VOLUME 25 · NUMBER 21 · JULY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Topotecan Is Active Against Wilms' Tumor: Results of a Multi-Institutional Phase II Study

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Submitted January 26, 2007; accepted April 16, 2007.

Supported by Grants No. CA-21765 and CA-23099 from the National Institutes of Health, grants from the American Lebanese Syrian Associated Charities of St Jude Children's Research Hospital, and a research grant from GlaxoSmithKline.

Presented in part at the 38th Congress of the International Society of Pediatric Oncology, September 17-21, 2006, Geneva, Switzerland.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2521-3130/$20.00

DOI: 10.1200/JCO.2007.10.9298

ABSTRACT

Purpose
A phase II study was conducted to evaluate the activity and safety of topotecan in pediatric patients with recurrent Wilms' tumor.

Patients and Methods
Patients with favorable histology Wilms' tumor (FHWT) and recurrence after at least one salvage chemotherapy regimen or with anaplastic histology Wilms' tumor (AHWT) in first or subsequent recurrence were eligible. Patients were stratified according to histology, with statistical considerations based on the FHWT stratum. Topotecan was administered intravenously over 30 minutes for 5 days on 2 consecutive weeks. Treatment dosages were adjusted to achieve a target area under the curve (AUC) of 80 ± 10 ng/mL*h. Tumor responses were measured after two cycles of treatment.

Results
Thirty-seven patients (26 patients with FHWT) were enrolled and received a total of 94 cycles of topotecan (range, one to six cycles). The median topotecan dosage required to achieve the target AUC was 1.8 mg/m^2 (range, 0.7 to 3.2 mg/m^2). Of 25 assessable patients with FHWT, 12 had partial response (PR), six had stable disease (SD), and seven had progressive disease (PD), for an overall response rate of 48% (95% CI, 27.8% to 68.7%). Of 11 assessable patients with AHWT, two had PR, one had SD, and eight had PD. The main toxicities were grade 3 and 4 neutropenia (median duration, 13 days) and thrombocytopenia (median duration, 7.5 days).

Conclusion
Topotecan administered on a protracted schedule is active against recurrent FHWT. Inclusion of topotecan in front-line clinical trials for patients with recurrent Wilms' tumor should be considered.

J Clin Oncol 25:3130-3136. © 2007 by American Society of Clinical Oncology

INTRODUCTION

The treatment of Wilms' tumor is one of the great success stories in oncology, but certain subgroups of patients do not fare well, including those with anaplastic histology, bilateral disease, and recurrent disease.[1-3] For patients with recurrent Wilms' tumor, relapse-free survival (RFS) has improved significantly since the 1980s with the use of intensive chemotherapy or high-dose therapy with autologous stem-cell rescue.[1,4-9] Despite the use of modern treatment regimens, 4-year RFS rate for patients treated initially with vincristine/dactinomycin is approximately 70%, and 4-year RFS rate for patients treated initially with vincristine/dactinomycin/doxorubicin is approximately 40%.[7,10] Patients with recurrent anaplastic Wilms' tumor have particularly poor salvage rates; fewer than 15% of such patients achieve durable survival.[2] Novel agents and treatment strategies are needed for patients with high-risk or recurrent Wilms' tumor.

Topotecan is a camptothecin analog that interacts with topoisomerase I and causes DNA double-strand breaks in an S phase–dependent manner.[11] Topotecan has previously shown activity against various pediatric solid tumors including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and medulloblastoma.[12-16] Xenograft studies have suggested that the activity of topotecan is schedule dependent, producing a higher frequency of responses when administered on a protracted schedule of administration rather than an intermittent high-dose regimen.[17] In Wilms' tumor xenograft models, six of eight favorable histology models and one anaplastic histology model responded to topotecan at systemic exposures that are achievable in patients.[18] On the

basis of the preclinical data and promising results of phase I studies,[19] we conducted a phase II study to estimate the response rate of topotecan in patients with recurrent Wilms' tumor.

PATIENTS AND METHODS

Patient Selection

The study of topotecan in children with recurrent Wilms' tumor was a multi-institutional phase II trial including St Jude Children's Research Hospital, Dana-Farber Cancer Institute, Alberta Children's Hospital, Texas Children's Hospital, Children's Hospital of Atlanta, and the Hospital for Sick Children in Toronto. Patients were eligible if they had recurrent or progressive favorable histology Wilms' tumor (FHWT) after primary treatment and at least one standard salvage treatment regimen or if they had recurrent or progressive anaplastic histology Wilms' tumor (AHWT) after primary treatment. Other eligibility requirements included age $\leq$ 21 years, absolute neutrophil count (ANC) $\geq$ 1,000/μL and platelet count $\geq$ 100,000/μL unsupported by transfusion, a serum bilirubin less than 1.5$\times$ the upper limit of normal for age, and an Eastern Cooperative Oncology Group performance status[20] of 0 to 2. The protocol was approved by the institutional review boards of all participating institutions, and all patients, parents, or guardians, as appropriate, were required to provide written informed consent in accordance with institutional and federal guidance.

Treatment Regimen

Topotecan was administered intravenously over 30 minutes daily for 5 days for each of 2 consecutive weeks [(daily $\times$ 5) $\times$ 2]. The initial dosage (2.4 mg/m^2/d; later modified to 1.8 mg/m^2/d) was adjusted to attain a target topotecan lactone systemic exposure (area under the curve [AUC]) of 70 to 90 ng/mL*h. Although a phase I study recommended a topotecan lactone AUC of 100 ng/mL*h as the systemic exposure to target in phase II studies,[19] the current study used a target AUC of 70 to 90 ng/mL*h based on early clinical experience showing significant toxicity in patients with recurrent Wilms' tumor at the higher systemic exposure (Dome, unpublished data). Subsequent cycles of topotecan were administered approximately 28 days after the beginning of the previous cycle once patients had achieved an ANC more than 1,000/μL and platelet count more than 50,000/μL. Patients received filgrastim 5 μg/kg/d subcutaneously 24 hours after the last dose of topotecan until the ANC exceeded 5,000/μL after the expected nadir. Trimethoprim-sulfamethoxazole for *Pneumocystis carinii* prophylaxis was withheld during the 2 weeks of topotecan administration.[21] Aerosolized pentamidine was used as an alternative prophylactic regimen.

Pharmacokinetically Guided Topotecan Dosing

Pharmacokinetically guided topotecan dosing was performed as previously described.[15,19] During the first and second cycle, plasma samples (2.5 mL) were obtained before infusion and at 5 minutes, 2 hours, and 3 hours after the end of topotecan infusion and processed immediately.[15,19] If the single-day topotecan lactone AUC was within target range after the first dose, then no dose adjustment and no further pharmacokinetic sampling was necessary for that cycle. If not, then the topotecan dosage was adjusted linearly based on the patient's topotecan lactone clearance to attain the target AUC, and repeat pharmacokinetic studies were performed until the patient's topotecan systemic exposure was within the target range. Up to three dose adjustments were permitted per cycle. Patients who required dose adjustments on cycle 2 also had pharmacokinetic studies performed in cycle 3. No pharmacokinetic studies were performed beyond the third cycle.

A two-compartment model was fit to the topotecan lactone plasma concentration using a maximum a posteriori Bayesian algorithm as implemented in ADAPT II (available at http://bmsr.usc.edu/Software/Adapt/adptmenu.html),[22] with published values (mean and variance) used as the Bayesian priors.[19] Model parameters estimated for each patient included the volume of the central compartment, elimination rate constant, and the intercompartment rate constants. These parameters were used to simulate the plasma concentration-time profile for each patient, from which the AUC from time zero to infinity was calculated. As in our previous studies, we used the following equation to adjust topotecan dosage: adjusted dosage (mg/m^2) = current topotecan dosage (mg/m^2)/current AUC $\times$ target AUC.[15,19]

Evaluations During Study

Baseline evaluations included a complete medical history and physical examination; computed tomography of the chest, abdomen, and pelvis; CBC count with differential; complete metabolic panel including electrolytes and liver and kidney function studies; urinalysis; and glomerular filtration rate determined either by a Tc99m-diethylene triamine pentaacetic acid renal/plasma clearance study or by a 24-hour urine collection for creatinine measurement. At the completion of two cycles of topotecan therapy, patients underwent diagnostic imaging of the primary and metastatic sites. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Response Criteria

Response to treatment was defined according to the Response Evaluation Criteria in Solid Tumors.[23] Diagnostic, end of the first cycle (when available), second cycle, and off therapy images were centrally reviewed by the study radiologist (F.A.H.) at St Jude. A measurable lesion was defined as a lesion whose longest diameter was greater than or equal to twice the computed tomography scan slice diameter. The longest diameter in the axial plane was recorded. All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total were defined as target lesions, measured, and recorded at baseline. At baseline, a sum of the longest diameter for all target lesions was calculated and reported. All other lesions were identified as nontarget lesions and were recorded at baseline without measurement. In the evaluation of target lesions, complete response was defined as the complete regression of all apparent tumor. A more than 30% decrease in the sum of the longest diameter of target lesions constituted a partial response (PR). A greater than 20% increase in the sum of the longest diameter represented progressive disease (PD), and stable disease (SD) was anything that did not qualify as either a PR or PD. In the evaluation of nontarget lesions, the disappearance of all nontarget lesions represented a complete response; incomplete response or SD was considered when one or more nontarget lesions persisted; and the appearance of any new lesion and/or unequivocal progression of existing nontarget lesions represented PD.

Statistical Considerations

This trial was designed to estimate the response rate after two cycles of topotecan in patients with FHWT. On the basis of a four-stage group sequential design[24] with a type I error rate of 10% and 90% power, 25 patients were needed to test whether the true response rate was less than 10%; a response rate of 30% was considered promising. The estimated response rate was presented with an exact binomial 95% CI. The rarity of AHWT precluded a formal statistical design for this group of patients.

Survival was defined as the time interval from date of study enrollment to date of death from any cause or to the last follow-up date. Event-free survival (EFS) was defined as the time interval from date of study enrollment to date of first event (relapsed or progressive disease or death from any cause) or to the last follow-up date. Survival and EFS were estimated using the Kaplan-Meier method. Fisher's exact test, the exact Wilcoxon rank sum test, and the exact Kruskal-Wallis test were used to compare characteristics between responders and nonresponders. Responders were defined as those patients who achieved at least a PR after two cycles of topotecan; nonresponders were patients who had either SD or PD after one or two cycles of topotecan.

RESULTS

Patient Characteristics

Between March 2003 and March 2006, 37 eligible patients were enrolled; 30 of the patients were enrolled at St Jude, and the other centers enrolled one or two patients each. Twenty-six patients (70%) had FHWT, and 11 patients (30%) had diffuse AHWT. Patient and treatment characteristics for all patients and for patients by histology

are listed in Table 1. Sixty percent of patients (n = 22) were female, and most patients (n = 30; 81%) were white. The median age at diagnosis of Wilms' tumor was 4.8 years, and the median age at enrollment onto the study was 6.1 years.

Study Withdrawals, Eligibility, and Assessability

Seven patients discontinued treatment before the end of the second topotecan cycle as a result of PD (three patients before completing the first cycle, three patients at the end of the first cycle, and one patient during the second cycle). One patient was removed from the study during the second cycle after suffering a stroke from a hemorrhage within a frontal lobe metastasis. This patient was not assessable for response because the CNS lesion could not be accurately measured after the hemorrhage and she did not complete two full topotecan cycles. In total, 22 patients with FHWT and seven patients with AHWT completed at least two cycles of topotecan (Table 2).

Topotecan Pharmacokinetics

The inter- and intrapatient variability in topotecan lactone clearance was assessed using the mixed-effects model, which allowed us to account for possible correlations between topotecan clearance and cycle with repeated measurements within each patient. The population average topotecan lactone systemic clearance was 20.7 L/h/m^2, with a range of 7.8 to 43.9 L/h/m^2. The estimated interpatient and intrapatient variances were 30.3% and 15.7%, respectively. This finding was consistent with several of our other studies in which interpatient variability in topotecan clearance exceeded intrapatient variability.[13,25] In the 37 children enrolled onto this study, we performed a total of 127 pharmacokinetic studies. The first pharmacokinetic study in each patient (n = 37) was performed after a fixed topotecan dosage (n = 9 at 2.4 mg/m^2 or n = 28 at 1.8 mg/m^2). All patients studied at the initial dosage of 2.4 mg/m^2 were above the topotecan target (range, 97 to 250 ng/mL*h), whereas when the initial dosage was reduced to 1.8 mg/m^2, 15 patients (54%) were within the target range on first dose. In subsequent studies using pharmacokinetically guided dosing, the overall pharmacokinetic targeting success rate was 70.2% (AUCs in 59 of 84 assessable studies were in the target range), although the target AUC was ultimately achieved in all cycles. The median topotecan dosage in the cycles in which the target AUC range was achieved was 1.8 mg/m^2 (range, 0.7 to 3.2 mg/m^2).

Table 1. Patient and Treatment Characteristics

Characteristic	All Patients (N = 37)		Favorable Histology Patients (n = 26)		Anaplastic Histology Patients (n = 11)	
	No.	%	No.	%	No.	%
Sex						
Male	15	40.5	10	38.5	5	45.5
Female	22	59.5	16	61.5	6	54.5
Race/ethnicity						
White	30	81.1	20	76.9	10	90.9
Black	3	8.1	3	11.5	0	0.0
Other	4	10.8	3	11.5	1	9.1
Age at initial diagnosis, years						
Median	4.8		4.3		4.9	
Range	0.4-14.7		0.4-14.7		3.9-7.2	
Age at study enrollment, years						
Median	6.1		6.6		5.8	
Range	1.3-19.0		1.3-19.0		4.7-7.9	
Sites of involvement at study enrollment*						
Local	6	16.2	3	11.5	3	27.3
Distant	19	51.4	14	53.9	5	45.4
Local + distant	12	32.4	9	34.6	3	27.3
Stage at initial diagnosis						
I	4	10.8	2	7.7	2	18.2
II	7	18.9	4	15.4	3	27.3
III	6	16.2	3	11.5	3	27.3
IV	12	32.4	12	46.2	0	0.0
V	8	21.6	5	19.2	3	27.3
Prior exposure to topotecan						
Yes	1	2.7	1	3.9	0	0
No	36	97.3	25	96.1	11	100
Previous ASCT						
Yes	4	10.8	4	15.4	0	0
No	33	89.2	22	84.6	11	0
No. of prior recurrences						
PD	11	29.7	7	26.9	4	36.4
1	18	48.7	11	42.3	7	63.6
2	8	21.6	8	30.8	0	0

Abbreviations: ASCT, autologous stem-cell transplantation; PD, progressive disease.
*Local indicates original tumor bed site; distant indicates outside the original tumor site.

Table 2. Patient Disposition

Patient Disposition	No. of Patients: Favorable Histology	No. of Patients: Anaplastic Histology
Patients enrolled	26	11
Patients withdrawing before the end of first cycle for PD	2	1
Patients treated with ≥ 1 cycle	24	10
Patients withdrawing after first cycle for PD	1	2
Patient withdrawing at the end of the first cycle for PD	0	1
Drug-related adverse event before end of second cycle	1	0
Patients treated with ≥ 2 cycles	22	7
Patients treated with ≥ 4 cycles	9	1

Abbreviation: PD, progressive disease.

Because this patient population was likely to have altered renal function and potentially decreased topotecan clearance (and elevated topotecan AUC values), one concern was that these patients would be overdosed. However, only 30 pharmacokinetic studies (24%) showed AUCs that were above the target range (ie, > 90 ng/mL*h), and only 19 (15%) showed AUCs that were more than 10% above the upper end of the target range. All of the AUCs in these patients were brought within the target with further pharmacokinetic studies. Conversely, only eight pharmacokinetic studies (6%) were more than 10% below the lower end of the target range (ie, < 60 ng/mL*h). Of these eight studies, three were with the initial fixed topotecan dosage, and the remaining five occurred after course 1, dose 2 (n = 1); course 2, dose 1 (n = 2); course 2, dose 3 (n = 1); and course 3, dose 1 (n = 1). In all eight studies, the topotecan target value was attained on subsequent pharmacokinetic studies.

Topotecan Response

Thirty-six of 37 patients were assessable for response (Table 3). The observed response rate for patients with FHWT (25 patients) was 48.0% (95% CI, 27.8% to 68.7%); 12 patients had PR, six patients had SD, and seven patients had PD. Among patients with AHWT, two patients had PR, one patient had SD, and eight patients had PD. The median duration of response was 158 days (range, 18 to 899 days). It was not feasible to measure the duration of response specifically to topotecan because most responders received additional treatment after discontinuing protocol therapy, including surgery, radiation therapy, and high-dose chemotherapy with autologous stem-cell rescue.

Table 3. Tumor Responses in Favorable and Anaplastic Histology Wilms' Tumor Patients

Response	No. of Patients: Favorable Histology (n = 26)	No. of Patients: Anaplastic Histology (n = 11)
Complete response	0	0
Partial response	12	2
Stable disease	6	1
Progressive disease	7	8
Not assessable*	1	0
Total response†		
No./total No.	12/25	2/11
%	48	18

*Patient was removed from study during the second cycle and before response assessment after suffering a stroke from a hemorrhage within a frontal lobe metastasis.
†Total response includes complete and partial responses.

Twelve (32%) of 37 patients were alive with a median follow-up time of 11.7 months (range, 1.9 to 37.7 months). Six of the survivors had no evidence of disease at last follow-up, and six were alive with disease. All survivors had been seen or contacted within 10 months of the analysis. Estimates of survival and EFS for all patients at 1 year were 29.5% ± 8.3% and 16.4% ± 6.1%, respectively.

Table 4 lists patient characteristics among responders and nonresponders for the 36 assessable patients. The only significant difference between responders versus nonresponders was a longer time from initial diagnosis to topotecan study therapy (median, 30.5 *v* 11.9 months, respectively) and a longer time from last treatment to study therapy (median, 3.2 *v* 1.3 months, respectively). We were not able to detect a relationship between topotecan systemic exposure and antitumor response (data not shown), given that we maintained a narrow range of systemic exposure values (AUC).

Topotecan Toxicity

Table 5 lists the most common grade 3 and 4 toxicities encountered in a total of 94 cycles of topotecan administered. The main toxicity was hematologic; all 37 patients had grade 3 or 4 toxicities. The median duration of grade 3 or 4 neutropenia was 13 days per episode (range, 2 to 31 days), and the median duration of grade 3 or 4 thrombocytopenia was 7.5 days (range, 1 to 40 days). There were 12 episodes of grade 3 bleeding/hemorrhage associated with thrombocytopenia, consisting mostly of skin bruises, nosebleeds, and mucosal bleeds. As described earlier, one patient had hemorrhage into a brain metastasis. There were 61 admissions for febrile neutropenia reported in 27 patients. Thirteen patients (35%) had a total of 18 episodes of documented infection (six catheter-related infections, two infections without neutropenia, and 10 episodes related to neutropenia). Renal toxicity consisted mainly of electrolyte imbalance partly attributable to the patients' underlying renal disease and previous therapy. One patient had a creatinine of 3.5 mg/dL at study entry and had PD that compromised the function of her sole remaining kidney, leading to grade 3 creatinine elevation. There were no toxic deaths.

DISCUSSION

This study demonstrates that topotecan has significant activity in children with FHWT when administered on a protracted schedule. The 48% response rate is especially promising given that the responses were observed in a population of heavily pretreated patients whose disease progressed after at least one salvage chemotherapy regimen. The response rate is comparable to response rates seen with other single agents that are commonly used for the treatment of Wilms' tumor including ifosfamide (20% to 50%),[26-28] etoposide (42%),[29] carboplatin (52%),[30] and doxorubicin (54%).[31] Among patients with AHWT, two responses were seen among 11 patients. Although the study was not statistically powered to assess response rate in patients

Table 4. Characteristics of Patients Assessable for Response to Topotecan

Characteristic	Responders* (n = 14)		Nonresponders (n = 22)		*P*
	No.	%	No.	%	
Sex					.99†
Male	6	43	9	41	
Female	8	57	13	59	
Race					.39†
White	10	71	19	86	
Nonwhite	4	29	3	14	
Age at initial diagnosis, years					.74‡
Median	4.8		4.4		
Range	0.4-13.0		0.9-14.7		
Histology					.142†
Favorable	12	86	13	59	
Anaplastic	2	14	9	41	
Stage at initial diagnosis					.99§‖
I/II	5	36	6	27	.44†¶
III/IV	5	36	12	54	
V	4	29	4	18	
Time from initial diagnosis to study treatment, months					.001‡
Median	30.5		11.9		
Range	7.4-193.1		5.1-34.0		
Time from last treatment to study treatment, months					.030‡
Median	3.2		1.3		
Range	0.8-19.4		0.4-13.7		
Ever had complete response before study					.142†
Yes	12	86	13	59	
No	2	14	9	41	
Sites of disease at study entry					.99†#
Local	2	14	4	18	.096‖**
Distant	5	36	14	64	
Local + distant	7	50	4	18	
Survival					
No. alive	7	50	5	23	—

*Responders are those who achieved partial response; nonresponders are those who had stable or progressive disease.
†*P* value derived from Fisher's exact test.
‡*P* value derived from the exact Wilcoxon rank sum test.
§Comparison of stages I/II *v* stages III/IV *v* stage V.
‖*P* value derived from the exact Kruskal-Wallis test.
¶Comparison of stages I/II *v* stages III/IV.
#Comparison of local only *v* distant/local + distant.
**Comparison of local *v* distant *v* local + distant as an ordered categorical variable.

with AHWT, the results suggest that topotecan has modest activity in this high-risk subgroup.

The results of the present trial differ from previous topotecan trials, which showed no responses in five patients with recurrent Wilms' tumor.[14,16,32] In contrast to the protracted schedule [(daily × 5) × 2] that we describe, topotecan was administered on a daily × 5 schedule (2 mg/m^2/d) or as a 72-hour continuous infusion (1.3 to 1.9 mg/m^2/d) in the earlier trials. It is possible that the higher cumulative topotecan dosage in the current trial improved the response rate. It is also possible that the protracted topotecan schedule was more active than the shorter schedules used in the previous studies. The selective cytotoxic action of the topoisomerase I poisons during S phase suggests that prolonged exposure to these drugs would maximize the number of cells susceptible to drug-induced death.[11,33]

Our study featured pharmacokinetically guided dosing of topotecan. The Wilms' tumor patient population was ideal for individualized topotecan therapy because the patients had only one kidney, and topotecan primarily undergoes renal elimination. The interpatient variance in topotecan lactone clearance was 30.2%, and a range of dosages (0.7 to 3.2 mg/m^2; median, 1.8 mg/m^2) was required to achieve the desired AUC. Despite this variability, only 15% of pharmacokinetic studies showed topotecan AUC values more than 10% above the upper end of the target range, and only 6% of studies showed AUC values more than 10% below the lower end of the target range. It would be helpful to have a reliable predictor of topotecan clearance (eg, serum creatinine or glomerular filtration rate), but no predictive relationship could be established (data not shown).

To guide future use of topotecan in patients with recurrent Wilms' tumor, we assessed predictors of topotecan response. The only significant differences between responders and nonresponders were the time from initial diagnosis to study therapy and the time from most recent treatment to study therapy. There are several potential mechanisms of resistance to topotecan, which can be inherent to the tumor or the host. Mutations in topoisomerase I,[34] decreased levels of

Table 5. Grade 3 and 4 Toxicities Observed During a Total of 94 Administered Cycles

Toxicity	Patients		No. of Episodes
	No.	%	
Hematologic	37	100	318
Anemia	36		98
Thrombocytopenia	37		101
Neutropenia	36		100
Renal	9	24	21
Electrolytes	9		19
Creatinine	1		2
GI	15	41	36
Diarrhea	4		4
Nausea/vomiting	12		14
Abdominal pain	5		7
Other*	6		11
Anorexia	9	24	9
Infection	13	35	18

*Other toxicities included colitis (three episodes), typhlitis (two episodes), ileus (one episode), mucositis/stomatitis (three episodes), elevated gamma-glutamic transferase (one episode), and not otherwise specified (one episode).

cellular topoisomerase,[35-37] and decreased cellular camptothecin accumulation[38] have all been described; however, studies of in vivo mechanisms of resistance were not performed, and further investigation is warranted in prospective trials.

In conclusion, topotecan is active against recurrent FHWT. Introduction of topotecan using this protracted schedule to front-line trials of high-risk recurrent Wilms' tumor should be considered.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A **Leadership:** N/A **Consultant:** Clinton F. Stewart, GlaxoSmithKline **Stock:** N/A **Honoraria:** N/A **Research Funds:** Clinton F. Stewart, Funds, GlaxoSmithKline; Jeffrey S. Dome, Funds, GlaxoSmithKline **Testimony:** N/A **Other:** N/A

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Acknowledgment

We thank Victor M. Santana, MD, for his insightful discussions and Debbie Poe for her outstanding data management.