-month period.

The steady state plasma concentrations,Css, were calculated as the average of at least three concentration values measured during the infusion. The steady state clearance was calculated by dividing the dose rate by the Css.

RESULTS

Patients. Fifteen patients were enrolled. The demographic characteristics are described in Table 1. Fourteen of the fifteen patients had normal serum creatinine for their age. One 17-year-old male had a creatinine of 1.5 mg/dl but a creatinine clearance of 92 ml/min/1.7 m². All patients were evaluable for response and toxicity. A total of 40 courses were administered. Two patients received prior nitrosourea therapy. Eight patients received >50-Gy prior radiation therapy.

Toxicity. Hematological toxicities are summarized in Table 2. Three of the four patients who received topotecan at the starting dose of 0.4 mg/m²/day for 21 days experienced dose-limiting neutropenia or thrombocytopenia. All four patients had grade 3 anemia. All these patients had received prior chemotherapy and radiation therapy. Because of this DLT, the starting dose was reduced for a cohort of patients. Seven patients received 20 courses at 0.3 mg/m²/day for 21 days. Only two patients experienced dose-limiting neutropenia or thrombocytopenia. Both had received >50-Gy radiotherapy. One patient experienced grade 4 lymphopenia.

Because prior therapy might influence the MTD of topotecan, we next enrolled four patients with limited prior therapy at 0.4 mg/m²/day for 21 days. One of these patients had received 12-Gy radiation to the lung. One of the four patients started radiation therapy to a painful pelvic mass on day 14 of the topotecan infusion and thus was not evaluable. Two of the three evaluable patients had grade 4 myelosuppression: one with neutropenia and thrombocytopenia and one with thrombocytopenia.

Two patients at each dose level experienced grade 4 neutropenia lasting >7 days. Grade 4 thrombocytopenia lasting >7 days occurred in 2 patients at 0.4 mg/m²/day. Two patients who experienced dose-limiting myelosuppression at 0.4 mg/m²/day subsequently tolerated 11 courses at 0.3 mg/m²/day with no grade 4 neutropenia or thrombocytopenia.

No patients experienced grade 3 or 4 mucositis or renal toxicity. Transient grade 3 elevation of transaminases was seen in one course. One patient with rhabdomyosarcoma at the 0.4 mg/m²/day level had PD and grade 4 hypertension and hypercalcemia as a terminal event; these adverse events were considered unrelated to the drug administration. Grade 3 leg cramps were observed in one patient treated at the 0.3 mg/m²/day dose level. Grade 1 or 2 abdominal pain, nausea, vomiting, constipation, and hyperbilirubinemia were seen in three or fewer courses of therapy. There were eight line infections in three patients, three cases of Herpes Zoster, and one case each of viral pneumonia, ear infection, and eye infection. Parenteral antibiotics were administered in 17 of the 40 courses, and parenteral antifungal therapy was administered during one course.

Data regarding topotecan infusions were obtained from all participating institutions. Most infusions were uneventful. The infusion was interrupted on four occasions in three patients due to pump malfunction; each interruption lasted <24 h. In addi-
tion, the infusion was prematurely stopped in three patients due to thrombocytopenia (day 10), Herpes Zoster (day 14), or bacterial sepsis (day 2).

**Concurrent Medications.** One patient developed bacterial sepsis and received G-CSF on days 24–26 of one course by his treating physician, although the ANC was in the normal range at that time. Another patient experienced grade 3 neutropenia for the first course at 0.3 mg/m²/day but experienced grade 4 neutropenia and grade 3 thrombocytopenia. The MRI scan after this course showed a 90% decrease in the product of the anterior-posterior and transverse diameters of the target lesion. This patient was taken off the study by the local investigator but received six additional courses with commercial topotecan according to the protocol, except that G-CSF was given. The disease progressed after the seventh course. One patient with ependymoma showed an increase in the size of a posterior fossa mass and leptomeningeal enhancement on an MRI scan 4 weeks after the first course of 0.4 mg/m²/day of topotecan. He had grade 4 myelosuppression at that dose. When this patient improved clinically over the next 3 months with no further treatment, a repeat MRI scan was done, which showed a decrease in the size of the posterior fossa mass and in the leptomeningeal enhancement. Consequently, this patient was placed back on the study and treated with eight additional courses of 0.3 mg/m²/day of topotecan over 11 months. There was further shrinkage in the size of the mass and loss of leptomeningeal enhancement before the mass recurred.

**Pharmacokinetics.** Steady-state pharmacokinetics of total topotecan were determined in 8 of the 15 patients enrolled in this trial (Table 3). Two of the five values determined at the 0.3-mg/m² dose level were below the assay limit of quantitation of 1.0 ng/ml but are reported because they are similar to the three values that were above the assay limit of quantitation. The mean Css and steady state clearance (Clss) values (± SD) for this patient cohort were 1.44 ± 0.50 ng/ml and 9.3 ± 2.8 liters/h/m², respectively. The mean Css and Clss values (± SD) for the patient cohort treated with 0.4 mg/m² topotecan were 2.13 ± 0.83 ng/ml and 8.9 ± 4.3 liters/h/m², respectively. Only the data for the patients with Css values >1.0 ng/ml were used to determine the total topotecan plasma clearance of 9.1 ± 3.3 liters/h/m² for the 21-day infusion.

**Responses.** Objective response was noted in 4 of the 15 treated patients. A patient with rhabdomyosarcoma had a PR with nearly complete resolution of multiple pulmonary nodules after one course at 0.4 mg/m²/day but experienced dose-limiting myelosuppression. When the counts recovered, she received two additional courses at 0.3 mg/m²/day, but disease progression was noted after the last course. A patient with retinoblastoma had a PR after one course at 0.3 mg/m²/day but experienced grade 4 neutropenia and grade 3 thrombocytopenia. The MRI scan after this course showed a 90% decrease in the product of the anterior-posterior and transverse diameters of the target lesion. This patient was taken off the study by the local investigator but received six additional courses with commercial topotecan according to the protocol, except that G-CSF was given. The disease progressed after the seventh course. One patient with ependymoma showed an increase in the size of a posterior fossa mass and leptomeningeal enhancement on an MRI scan 4 weeks after the first course of 0.4 mg/m²/day of topotecan. He had grade 4 myelosuppression at that dose. When this patient improved clinically over the next 3 months with no further treatment, a repeat MRI scan was done, which showed a decrease in the size of the posterior fossa mass and in the leptomeningeal enhancement. Consequently, this patient was placed back on the study and treated with eight additional courses of 0.3 mg/m²/day of topotecan over 11 months. There was further shrinkage in the size of the mass and loss of leptomeningeal enhancement before the mass recurred.

The maximum decrease in the area of the target lesion by MRI scan was 39%. This patient had STBD for 10 months. Another patient with ependymoma had progressive improvement in MRI scans for 12 months, with a maximum decrease in the area of the target lesion of 72%. She stopped treatment after 14 courses because central venous access was no longer possible. Her response duration was 20 months. None of these patients had positive cerebrospinal fluid (CSF) cytology.

**DISCUSSION**

Although the starting dose of 0.4 mg/m²/day for 21 days was 80% of the dose tolerated in adults with prior chemotherapy (20, 21, 24), it was still not tolerated in our patients. In this pediatric trial, myelosuppression was dose-limiting in three of four patients who were heavily pretreated and in three of four
with more limited prior therapy. It is unlikely that G-CSF or granulocyte macrophage colony-stimulating factor would allow dose escalation because grade 4 thrombocytopenia was as common as neutropenia. A dose of 0.3 mg/m²/day for 21 days was well-tolerated because only two of seven patients experienced reversible grade 4 neutropenia or thrombocytopenia. Contrary to what has been observed in other Phase I trials using higher doses of topotecan infusion, no grade 3 or 4 mucositis or diarrhea was observed in this pediatric trial (19, 25, 26, 27).

The administration of topotecan as a 21-day continuous infusion was technically feasible in these pediatric patients through the use of portable electrical pumps and central venous access. Interruption of the infusions due to pump malfunction was rare and lasted for <24 h. Clotting of the lines was reported during only one infusion despite the slow infusion rate and lack of anticoagulants in the infusate. Line-related infections were seen in only three patients.

The steady-state pharmacokinetics of total topotecan rather than topotecan lactone were studied in this trial for several reasons. First, topotecan was administered by a low dose on this extended infusion schedule. Others found that topotecan lactone was not detectable during such a prolonged infusion at a similar dose (27). Second, the total topotecan Css value is related to hematological toxicity (30–32). In fact, based on their review of the literature, Herben and colleagues (33) concluded that the area under the plasma concentration time curve (AUC) andCss for total topotecan were equally or better related to hematological toxicity than the AUC or Css for topotecan lactone. Third, it is difficult to accurately measure topotecan lactone in a group-wide trial due to rapid interconversion between the lactone and carboxylate.

The total topotecan plasma clearance in this study (9.1 ± 3.3 liters/h/m²) was similar to that reported in other pediatric studies of continuous infusion topotecan. The mean total topotecan plasma clearance during 24-h (23) and 72-h (31) infusions to children with solid tumors was 9.8 and 6.5 liters/h/m², respectively. The topotecan plasma clearance in children was ~30% lower than the plasma clearance in adults. The total topotecan plasma clearance values in two adult Phase II trials, where 0.5 mg/m²/day or 0.4 mg/m²/day topotecan was given by a 21-day continuous infusion, were 12.4 liters/h/m² (the literature value of 0.35 liters/min was adjusted for the adult mean body surface area of 1.7 m²: Ref. 21) and 13.6 liters/h/m² (24). The effect on the MTD of lower topotecan plasma clearance in children compared to adults is unclear.

Adult trials have shown that topotecan pharmacokinetics are not dose-dependent and that Css increases linearly with dose (28, 30–32). The higher topotecan doses administered in the adult Phase II trials resulted in Css values of 1.94 ± 0.47 ng/ml (21) and 1.28 ± 0.25 ng/ml (24), respectively, which were above and below the Css (1.44 ± 0.5 ng/ml) achieved at the MTD in this study. Thus, other factors more likely contribute to the difference in MTD between adults and children.

With other schedules of administration, adults also appear to tolerate higher doses than children do. In Phase I trials of continuous infusion topotecan, the MTD was 7.5 mg/m²/day in children versus 10 mg/m²/day in adults for a 24-h infusion. For a 72-h infusion, the MTD was 1.0 mg/m²/day in children versus 1.6 mg/m²/day in adults for a 72-h infusion (6). Bowman and coworkers (18) conducted a Phase I trial of daily oral doses of a topotecan solution for 21 days and for 5 days/week for 3 weeks in children with solid tumors. The MTD for both schedules was 0.8 mg/m²/day. In contrast, the MTD was 1.2 mg/m²/day for adults given oral topotecan tablets bid for 21 days (19).

Adult trials of 21-day infusions of topotecan have shown that patients with a median of two prior regimens initially tolerated 0.53 mg/m²/day, but half required dose reduction to 0.4 mg/m²/day for subsequent courses (20). Less heavily treated patients tolerated as much as 0.7 mg/m²/day (20, 28). Children in this study did not tolerate a dose of even 0.4 mg/m²/day. These observed differences in the MTD between the adult and pediatric Phase I trials might be related to a higher intensity of prior therapy in pediatric patients. Almost all children with cancer who are enrolled in Phase I trials have received prior therapy with multiple myelosuppressive agents (34, 35). Even the patients with limited prior therapy in this study had received several courses of intensive chemotherapy prior to enrolling on this study.

Objective response was observed in four patients. PRs were seen in one patient with metastatic rhabdomyosarcoma and in one patient with retinoblastoma after one course of therapy. PD was noted after the third and seventh courses in these two patients, respectively. Two patients with ependymoma had STBD, one for 10 months and the other for 20 months of treatment.

The optimal schedule for topotecan is not known. These compounds bind to topoisomerase I and stabilize covalent topoisomerase I-DNA complexes. This leads to single-strand breaks primarily in areas of active transcription and to double-stranded breaks at replication forks in DNA. This latter effect is probably the main mechanism of cytotoxicity when these derivatives are used alone. Cells in the S phase are up to 1000-fold more sensitive to the effects of these agents than cells in G₁ or G₂ (36). This observation suggests that prolonged exposure to these compounds may be more effective than short exposures because more cells will go into the S phase of the cell cycle.

Preclinical data in tissue culture and in human xenograft models confirm the advantage of prolonged drug dosing (11, 37, 38). Optimal activity in these xenograft models was shown with short daily exposures, usually 5 days/week for several weeks. Recently, Danks and coworkers (39) have raised concerns that longer exposure of cells to topotecan can lead to subcellular redistribution of topoisomerase I from the nucleolus, a decrease in covalent topoisomerase I-DNA complexes, and a decrease in cytotoxicity. This subcellular redistribution appears to occur only at high topotecan concentrations and may not occur at the concentrations achieved clinically with long continuous infusions (40, 41). A recent trial compared a 24-h infusion with 5 daily doses of topotecan in women with previously treated ovarian cancer. The short infusion was less toxic and less effective (42). Additional studies are needed to compare equitoxic doses of topotecan by longer infusions with a daily × 5 schedule.

This study has shown that a continuous infusion of 0.3 mg/m²/day of topotecan for 21 days is well-tolerated. There were encouraging responses in some patients. A Phase II trial at this dose has been initiated by the Children’s Cancer Group. If
APPENDIX

Participating principal investigators—Children’s Cancer Group

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<tr>
<td>Group Operations Center</td>
<td>W. Archie Bleyer, MD Anita Khayat, PhD Harland Sather, PhD Mark Krailo, PhD Jonathan Buckley, MBBS, PhD Daniel Stram, PhD Richard Sposto, PhD</td>
<td>CA13539</td>
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<td>University of Michigan Medical Center</td>
<td>Raymond Hutchinson, MD</td>
<td>CA02971</td>
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<tr>
<td>Ann Arbor, MI</td>
<td>Katherine Matthey, MD</td>
<td>CA17829</td>
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<tr>
<td>University of California Medical Center</td>
<td>J. Russell Geyer, MD</td>
<td>CA10382</td>
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<tr>
<td>San Francisco, CA</td>
<td>Gregory Reaman, MD</td>
<td>CA03888</td>
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<tr>
<td>Children's Hospital &amp; Medical Center</td>
<td>Beverly Lange, MD</td>
<td>CA11796</td>
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<tr>
<td>Seattle, WA</td>
<td>Gerald Gilchrist, MD</td>
<td>CA28882</td>
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REFERENCES


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