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Phase I Trial of Two Schedules of Vincristine, Oral Irinotecan, and Temozolomide (VOIT) for Children with Relapsed or Refractory Solid Tumors: A Children's Oncology Group Phase I Consortium Study

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Abstract

Background—In pre-clinical models, temozolomide and vincristine are additive or synergistic with irinotecan. We examined this 3-drug combination in children with relapsed solid tumors. Patients received orally administered irinotecan together with temozolomide and vincristine on two different schedules, using cefixime to reduce irinotecan-associated diarrhea.

Methods—Oral irinotecan was given daily on days 1-5 and 8-12 (Schedule A), or on days 1-5 (Schedule B). Temozolomide was given on days 1-5, with vincristine 1.5 mg/m^2 administered on days 1 and 8 (Schedule A) or day 1 (Schedule B) in 21-day courses.

Results—On Schedule A, the maximum tolerated dose of oral irinotecan was 35 mg/m^2/day combined with temozolomide 100 mg/m^2/day and vincristine on days 1 and 8. Dose-limiting toxicities in 4 of 12 patients included hepatotoxicity, abdominal pain, anorexia, hypokalemia and thrombocytopenia at 50 mg/m^2/day. Using Schedule B, 0 of 6 patients experienced dose-limiting toxicity at the highest doses studied of oral irinotecan 90 mg/m^2/day, temozolomide 150 mg/m^2/day × 5, and vincristine on day 1. First-course and cumulative toxicity was greater with Schedule A. *UGT1A1*28* genotype did not correlate with dose-limiting toxicity. At the irinotecan dose of 90 mg/m^2/day, the mean SN-38 AUC_{inf} was 63 ng/ml*h. Activity was seen in sarcoma patients, and overall 8 patients received ≥ 6 courses.

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Conclusions—The 5-day schedule of VOIT was well tolerated and provided SN-38 exposures similar to those achieved with intravenous IRN. Activity on this and prior studies suggests a potential role for VOIT in a spectrum of childhood solid tumors.

Keywords

temozolomide; oral irinotecan; SN-38; vincristine; cefixime

Introduction

The use of non-cross-resistant chemotherapy combinations is the mainstay of treatment for pediatric solid tumors. Efforts are ongoing to identify additional novel combinations that are both synergistic and well tolerated in this patient population. In this regard, the camptothecin derivative irinotecan has generated interest, based on modest single-agent activity [1-3], minimal myelosuppression [4], and preclinical synergy seen when camptothecins are combined with vincristine [5] or temozolomide [6]. Clinical trials have confirmed the activity of the combination of vincristine + irinotecan for metastatic rhabdomyosarcoma [2], and of temozolomide + irinotecan for relapsed neuroblastoma [7,8] and Ewing sarcoma [9,10].

We hypothesized that the combination of vincristine, irinotecan and temozolomide would leverage potential synergistic interactions while remaining tolerable. Preclinical studies suggested irinotecan activity was greatest with protracted administration [11]. However, a recent randomized trial of patients with relapsed rhabdomyosarcoma found no advantage for irinotecan administered on a daily for 5 days every 2 week schedule (daily×5×2) versus a daily for 5 day for 1 week schedule (daily×5×1) [12]. We therefore amended the study reported here to investigate both the one-week and two-week schedules of irinotecan administration. Because intravenous administration of protracted irinotecan is both expensive and inconvenient, we chose to administer the irinotecan orally, as has been successfully piloted in previous pediatric trials [8,13]. In addition, we explored increasing temozolomide dose intensity when feasible. We now report the clinical and pharmacologic findings of our Phase I trial examining two different schedules of the VOIT combination in children with relapsed or refractory solid tumors.

Patients and Methods

Study Population

Patients older than 12 months and ≤ 21 years with solid tumors refractory to standard therapy and no other curative option were eligible. All patients had measurable or evaluable disease, and Karnofsky (age > 10 years) or Lansky (age ≤ 10 years) performance scores of ≥ 50. Required organ function included an absolute neutrophil count ≥ 1,000/μL, hemoglobin ≥ 8.0 gm/dL, transfusion-independent platelet count of ≥100,000/μL, glomerular filtration rate or creatinine clearance ≥ 70 ml/min/1.73 m^2 or normal serum creatinine for age, total bilirubin ≤ 1.5 × upper limit of normal, AST of ≤ 110 U/L (approximately 2.5 × upper limit of normal), and serum albumin ≥ 2 g/dL. Exclusion criteria included myelosuppressive chemotherapy within 3 weeks of enrollment, anticancer biologic therapy or hematopoietic growth factors within 7 days, local palliative radiotherapy within 2 weeks, craniospinal or extensive pelvic radiotherapy within 6 months, other substantial bone marrow radiotherapy within 6 weeks, known metastatic marrow disease, allergy to dacarbazine or cephalosporins, treatment with increasing doses of dexamethasone, treatment with agents known to affect irinotecan metabolism (e.g., enzyme-inducing anticonvulsants), uncontrolled infection, concurrent treatment for *C difficile* enteritis, or administration of other investigational or anticancer agents. Patients were also excluded if they had previous treatment with

temozolomide + irinotecan, or prior progression with either agent. The study was approved by the institutional review board of each institution from which patients were enrolled. Informed consent was obtained from the patient or their parent/guardian, and assent was obtained as appropriate before enrollment.

Drug Formulation and Administration

The injectable formulation of irinotecan was obtained commercially in 20 mg/ml vials. One course (either 5 or 10 doses) was drawn in individual oral syringes and dispensed with instructions to refrigerate until administration. Irinotecan was mixed with cranberry-grape juice immediately before administration to mask the bitter flavor [8,13]. Temozolomide was obtained commercially, and patients unable to swallow capsules were allowed to open them and mix with apple sauce or juice. Vincristine was administered intravenously over one minute at the set dose of 1.5 mg/m^2 (maximum 2 mg).

Previous studies suggest that prophylactic administration of cephalosporin antibiotics can ameliorate irinotecan-associated diarrhea by reducing the enteric bacteria responsible for producing beta-glucuronidase [14]. This enzyme effectively re-activates toxic metabolites in the gut by cleaving the glucuronide moiety from SN-38. Based on this experience, we administered oral cefixime once daily (Figure 1) at a dose of 8 mg/kg (maximum 400 mg). If cefixime was unavailable, cefpodoxime 5 mg/kg/day twice daily was substituted (maximum 200 mg bid). On days of co-administration, temozolomide was given at least one hour before vincristine and/or irinotecan.

Study Design

As shown in Figure 1, irinotecan daily×5×2 was studied first (Schedule A) followed by irinotecan daily×5×1 (Schedule B). Dose escalations were made using a traditional 3+3 design in which cohorts of 3-6 patients were studied per dose level. If 0/3 patients at a dose level experienced first-course dose-limiting toxicity (DLT), subsequent patients were enrolled on the next highest dose level. If 1 of 3 patients in a cohort experienced DLT, the cohort was expanded to include up to 6 patients, with the MTD defined as the highest dose in which no more than 1 of 6 patients experienced first-course DLT. In order to reduce the potentially confounding impact of non-dose related toxicities on final dose recommendation, if DLTs were of different classes, unrelated to dose based on prior studies of these agents, and readily reversible, then a cohort could be expanded up to 12 patients.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 3.0. Hematologic DLT was defined as: grade 4 neutropenia or thrombocytopenia > 7 days, grade 3-4 thrombocytopenia requiring platelet transfusion on > two occasions per course, or failure to recover blood counts to eligibility criteria resulting in a delay of ≥ 14 days between treatment courses. For patients enrolled on Schedule A, any grade 4 neutropenia or thrombocytopenia occurring before completion of irinotecan (Day 12) was also considered hematologic DLT. Non-hematologic DLT included any grade 3-4 toxicity excluding: grade 3 nausea, vomiting, or dehydration; grade 3 diarrhea lasting < 3 days or failure to receive cefixime and loperamide; grade 3 fever, febrile neutropenia, or infection; grade 3 AST/ALT elevation resolving to eligibility criteria prior to next course; grade 3 GGT; grade 3 electrolyte abnormalities that improve to ≤ grade 2 within 7 days with or without supplements; vincristine-related neuropathy in patients previously treated with vincristine; and alopecia. Additional courses were started every 21 days provided toxicity resolved to eligibility criteria and there was no disease progression. Patients not meeting eligibility criteria within 35 days from the start of a course were taken off protocol therapy.

Patient Evaluation

A history and physical examination were performed before study entry, weekly during the first course, and prior to starting each subsequent course. Complete blood counts were obtained twice weekly during the first course, and at least weekly thereafter. Blood chemistries were assessed weekly during the first course, and then prior to each additional course. Tumor response was evaluated after courses 2 and 4, and then after every subsequent 4 courses. Response Evaluation Criteria in Solid Tumors were used for non-CNS tumors [15], while responses of CNS tumors were evaluated using MacDonald criteria [16]. Two response determinations, separated by at least a three-week interval, were required to determine the patient's best overall response. Responding patients underwent central radiology review.

Pharmacokinetic Studies

After consent was obtained for optional studies, blood samples were collected before and at 0.17, 1, 3, 6 and 24 hours after the first dose of irinotecan. Plasma was isolated and stored at -80°C for batched analysis, which included assessment for irinotecan, the active metabolite SN-38, and the inactive metabolite APC using validated, sensitive and specific isocratic high-performance liquid chromatography (HPLC) methods [17]. SN-38G concentrations were determined in a separate portion of each plasma sample in which SN-38G was hydrolyzed to SN-38 by incubation with ß-glucuronidase. SN-38 concentrations determined following incubation of plasma with ß-glucuronidase were labeled as total SN-38 (i.e., sum of unconjugated SN-38 and conjugated SN-38). Plasma concentrations of SN-38G were estimated as the difference between the total SN-38 concentration and the SN-38 concentration. Irinotecan, SN-38 and SN-38G plasma concentration data were analyzed by non-compartmental methods [18]. The apparent terminal elimination rate constants (λ_z) were determined by linear least-squares regression through the 4 and 24 h plasma-concentration time points. The apparent elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Area under the plasma concentration-time curves ($AUC_{0\text{-}24h}$) was determined using the linear trapezoidal rule from time zero to the 24 h sample time. Area under the plasma concentration-time curves through infinite time ($AUC_{0\text{-}\infty}$) was calculated by adding C_T/λ_z to $AUC_{0\text{-}24h}$. The clearance of irinotecan was calculated as dose/$AUC_{0\text{-}\infty}$, where dose is the administered dose of irinotecan expressed in free base equivalents.

Pharmacogenetic Studies

After consent was obtained for optional studies, genomic DNA was extracted from blood samples using Gentra Autopure standard procedures (Qiagen Inc., Valencia, CA), and 100 ng of DNA was used for genotyping. The *UGT1A1*28* promoter polymorphism was genotyped by PCR amplification with fluorescently labeled primers specific for the region containing the polymorphism, followed by fragment size analysis using an ABI Prism 3730 DNA Analyzer. Genotypes were denoted as 5/6, 6/6, 6/7, or 7/7 depending on the number of TA repeats found in each allele. The genotype with six TA repeats has normal activity.

Results

Thirty-six of the 42 patients enrolled were fully evaluable for toxicity (Table I). Three toxicity inevaluable patients had disease progression during the first course, one withdrew consent prior to treatment, one was unable to take temozolomide, and one was removed for noncompliance. None of these six patients experienced DLT. A total of 55 courses (median 2, range 1-8) were administered to 18 patients on Schedule A, including 24 courses administered to 6 patients at the MTD. For Schedule B, 72 courses (median 3.5, range 1-16) were given to 18 patients, with 25 courses administered to 6 patients at the highest studied dose.

Toxicity

For Schedule A, only 1/6 patients experienced first-course DLT (hypoalbuminemia) at the starting irinotecan dose level of 35 mg/m^2/day (Table II). However, 4/12 patients treated at 50 mg/m^2/day experienced a spectrum of DLTs, including thrombocytopenia, anorexia, hepatotoxicity, hypokalemia, and abdominal pain. One of these patients had metastatic sarcoma in the porta hepatis and experienced fatal liver failure possibly attributable to protocol therapy (although infrequent, hepatic toxicity has been reported with irinotecan administration [19]). This patient had a baseline bilirubin of 0.4 mg/dl, a normal 6/6 *UGT1A1* genotype, and a modest SN-38 AUC of 36.5 ng/ml*h. The MTD for Schedule A was thus oral irinotecan 35 mg/m^2/day ×5×2 together with temozolomide 100 mg/m^2/day × 5 and vincristine 1.5 mg/m^2 on days 1 and 8.

The daily×5×1 schedule of irinotecan used in Schedule B resulted in less grade 3-4 toxicity. The starting oral irinotecan dose, 70 mg/m^2/day, was twice the MTD determined on Schedule A. Once this proved tolerable, patients received oral irinotecan 90 mg/m^2/day, with 1/6 patients having dose-limiting nausea and vomiting. As little myelosuppression was observed, temozolomide was then escalated to 125 and then 150 mg/m^2/day. DLT did not occur in 6 patients treated at the highest dose of oral irinotecan 90 mg/m^2/day and temozolomide 150 mg/m^2/day, with vincristine given on day 1.

Non-dose-limiting toxicities are summarized in Table III. Myelosuppression was readily manageable, with only 6 patients experiencing ≥ grade 3 infections and only one developing grade 4 thrombocytopenia. Two patients with dose-limiting neutropenia in later courses received filgrastim. With the use of cefixime prophylaxis, grade 3 diarrhea was seen in only 11% of all evaluable patients. There were no recognized complications attributed to cefixime prophylaxis. During later cycles, no patients required dose reduction for toxicity. Cumulative nausea, fatigue, weight loss, and dose-limiting neutropenia were reported with the daily×5×2 schedule, and these symptoms contributed to 4 patients with responding or stable disease stopping protocol therapy.

Pharmacokinetics

Irinotecan pharmacokinetics were characterized for 21 patients (Table IV). Peak concentrations were achieved within 3 hours and remained quantifiable at 24 hours for all dose levels. Although there was a high degree of inter-patient variability observed, the mean C_{max} and AUC of irinotecan and metabolites appeared to increase with dose. There was no clear relationship observed between SN-38 exposures and either dose-limiting toxicity or response. The AUC ratios estimating the relative extent of conversion (REC), glucuronidation (REG), and metabolism (REM) following oral administration of irinotecan are defined and reported in Table IV. Overall, mean values for REC, REG, and REM were 0.27 (range, 0.1 - 0.76), 1.91 (range, 0.39 - 6.33), and 0.66 (range, 0.28 to 1.64), respectively.

UGT1A1*28 Genotyping

Blood samples for *UGT1A1*28* genotyping were collected from 16 children treated on schedule A,15 on schedule B, and 2 who were not evaluable for toxicity (Table I). First-course DLT occurred in 5 of these 31 evaluable patients, but none with DLT had high-risk features defined *a priori* by the protocol as consisting of a genotype of 7/7, or a 6/7 genotype with a serum bilirubin level of ≥ 0.6 mg/dL. Five patients met this definition of high-risk, and none of these five experienced first-course DLT. Therefore, no association was seen between *UGT1A1*28* genotype and dose-limiting toxicity with either schedule.

Antitumor Activity

Thirteen (33 %) of 39 evaluable patients had evidence of either decreasing tumor size or stable disease through at least 4 courses (Table V). One patient with osteosarcoma treated at the MTD of Schedule A had a confirmed partial response before coming off study after 3 courses for toxicity. Two patients with Ewing sarcoma had responses evident on the initial response assessment scans, but did not have further follow-up imaging performed. The first of these patients had complete resolution of a 2 cm lung metastasis before withdrawing due to transaminitis. The second patient had a partial response of biopsy-proven lung metastases, but was taken off study due to the development of new lung nodules after course 2. These new nodules were subsequently biopsied and demonstrated to be fungal disease. Ten patients had stable disease on at least two serial scans, and eight patients received ≥ 6 courses, including two each with medulloblastoma and neuroblastoma.

Discussion

This phase I trial provides a comparison of the toxicities and drug exposures seen in children receiving different schedules of oral irinotecan, vincristine and temozolomide. Although preclinical data suggested the d×5×2 schedule of irinotecan is superior, randomized trials of children with rhabdomyosarcoma [12] and adults with colon cancer [20] have not demonstrated advantages for more protracted administration of irinotecan compared to shorter schedules. In our trial, the longer d×5×2 schedule was associated with a higher frequency of DLT both during the first course and during subsequent courses. In fact, all 5 patients withdrawing after course 1 for toxicity were treated on Schedule A. This degree of first-course and cumulative toxicity was not seen in a previous pediatric trial of oral irinotecan and temozolomide, in which the irinotecan MTD was 60 mg/m^2/day×5×2 together with temozolomide 75 mg/m^2/day ×5 [8]. It is unclear whether these differences are due to the populations studied (children with relapsed neuroblastoma vs. predominantly other pediatric solid tumors), the inherent variability in studying small cohorts of children with relapsed cancer, or other reasons.

In contrast to the d×5×2 schedule, patients receiving the shorter Regimen B experienced less toxicity, which allowed for greater dose intensity of both irinotecan and temozolomide. The importance of achieving maximum dose intensity for irinotecan, however, has not been well studied, and objective responses at doses below irinotecan's single-agent MTD have been observed [8-10]. For schedule B, considering that the daily oral irinotecan dose of 90 mg/m^2 exceeded the previously reported single-agent MTD [21-23], that SN-38 exposures comparable to other studies were achieved at this dose, and that temozolomide doses > 150 mg/m^2/day were unlikely to be tolerable in 3-week courses, no further dose escalations were attempted.

Consistent with prior studies, SN-38 exposures in our patients generally increased with dose, suggesting no saturation in conversion from oral irinotecan. Although higher doses of irinotecan are required when administering the drug orally to overcome its limited bioavailability, oral administration appears to result in more efficient conversion to SN-38, and exposures achieved were within the general range previously reported with oral irinotecan [8,13,21] and with protracted intravenous irinotecan [3,4,24] when accounting for the typically wide interpatient variability. For example, in a pediatric Phase II trial of single-agent intravenous irinotecan given on a d×5 schedule, the mean (± SD) $AUC_{0-\infty}$ (ng·h/mL) for 79 patients was 84±67 ng·h/mL [3]. This overlaps with the range of exposures seen in our 7 tested patients (median 63, range 15-113). The relative extent of conversion for oral irinotecan dosing was about 5-fold higher than that following intravenous administration, a finding comparable to that observed in adult patients [21]. Two patients with the highest SN-38 exposures experienced significant toxicity at the dose of 50 mg/m^2/day, but we were

unable to demonstrate a clear correlation between exposure and toxicity in this small study. Previous trials have suggested that neither vincristine nor temozolomide affect the pharmacokinetics of irinotecan [2,25], and the similar drug exposures achieved on our study would support those observations.

As predicted by single-agent and combination studies with these agents [1,2,7-10,26,27], we observed responses or prolonged stable disease in patients with sarcoma, neuroblastoma, and medulloblastoma (Table V). While objective responses were observed on schedule A, one-third of evaluable patients treated on schedule B had stable disease for a median of 8 courses (range 4-16). As this trial was designed to estimate maximum tolerated doses and describe toxicities, no formal comparison of the relative efficacy of these schedules can be made.

Hepatic metabolism of the active metabolite SN-38 is under the control of UGT1A1, which detoxifies the compound through the process of glucuronidation. Previous studies in adults receiving single large doses of irinotecan once every 1-3 weeks had correlated increased irinotecan toxicity with specific *UGT1A1* genotypes and to a lesser extent serum bilirubin level [28]. However, in our study the combination of *UGT1A1* genotyping and bilirubin measurement at enrollment failed to prospectively identify patients at highest risk for developing first-course toxicity, despite a previous adult Phase I trial showing differences in the MTD of an irinotecan-containing regimen when stratifying for genotype [29]. Our findings are consistent with earlier reports showing no association between *UGT1A1* genotype and severe irinotecan toxicity when protracted schedules are used [3,8,30], suggesting factors other than *UGT1A1*28* genotype may be responsible.

In summary, the daily×5×1 schedule of the VOIT combination was well tolerated and resulted in greater dose intensity of irinotecan and temozolomide than the daily×5×2 schedule. Given the similar activity and toxicity seen in relapsed rhabdomyosarcoma patients receiving irinotecan over one vs. two weeks [12], it is likely this shorter schedule will be employed in future trials. Oral administration was feasible and yielded SN-38 exposures similar to those seen following intravenous administration. The improved convenience and lower costs associated with oral administration makes this an attractive option for salvage therapy, and for additional clinical studies in relevant tumor types. The recommended phase 2 dose for this combination is vincristine 1.5 mg/m^2 × 1 day, oral irinotecan 90 mg/m^2/d × 5 days and temozolomide 150 mg/m^2/d × 5 days repeated every 3 weeks. This 3-drug combination may be well suited for further investigation in the treatment of a spectrum of pediatric solid tumors, and given its tolerability in this heavily pre-treated population may also lend itself to studies in combination with targeted therapies.

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Figure 1.
Treatment Schema for Schedules A and B.

Table I
Patient Characteristics (N=42 eligible patients)

	Number
Age, years	
Median (range)	9.7 (1-21)
Sex (male/female)	23/19
Race	
White	32 (76%)
African-American	4 (9%)
Asian	1 (2%)
American Indian/Alaskan Native	1 (2%)
Unknown	4 (10%)
Diagnosis	
Sarcoma	
Ewing sarcoma	5 (12%)
Osteosarcoma	3 (7%)
Rhabdomyosarcoma	6 (14%)
Synovial sarcoma	2 (5%)
Spindle cell sarcoma	1 (2%)
Undifferentiated sarcoma	1 (2%)
Alveolar soft parts sarcoma	1 (2%)
Neuroblastoma	2 (5%)
Hepatolastoma	3 (7%)
Wilms tumor	2 (5%)
Brain tumor	
Ependymoma	6 (14%)
Medulloblastoma	2 (5%)
Malignant glioma	4 (10%)
Fibrillary astrocytoma	1 (2%)
Atypical teratoid rhabdoid tumor	1 (2%)
Paraganglioma	1 (2%)
Pleuropulmonary blastoma	1 (2%)
Prior therapy	
Chemotherapy regimens	
Median (range)	2 (0-8)
Prior radiotherapy	28 (67%)
Baseline serum bilirubin level	
< 0.6 mg/dL	30 (71%)

	Number
≥ 0.6 mg/dL	10 (24%)
Not performed	2 (5%)
UGT1A1 genotype	
5/6	1 (2%)
6/6	13 (31%)
6/7	16 (38%)
7/7	3 (7%)
Not performed	9 (22%)

Table II

Summary of First-Course Dose-Limiting Toxicities

Schedule	Oral irinotecan*	Temozolomide*	Vincristine*	Patients Entered	Evaluable Patients	Patients with first-course DLT	Type of DLT(n)
A	35	100	1.5 × 2	8	6	1	Hypoalbuminemia
A	50	100	1.5 × 2	13	12	4	Platelets(1) Anorexia(1) ALT, SGPT(1) Hypokalemia(1) Abdominal pain (1) Hepatic failure (1)
B	70	100	1.5	3	3	0	
B	90	100	1.5	7	6	1	Nausea(1), Vomiting(1)
B	90	125	1.5	4	3	0	
B	90	150	1.5	7	6	0	

*doses in mg/m^2/day

Table III

Summary of non-dose-limiting toxicities observed in evaluable patients

Schedule A								
Toxicity Type	**Course 1 (total, 18 courses)**				**Courses 2 to 8 (total, 37 courses)**			
	Maximum grade across course 1				**Maximum grade across courses 2 to 8**			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	4	3			2	3	1	
Leukocytes	5	3	2		2	3	3	1
Lymphopenia	1	2	3	2	1		3	2
Neutrophils/granulocytes	3	2	4		2		2	5
Platelets	4			1	2	1	1	
Fatigue	4	1			2	1	1	
Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 × 10e9/L)	1	1			1			
Weight loss	1	3					2	
Anorexia		1	1			2	1	
Constipation	1	1			1	1		
Diarrhea	4	4	2		2	3	1	
Nausea	5	2			1	2	1	
Vomiting	3	3			2	2		
Hypoalbuminemia		2	1			1		
Alkaline phosphatase	1		1		1			
ALT, SGPT	6	1	1	1	3	2	1	
AST, SGOT	3			1	4	2		
Hypocalcemia	2		1		1			
Hypermagnesemia	2							
Hypophosphatemia	1	1					1	
Hypokalemia	1			1	2			
Hyponatremia	2				2			
Abdominal pain	2	2	1		2		1	
Joint pain	2	1				1		

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Schedule B								
Toxicity Type	Course 1 (total, 18 courses)				Courses 2 to 8 (total, 54 courses)			
	Maximum grade of toxicity Course				Maximum grade of toxicity Course			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	7	2			3	3		
Leukocytes (total WBC)	9	3			4	2		
Lymphopenia	3	6			3	1	2	
Neutrophils/granulocytes (ANC/AGC)	1	2	3			2	2	
Platelets	5				5	1		
Fatigue	3	1			2			
Anorexia		2						
Constipation	3	1			1			
Diarrhea	3	4	1		1	4		
Nausea	3				2	2		
Vomiting	1	2	2		3	2	2	
Alkaline phosphatase	1	1			2			
ALT, SGPT	3	1	1		2	1		
AST, SGOT	3	1			4			
Hyperbilirubinemia	3							
Hypophosphatemia	2					1		
Hypokalemia	2				3			
Hyponatremia	1		1		4			
Abdominal Pain	3	1			1			
Jaw Pain	1	1						

Table IV

Summary of pharmacokinetic data, with comparison to intravenous dosing from previous study

Dose (mg/m^2/day)		35	50	70	90	50*
N		2	9	3	7	79
Irinotecan	Cmax (ng/mL)	16.7, 38.4	17.6 (4.3-40.5)	36.6 (17.2-58.6)	60.6 (29.1-92.9)	726 (482)
	Tmax (h)	1.0	2.0 (1.0-6.0)	1.0 (0.9-1.0)	2.6 (1.0-6.1)	NR
	$AUC_{0-\infty}$ (ng·h/mL)	133	200 (28.3-466)[a]	149 (74.5-233)	340 (138-648)	2,626 (1,443)
	$t_{1/2}$ (h)	1.64	6.7 (1.8-21.2)[a]	1.8 (1.7-2.0)	2.3 (1.3-3.8)	4.7 (2.3)
SN-38	Cmax (ng/mL)	2, 8.4	3.1 (0.9-8.7)	4.2 (2.8-5.1)	6.6 (2.9-12.3)	13 (5.8)
	Tmax (h)	1.05, 3	2.8 (1.0-6.0)	3.0 (2.9-3.0)	2.6 (1.0-6.1)	NR
	$AUC_{0-\infty}$ (ng·h/mL)	26.8	50.4 (8.8-131)[b]	56.3 (33.4-79.1)	63.0 (15.4-113)	84 (67)
	$t_{1/2}$ (h)	2.1	7.7 (2.1-27.2)[b]	11.1 (6.7-16.3)	8.2 (1.6-21.7)	7.6 (11)
SN-38G	Cmax (ng/mL)	4.6, 9.9	6.0 (1.3-15.0)	6.5 (1.6-9.9)	11.7 (4.1-16.7)	29 (15)
	Tmax (h)	2.9, 3	3.9 (1.0-6.0)	2.3 (1.0-3.0)	2.6 (1.0-6.1)	NR
	$AUC_{0-\infty}$ (ng·h/mL)	49.1, 93.4	58.4 (5.2-178)[c]	77.9 (21.8-156)	127 (19.1-213)	269 (178)
	$t_{1/2}$ (h)	1.9, 11.9	4.3 (2.0-7.7)[c]	12.1 (9.6-14.3)	7.0 (1.8-13.3)	12.6 (21)
APC	Cmax (ng/mL)	8.7, 22.7	7.1 (1.1-15.1)	13.1 (8.0-16.7)	19.7 (6.7-33.2)	58 (51)
	Tmax (h)	2.9, 3.0	3.7 (1.0-6.0)	2.3 (1.0-3.0)	3.2 (1.1-6.1)	NR
	$AUC_{0-\infty}$ (ng·h/mL)	114, 218	64.5 (8.0-166)[a]	117 (72.5-161)	179 (50.5-321)	511 (500)
	$t_{1/2}$ (h)	4.6, 5.6	3.6 (1.6-5.3)[a]	4.3 (3.1-5.5)	3.6 (2.5-4.7)	4.6 (2)
AUC Ratios	REC (SN-38/irinotecan)	0.20	0.26 (0.17-0.30)[c]	0.44 (0.24-0.76)	0.20 (0.10-0.50)[c]	0.05 (0.01-0.25)
	REG (SN-38G/SN-38)	1.83	1.49 (0.59-2.51)[c]	1.35 (0.39-1.96)	2.52 (1.12-6.33)	2.24 (0.39-9.6)
	REM (APC/irinotecan)	1.64	0.47 (0.28-0.61)[c]	0.83 (0.69-0.97)	0.59 (0.29-0.86)[c]	0.15 (0.02-0.71)

*Phase II trial of single-agent intravenous irinotecan administered at 50 mg/m^2/day × 5, with standard deviation in parentheses [reference 3]. Values listed are mean values with ranges in parentheses. Individual PK parameters are listed if N<3.

a) N=7;

b) N=8;

[c] N=6.

REC, relative extent of conversion; REG, relative extent of glucuronidation; REM, relative extent of metabolism; NR, not reported.

Table V

Details for Patients with Response or Prolonged Stable Disease

Tumor type	Schedule	Irinotecan Dose	Temozolomide Dose	No. Courses	Imaging Response	Response Confirmed	Reason for Coming off Study
Osteosarcoma	A	35	100	3	PR	Yes	Weight loss, nausea, infection
Ewing sarcoma	A	50	100	2	CR	No	Transaminitis
Ewing sarcoma	A	35	100	2	PR	No	New lung lesions, (later proven fungal)
Ewing sarcoma	A	35	100	8	SD	Yes	PD
Medulloblastoma	A	35	100	7	SD	Yes	Infection
Neuroblastoma	A	50	100	6	SD	Yes	Weight loss
Hepatoblastoma	A	50	100	4	SD	Yes	PD
Alveolar soft parts sarcoma	B	70	100	6	SD	Yes	PD
Synovial sarcoma	B	90	100	4	SD	Yes	PD
Pleuropulmonary blastoma	B	90	125	16	SD	Yes	Off for other therapy
Neuroblastoma	B	90	125	8	SD	Yes	PD
Medulloblastoma	B	90	150	12	SD	Yes	PD
Brainstem glioma	B	90	150	8	SD	Yes	PD

PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease

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