Original Article

Phase 1 Study of Oxaliplatin and Irinotecan in Pediatric Patients With Refractory Solid Tumors

A Children's Oncology Group Study

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BACKGROUND: For this report, the authors estimated the maximum tolerated dose (MTD) and investigated the toxicities of oxaliplatin combined with irinotecan in children with refractory solid tumors. **METHODS:** Oxaliplatin was administered on Days 1 and 8 in combination with irinotecan on Days 1 through 5 and Days 8 through 12 of a 21-day cycle. An oral cephalosporin was administered daily to ameliorate irinotecan-associated diarrhea. Pharmacokinetic studies of oxaliplatin and uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) genotyping were performed. **RESULTS:** Thirteen patients were enrolled. Dose-limiting diarrhea (n = 3), serum lipase elevation (n = 3), serum amylase elevation (n = 2), colitis, abdominal pain, and headache (n = 1 each) occurred at the first dose level (oxaliplatin at a dose of 60 mg/m^2; irinotecan at a dose of 20 mg/m^2). Only 1 of 7 patients who received reduced doses of both agents (40 mg/m^2/dose oxaliplatin; 15 mg/m^2/dose irinotecan) experienced a dose-limiting toxicity (DLT): diarrhea. When the oxaliplatin dose was re-escalated (60 mg/m^2) with irinotecan at a dose of 15 mg/m^2, 2 of 3 patients had a DLT (1 episode of diarrhea, 1 episode of hypokalemia). Myelosuppression was minimal. One patient had a complete response, and another patient had stable disease for 6 cycles of therapy. The median oxaliplatin area under the concentration versus time curve ($AUC_{0\rightarrow\infty}$) was 5.9 μg · hour/mL (range, 1.8-7.6 μg · hour/mL). The frequency of the 6/6, 6/7, and 7/7 *UGT1A1* promoter genotypes was 5 of 10, 4 of 10, and 1 of 10, respectively. **CONCLUSIONS:** The oxaliplatin MTD was 40 mg/m^2 per dose on Days 1 and 8 in combination with irinotecan 15 mg/m^2 per dose on Days 1-5 and Days 8-12. There was some evidence of antitumor activity; however, severe toxicity, both expected (diarrhea) and unexpected (elevation in pancreatic enzymes), was observed. **Cancer 2009;115:1765–75. © 2009 American Cancer Society.**

KEY WORDS: child, adolescent, phase 1 clinical trial, oxaliplatin, irinotecan.

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On the basis of observations of additive or synergistic antitumor activity in preclinical models,[1-3] the combination of a platinating agent with a topoisomerase I poison has been of interest in treating pediatric tumors.[4-6] A limited number of responses to the combination of cisplatin[6] or carboplatin[5] plus topotecan have been observed in children with rhabdomyosarcoma, Ewing sarcoma, hepatoblastoma, and ependymoma. Unfortunately, myelotoxicity limited further development of these platinum analogs in combination with topoisomerase I inhibitors.

Oxaliplatin or *trans*-l-1,2-diaminocyclohexane (DACH) oxalatoplatinum, is a novel platinum agent more potent than cisplatin in vitro[7-11] that has demonstrated efficacy in preclinical and clinical studies against a spectrum of tumors, including tumors that are cisplatin resistant.[8-14] DNA adducts formed by oxaliplatin are bulkier and, thus, more effectively inhibit DNA synthesis than those formed by cisplatin and carboplatin.[15,16] Cisplatin-resistant cell lines may be sensitive to oxaliplatin because the loss of mismatch repair contributes to cisplatin resistance, but not oxaliplatin resistance, and replicative bypass of DNA adducts contributes more significantly to cisplatin resistance than to oxaliplatin resistance.[17]

Irinotecan, a potent inhibitor of topoisomerase I, has antitumor activity in recurrent[18-20] and newly diagnosed[21] rhabdomyosarcoma, neuroblastoma,[20,22,23] pediatric brain tumors,[24,25] non-Hodgkin lymphoma,[18] and hepatoblastoma.[22] In preclinical xenograft models of various childhood tumors, a protracted schedule of irinotecan administration has been associated with better disease responses.[20,26,27] A variety of schedules has been used in phase 1 studies of irinotecan in children. A protracted dosing schedule of intravenous irinotecan administered to children with refractory solid tumors daily for 5 days of 2 consecutive weeks every 3 weeks ([every day $\times$ 5] $\times$ 2) produced 1 of the better reported objective response rates.[20] The predominant reported toxicity associated with this protracted schedule of irinotecan has been diarrhea with minimal dose-limiting myelosuppression.[18,20] Irinotecan has been administered to children with rhabdomyosarcoma in several studies. At a dose of 20 mg/m^2 daily administered ([every day $\times$ 5] $\times$ 2), 8 of 19 patients (42%) with newly diagnosed rhabdomyosarcoma had a partial response,[21] whereas 3 of 4 patients (75%) with recurrent rhabdomyosarcoma demonstrated a complete or partial response.[18] In contrast, in patients with recurrent rhabdomyosarcoma, only 4 of 35 patients (11%) had an objective response to 600 mg/m^2 per dose of irinotecan administered every 3 weeks,[19] and 1 of 18 patients (5.6%) had an objective response to 50 mg/m^2 daily for 5 days.[28] These clinical results supported the preclinical studies indicating that irinotecan may be more effective when administered on a protracted schedule in childhood malignancies.

The combination of oxaliplatin and irinotecan has additive or synergistic effects in colon carcinoma cell lines and xenografts.[1,29] In adult colorectal carcinoma trials that used dosing schedules from weekly to once every 2 to 3 weeks, the combination was tolerable and effective.[30-34] Pharmacokinetic studies from 2 adult trials of the combination indicated that there were no significant alterations in the pharmacokinetics of either drug.[32,35] The major toxicities included diarrhea, myelosuppression, and peripheral sensory neuropathy.

Herein, we report the results of a pediatric phase 1 trial of the combination of irinotecan and oxaliplatin. The irinotecan schedule of ([every day $\times$ 5] $\times$ 2) was selected because of its promising activity noted in preclinical and early clinical trials. To maximize simultaneous drug exposure, thereby potentially increasing synergy, and because weekly oxaliplatin was tolerable in pediatric patients,[36] oxaliplatin was administered at the start of each week of irinotecan. Because the pharmacokinetics of irinotecan are well described in the pediatric population,[20,23,28,37-41] and there is no evidence of a pharmacokinetic interaction when oxaliplatin is administered with irinotecan,[32,33,42,43] only oxaliplatin pharmacokinetic studies were obtained during this trial. Because the uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1*28 (*UGT1A1*28*) genotype is associated with increased irinotecan-associated toxicity in adults receiving irinotecan every 3 weeks,[44] *UGT1A1* promoter genotyping was performed.

MATERIALS AND METHODS

Patient Eligibility

Patients ages 1 to 22 years with a histologically verified solid tumor that was refractory to conventional therapy, a

weight >10 kg, and a Karnofsky or Lansky score ≥50% were eligible. Patients must have recovered from the acute toxic effects of prior therapy with no evidence of active graft versus host disease and could not have received 1) myelosuppressive therapy within 3 weeks (nitrosourea within 6 weeks); 2) hematopoietic growth factors or biologic (antineoplastic) agents within 1 week; 3) small-port palliative radiation therapy within 2 weeks; 4) total body, craniospinal, whole spinal, whole lung/abdomen, or >50% pelvic radiation within 6 months; 5) other substantial bone marrow radiation within 6 weeks; and 6) stem cell transplantation within 3 months. No previous oxaliplatin exposure was allowed. Organ function requirements included 1) bone marrow (peripheral absolute neutrophil count ≥1000/μL, platelet count ≥100,000/μL [transfusion independent], and hemoglobin ≥8 g/dL); 1) renal (normal serum creatinine for age or a glomerular filtration rate ≥70 mL/minute/1.73 m^2 and grade ≤1 serum electrolyte abnormalities [supplementation allowed]); 3) liver (grade ≤1 hyperbilirubinemia, grade ≤2 hypoalbuminemia, and grade ≤2 elevation in alanine transferase levels); 4) cardiac (no arrhythmia on electrocardiogram); and 5) pulmonary (no dyspnea at rest, no exercise intolerance, no radiographic evidence of pulmonary fibrosis, and pulse oximetry >94% on room air if the patient had a history of pulmonary abnormalities). Pregnant or breastfeeding patients were excluded. Patients of reproductive age had to agree to use an effective contraceptive method. Patients who were receiving other investigational or anticancer agents or drugs that interact with cytochrome P450, family 3 subfamily A (CYP3A) (phenytoin, carbamazepine, oxcarbazepine, barbiturates, rifampicin, phenobarbital, azole antifungal agents, aprepitant, and St. John wort) were excluded. Patients who were on corticosteroids had to receive a stable or decreasing dose for ≥7 days before enrollment. Other exclusions included 1) uncontrolled infection, 2) inability to comply with protocol monitoring, 3) life-threatening allergy to protocol-required agents, 4) grade >1 peripheral neuropathy, and 5) inability to tolerate enteral medications. After the observation of dose-limiting elevations in serum lipase and amylase in the first patient cohort, the study was amended to exclude patients with grade >1 elevation in serum amylase or lipase.

Informed consent was obtained from patients, parents, or legal guardians, and assent as appropriate. The protocol was approved by institutional review boards of participating institutions.

Drug Administration and Study Design

Oxaliplatin (Eloxatin; Sanofi-Aventis, Bridgewater, NJ) was supplied by the Cancer Therapy Evaluation Program (National Cancer Institute [NCI], Bethesda, Md). The drug was reconstituted in water with 5% dextrose and infused intravenously over 2 hours after administering an antiemetic. The infusion duration was increased to 6 hours in patients who experienced pharyngolaryngeal dysesthesia.

Irinotecan (Camptosar; Pfizer, New York, NY) was obtained from commercial suppliers, diluted in water with 5% dextrose, and infused intravenously over 1 hour. Oral cefixime (8 mg/kg daily; maximum dose. 400 mg) or cefpodoxime (10 mg/kg daily; maximum dose, 400 mg daily divided twice daily) was administered for 21 days starting on Day 1 of each course to decrease irinotecan-associated diarrhea.[45] Guidelines were provided for treating acute irinotecan-associated diarrhea with atropine and for treating late diarrhea with loperamide.

The starting dose for oxaliplatin was 60 mg/m^2 per dose on Days 1 and 8 and, for irinotecan, the starting dose was 20 mg/m^2 per dose on Days 1 through 5 and Days 8 through 12 of a 21-day cycle with planned escalation of oxaliplatin to 85 mg/m^2 per dose. Because all patients in the first cohort experienced dose-limiting toxicity (DLT), the next cohort received reduced doses of both irinotecan (15 mg/m^2 per dose) and oxaliplatin (40 mg/m^2 per dose). Then, oxaliplatin was escalated as described above while the irinotecan dose remained 15 mg/m^2. Irinotecan was administered immediately after oxaliplatin on Days 1 and 8. Intrapatient dose escalation was not allowed. Up to 17 courses of therapy were allowed in the absence of disease progression if adequate organ function was maintained.

At least 3 evaluable patients were treated at each dose level. If 1 of 3 patients at a given level experienced a DLT, then 3 more patients were accrued at that level. If ≥2 patients experienced DLT, then the maximum tolerated dose (MTD) was exceeded, and 3 more patients were treated at the next lower dose level. The MTD was the dose level at which ≤1 patient experienced a DLT with

≥2 of 3 to 6 patients experiencing a DLT at the next higher level.

Patient Evaluation

Patient histories and physical examinations were obtained before enrollment, weekly during Course 1 of therapy, and before each subsequent course. Routine complete blood counts, serum electrolytes, renal and liver function tests, and pregnancy tests (if applicable) were obtained. Serum amylase and lipase were monitored after the first cohort.

Adverse events were assessed using the NCI Common Terminology Criteria for Adverse Events, version 3.0.[46] Nonhematologic DLT was defined as any grade 3 or 4 nonhematologic toxicity attributable to the investigational drug, with the exclusion of 1) grade 3 nausea, vomiting, dehydration, or anorexia that required <7 days of intravenous fluids, tube feedings, or total parenteral nutrition; 2) grade 3 liver enzyme elevation that returned to baseline before the next course; 3) grade 3 fever or infection; 4) grade 3 electrolyte abnormality; 5) grade 3 diarrhea that persisted for <24 hours; and 6) grade 3 diarrhea without protocol-defined supportive care (cefixime, loperamide, and atropine). Grade 2 peripheral neurotoxicity that persisted to Day 21 of Course 1 was defined as a DLT. Hematologic DLT was defined as grade 4 neutropenia or thrombocytopenia that lasted for >7 days or myelosuppression that caused a delay >14 days between treatment courses. Patients with bone marrow involvement by tumor were not evaluable for hematologic DLT.

Patients underwent disease-appropriate evaluations within 2 weeks before study entry, after Course 1 of therapy, and every other course thereafter. If a patient had a documented response, then studies were repeated after the next consecutive course. Tumor response was assessed by using the Response Evaluation Criteria in Solid Tumors.[47]

Oxaliplatin Pharmacokinetic Studies

In consenting patients, blood samples (5 mL) were collected before oxaliplatin infusion on Day 8 of Course 1 and then 3 hours, 4 hours, and 48 hours postinfusion. An additional level was drawn before the next oxaliplatin infusion on Day 1 of Course 2 (≈336 hours postinfusion). Samples were processed as described previously,[48] and the plasma ultrafiltrate (PUF) platinum (Pt) concentration was measured by inductively coupled plasma mass spectrometry at ABC Laboratories (Columbia, Mo). The lower limit of quantitation was 1 ng/mL; within-run and between-run precision (*CV*%) was <10%.

Pharmacokinetic analyses were performed by nonlinear mixed effects modeling with S-ADAPT,[49] and data were described by a 2-compartment pharmacokinetic model with first-order elimination. The model parameters that we estimated were the elimination rate constant (k_e), volume of distribution of the central compartment (V), and intercompartmental rate constants (k_{12}, k_{21}). We assumed that parameter distribution was log normal; thus, intersubject (IIV) was modeled using an exponential error model (Eq. 1):

$$\theta_i = \theta_{pop} e^{\eta_i} \quad (1)$$

in which θ_i is the estimated pharmacokinetic parameter for the ith individual, θ_{pop} is the population parameter estimate, and η_i is the individual deviation of θ_i from the population estimate. Intraindividual variability or residual error was evaluated by a mixed proportional and additive error model (Eq. 2):

$$\mathrm{Cp}_{ik} = \hat{\mathrm{C}}\mathrm{p}_{ik}(1 + \varepsilon_{ik}^{rel}) + \varepsilon_{ik}^{abs} \quad (2)$$

in which Cp_{ik} and $\hat{\mathrm{C}}\mathrm{p}_{ik}$ represent the kth actual and predicted PUF Pt concentrations, respectively, in individual i. The error terms ε^{rel} and ε^{abs} are components of the proportional (relative error) and additive error (absolute error), respectively. We assumed that all error model parameters were distributed normally. Residual error components were obtained in terms of standard deviation. The area under the concentration versus time curve ($AUC_{0\rightarrow\infty}$) was calculated with the simulated concentrations obtained by the empirical Bayesian estimates parameters using ADAPT II.

Pharmacogenetic Studies

In consenting patients, a 5-mL sample of whole blood that was collected before drug administration was shipped on ice to the reference laboratory at St. Jude Children's Research Hospital. Genomic DNA (10 ng) extracted from peripheral blood mononuclear cells was used to genotype the *UGT1A1*28* promoter by polymerase chain reaction amplification followed by fragment size analysis as described previously.[50]

RESULTS

From April 2005 to February 2006, 14 patients were enrolled. One patient had grade 3 neutropenia before the first dose of therapy and, thus, was ineligible. Table 1 summarizes the characteristics of the 13 eligible patients who received 27 courses of therapy (median, 2 courses; range, 1-6 courses).

Table 1. Characteristics of Eligible Patients (n = 13)

Characteristic	No. of Patients (%)
Age, y	
Median	16
Range	5-21
Sex	
Boys	4 (30.8)
Girls	9 (69.2)
Race	
White	11 (84.6)
Black or African American	1 (7.7)
Unknown	1 (7.7)
Ethnicity	
Non-Hispanic	13 (100)
Diagnosis	
Osteosarcoma	3 (23)
Astrocytoma	2 (15.4)
Renal cell carcinoma	2 (15.4)
Rhabdomyosarcoma	2 (15.4)
Ewing sarcoma	1 (7.7)
Ganglioglioma	1 (7.7)
Medulloblastoma	1 (7.7)
Neuroblastoma	1 (7.7)
Prior therapy	
No. of chemotherapy regimens	
Median	1
Range	1-3
No. of patients with prior radiotherapy	5

Toxicity

All 3 patients at the first dose level (60 mg/m^2 per dose oxaliplatin, 20 mg/m^2 per dose irinotecan) experienced similar DLTs, and all required admission to the hospital during the third week of Course 1 (Table 2). Two of the 3 patients were admitted with grade 3 diarrhea and subsequently developed elevated serum lipase levels, and 1 of those 2 patients had elevated an serum amylase level and also had grade 2 abdominal pain. The third patient was admitted with nausea, vomiting, dehydration, and subsequent severe diarrhea during the third week. Grade 3 colitis and abdominal pain along with elevation of serum amylase and lipase developed during the fourth week of Course 1. Because of the length and severity of these toxicities, all of these patients were removed from protocol therapy after the first course. None of them had a history of pancreatitis, diabetes mellitus, or the use of concomitant medications that would be associated with pancreatitis (such as corticosteroids or asparaginase). Two of the 3 patients had received cefixime as prescribed in the protocol. One patient missed >50% of the prescribed doses because of nausea.

Because of severe toxicity and unexpected dose-limiting pancreatitis, the next cohort received reduced doses of oxaliplatin (40 mg/m^2 per dose) and irinotecan (15 mg/m^2 per dose). No DLTs occurred in the initial 3-patient cohort at this dose level. Re-escalation of the oxaliplatin dose to 60 mg/m^2 with the reduced irinotecan dose of 15 mg/m^2 resulted in 2 of the 3 patients experiencing DLT (diarrhea, hypokalemia). Therefore, the oxaliplatin 40 mg/m^2-irinotecan 15 mg/m^2 dose level was expanded to 6 patients; 1 patient received an incorrect irinotecan dose of 20 mg/m^2 per dose and was replaced. One patient

Table 2. Summary of Dose-limiting Toxicities

Dose Level					
Oxaliplatin, mg/m^2/dose	Irinotecan, mg/m^2/dose	No. Entered	No. Evaluable	No. of DLTs	DLTs (No. of Patients)
60	20	3	3	3	Diarrhea (3), lipase (3), amylase (2), colitis (1), abdominal pain (1), headache (1)
40	15	7*	6	1	Diarrhea (1)
60	15	3	3	2	Diarrhea (1), hypokalemia (1)

DLTs indicates dose-limiting toxicities.
* One patient received an incorrect irinotecan dose of 20 mg/m^2/d.

Table 3. Nondose-limiting Hematologic Toxicities Observed in 13 Evaluable Patients*

	No. of Toxicities							
	Course 1, n = 13				Courses 2 to 6, n = 14			
Type of Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	1	2	1			4		
Leukocytes	4	2	2			2	1	1
Lymphopenia	1	2	3	1		1	1	
Neutrophils	1	3	1	1		2		4
Platelets	1	1			1		2	1

*This table lists nondose-limiting hematologic toxicities independent of frequency and attribution.

Table 4. Nondose-limiting Nonhematologic Toxicities Related to Protocol Therapy and Observed in >10% of 13 Evaluable Patients

	No. of Toxicities					
	Course 1, n = 13			Courses 2 to 6, n = 14		
Type of Toxicity	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Fatigue		2			1	
Weight loss	4		1			
Anorexia	1		3	1		3
Dehydration			5			1
Diarrhea	4	2	1	4		2
Nausea	1	2	1	1	1	1
Emesis	2	2	1	1	2	1
Paresthesia/dysesthesia	2					
Pancreatitis	1	1			1	
Hypoalbuminemia	1	2		2		
ALT	3	1	1	2	1	
AST	2		1	2		
Hypocalcemia	2	1		2	2	
GGT	1	1		1	1	
Lipase		2		2		
Hypomagnesemia	2			1		1
Hypokalemia	2			1		
Abdominal pain, NOS	2	2				2

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-gluamyltransferase; NOS, not otherwise specified.

in this expanded cohort experienced dose-limiting diarrhea, and another patient had grade 3 diarrhea that was not considered dose-limiting because loperamide was not used; the patient who received the incorrect irinotecan dose did not experience DLT. Four of the 7 patients in this expanded cohort received 2 or more courses. None of these patients discontinued protocol therapy because of toxicity.

Therapy was discontinued secondary to toxicity in 6 of the 13 evaluable patients. Tables 2, 3, and 4 summarize DLTs, hematologic adverse events, and nonhematologic adverse events, respectively. One patient had nondose-limiting grade 4 neutropenia that lasted for 2 days.

Antitumor Activity

Five patients were removed from treatment before response assessment. Another 4 patients were removed for progressive disease after 1 to 3 courses. One patient with recurrent metastatic rhabdomyosarcoma had who received previous adjuvant treatment with irinotecan had a complete response after 1 course that was sustained through the fourth course (see Fig. 1). She voluntarily withdrew at that point to pursue other therapy. Another patient with refractory neuroblastoma had disease stabilization through 6 courses of therapy. Both of these patients were treated at the MTD.

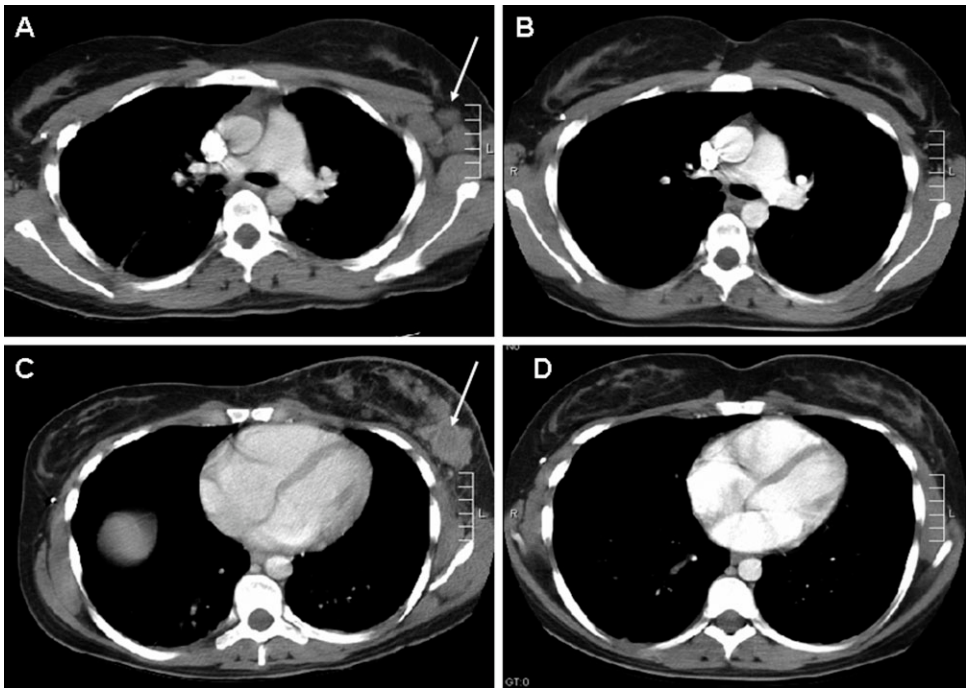

FIGURE 1. Response of metastatic alveolar rhabdomyosarcoma in left axillary lymph nodes (A and B) and left breast (C and D) to protocol therapy. The arrows in Panels A and C indicate pretherapy disease, and response to therapy is shown in Panels B and D.

Pharmacokinetics

Seven patients consented to pharmacokinetic studies. PUF Pt data were evaluable for pharmacokinetic modeling from 6 patients. Samples from 1 patient could not be used because of preparation issues (ie, plasma not PUF). Population pharmacokinetics of PUF Pt were described by a 2-compartment model (Fig. 2). Population pharmacokinetic parameters (±standard error) obtained were for k_e 0.035 ± 0.002 hours, V 320.8 ± 57.9 L/m^2, k_{12} 0.024 ± 0.004 hours, and k_{21} 0.0086 ± 0.002 hours. Interindividual variabilities for PUF Pt k_e and V were 11% and 42%, respectively. The proportional component of residual variability was 17%, in accordance with the analytical assay error, whereas the additive error was fixed considering the assay's quantitation limit. The median AUC calculated to the last data point and the $AUC_{0\rightarrow\infty}$ were 5.8 μg · hour/mL (range, 1.6-7.5 μg · hour/mL) and 5.9 μg · hour/mL (range, 1.8-7.6 μg · hour/mL), respectively. The median terminal half-life was 142 hours (range, 132-166 hours).

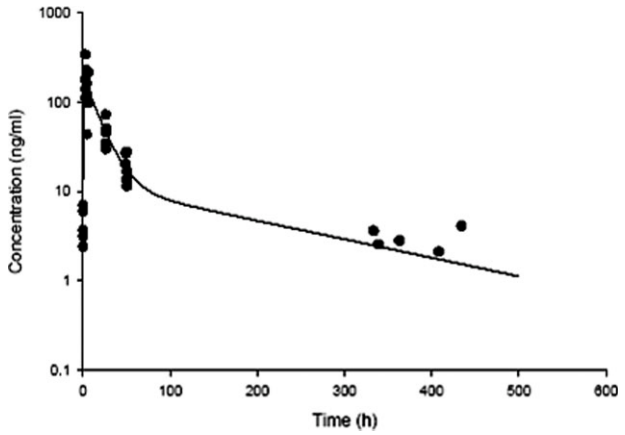

FIGURE 2. Plasma ultrafiltrate platinum (oxaliplatin) concentration versus time profile. Observed plasma concentrations are plotted (dots), and the solid line represents the model-predicted concentrations (considering the base model).

Pharmacogenetics

Ten patients consented to pharmacogenetic studies. The frequencies of the 6/6, 6/7, and 7/7 *UGT1A1* promoter genotypes were 5 of 10, 4 of 10, and 1 of 10, respectively. Genotype and toxicity demonstrated no clear correlation.

DISCUSSION

The MTD of oxaliplatin and irinotecan plus an oral cephalosporin was oxaliplatin at a dose of 40 mg/m^2 per dose

on Days 1 and 8 with irinotecan at a dose of 15 mg/m^2 per dose on Days 1 through 5 and Days 8 through 12. The most common DLT was diarrhea. However, at higher doses, the combination unexpectedly resulted in significant elevations in serum amylase and lipase. Myelosuppression was not significant, and no patient experienced dose-limiting hematologic toxicity. Pharyngolaryngeal dysesthesia was not common, but this was expected given the low single dose of oxaliplatin that was used. The peripheral neuropathy that was observed in adults who received higher cumulative doses of oxaliplatin was not observed in this trial; however, only 1 patient received a significant cumulative dose of oxaliplatin (480 mg/m^2).

The combination of irinotecan (175-200 mg/m^2 per dose) with oxaliplatin (85-130 mg/m^2 per dose) every 3 weeks[51,52] or of irinotecan (50 mg/m^2 per dose) with oxaliplatin (60 mg/m^2 per dose) weekly[33] has been tolerated well in adults. The novel schedule studied here in children did not prove feasible. The basis for this decreased tolerance is unclear, but a drug interaction resulting in unexpectedly high irinotecan exposures is unlikely to be the cause. The lack of pharmacokinetic interactions observed in previous studies in adults,[32,33,42,43] coupled with the differences in metabolism and elimination mechanism of oxaliplatin[53] and irinotecan,[54] does not support such a hypothesis, although this was not studied directly in the current trial. The most likely basis is a schedule-dependent pharmacodynamic difference in drug tolerance of the combination on a protracted schedule.

The finding of clinically mild pancreatitis with marked elevations in serum amylase and lipase was unexpected, because pancreatitis or elevations in serum lipase or amylase have not been reported in published trials of adults receiving the combination of oxaliplatin and irinotecan either with[42,43] or without[32-34] fluorouracil/leucovorin. It is noteworthy that a study on the use of irinotecan with carboplatin[55] reported mild pancreatitis in 1 of 9 patients with nonsmall cell lung cancer. There also is a report of pancreatitis in a patient with hepatic metastases from colorectal carcinoma receiving oxaliplatin through hepatic arterial infusion in combination with folinic acid and 5-fluorouracil.[56] However, it was unclear whether that patient's underlying disease contributed to the pancreatitis. Thirty-eight cases of pancreatitis or elevated pancreatic enzymes have occurred in clinical trials during Sanofi-Aventis' postmarketing experience (unpublished results). Most patients had alternative possible explanations for the pancreatitis, including concomitant medications or relevant medical history. Thus, it is unclear whether the combination of oxaliplatin and irinotecan on this schedule caused pancreatitis directly or whether elevated serum amylase and lipase were the result of severe diarrhea, as described in patients with infectious diarrhea.[57]

The pharmacokinetic limited sampling model used for oxaliplatin pharmacokinetic studies consisted of only 4 plasma samples. Because data were sparse, we used a nonlinear mixed-effects modeling analysis that uses the Monte Carlo parametric expectation maximization algorithm as implemented in S-ADAPT. With this population approach, PUF Pt pharmacokinetics after a 2-hour infusion of oxaliplatin was described adequately by a 2-compartment model. Population estimates of PUF Pt pharmacokinetic parameters are similar to those reported in pediatric and adult patients.[48,58] We observed that the mean clearance was 11.2 L/hour/m^2, which is within the body surface area-normalized clearance ranges of 5.3 to 18.2 L/hour/m^2 observed in adult patients.[53,59]

Current US Food and Drug Administration guidelines recommend that a patients' *UGT1A1* promoter genotype should be considered when prescribing irinotecan, because adult patients with the 7/7 genotype have an increased incidence of neutropenia after every-21-day dosing of irinotecan.[60] However, recent studies have reported no correlation of toxicity with *UGT1A1* genotype when irinotecan was administered on a low-dose, protracted schedule in pediatric patients.[50,61] We also did not observe a relation between *UGT1A1* genotype and irinotecan-induced toxicity, but our patient numbers were small.

One complete response to the oxaliplatin and irinotecan combination was observed in a patient with metastatic alveolar rhabdomyosarcoma. Even with a reduced dose of irinotecan, the combination was effective, consistent with preclinical reports of synergy when these 2 agents are combined.[1,29] Despite signs of clinical activity, the combination of oxaliplatin with irinotecan administered on a protracted schedule was poorly tolerated. Even at the MTD, 2 patients had grade 3 diarrhea, although 1 was not considered dose-limiting because of noncompliance

with loperamide therapy. Alternative schedules in pediatric patients would need to be evaluated should additional data emerge that would support further clinical evaluation of this combination.

Conflict of Interest Disclosures

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