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A Phase I Trial and Pharmacokinetic Study of Sorafenib in Children with Refractory Solid Tumors or Leukemias: A Children's Oncology Group Phase I Consortium Report

Brigitte C. Widemann[1], AeRang Kim[1,2], Elizabeth Fox[3], Sylvain Baruchel[4], Peter C. Adamson[3], Ashish M. Ingle[5], Julia Glade Bender[6], Michael Burke[7], Brenda Weigel[7], Diana Stempak[4], Frank M. Balis[3], and Susan M. Blaney[8]

Abstract

Purpose: To determine the dose-limiting toxicities (DLT), maximum tolerated dose (MTD), pharmacokinetics, and pharmacodynamics of sorafenib in children with refractory extracranial solid tumors and evaluate the tolerability of the solid tumor MTD in children with refractory leukemias.

Experimental Design: Sorafenib was administered orally every 12 hours for consecutive 28-day cycles. Pharmacokinetics (day 1 and steady-state) and pharmacodynamics were conducted during cycle 1.

Results: Of 65 patients enrolled, 60 were eligible. In the solid tumor cohort ($n = 49$), 4 of 6 patients experienced a DLT [hypertension, pain, rash/urticaria, thrombocytopenia, alanine aminotransferase (ALT)/aspartate aminotransferase (AST)] at the starting dose (150 mg/m^2/dose) which resulted in de-escalation to 105 mg/m^2/dose. After eligibility criteria modification and dose re-escalation, the MTD was 200 mg/m^2/dose for solid tumors and 150 mg/m^2/dose for leukemias. Sorafenib exposure was highly variable between patients but was within the ranges reported in adults. The apparent sorafenib clearance increased with patient age. Diarrhea, rash, fatigue, and increased ALT/AST were the most common sorafenib-related toxicities. Stable disease for 4 or more cycles was observed in 14 solid tumor patients, and 2 patients with acute myeloid leukemia (AML) and FLT3 internal tandem duplication (FLT3ITD) experienced a decrease in bone marrow blasts to less than 5%.

Conclusions: The recommended phase II dose of sorafenib administered every 12 hours continuously for children with solid tumors is 200 mg/m^2/dose and 150 mg/m^2/dose for children with leukemias. Sorafenib toxicities and distribution in children are similar to adults. The activity of sorafenib in children with AML and FLT3ITD is currently being evaluated, and a phase II study for select solid tumors is ongoing. *Clin Cancer Res; 18(21); 6011–22. ©2012 AACR.*

Introduction

Sorafenib (Nexavar) is an orally bioavailable small-molecule inhibitor (molecular weight, 465 g/mole) of multiple kinases controlling tumor growth and angiogenesis, including C- and BRAF, VEGFR-1,-2,-3, PDGFR-β, RET, Flt3, c-KIT (1). Sorafenib received U.S. Food and Drug Administration (FDA) approval at a dose of 400 mg twice daily on a continuous schedule for adults with unresectable hepatocellular carcinoma (HCC; ref. 2) and advanced renal cell carcinoma (RCC; refs. (3, 4). The most common sorafenib toxicities reported are reversible skin rash, hand foot skin reaction, diarrhea, anorexia, alopecia, abdominal pain, fatigue, hypertension, laboratory abnormalities, including hypophosphatemia and asymptomatic lipase elevation, and mild myelosuppression (5, 6).

Evaluation of sorafenib in the pediatric preclinical testing program has shown *in vitro* activity at low micromolar concentrations. In *vivo* antitumor activity consisted exclusively of growth inhibition observed in multiple tumor types (7).

Sorafenib has been evaluated in 2 phase I studies for children in combination with other agents (8, 9). In a phase I study of sorafenib, bevacizumab and low-dose cyclophosphamide for solid tumors, rash, and febrile neutropenia

Authors' Affiliations: [1]Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland; [2]Children's National Medical Center, Washington, District of Columbia; [3]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [4]Hospital for Sick Children, Toronto, Ontario, Canada; [5]Children's Oncology Group, Operations Center, Arcadia, California; [6]Columbia University Medical Center, New York, New York; [7]University of Minnesota Medical Center-Fairview, Minneapolis, Minnesota; and [8]Texas Children's Cancer Center, Houston, Texas

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Corresponding Author: Brigitte C. Widemann, NCI, Pediatric Oncology Branch, 10 Center Drive, Building 10 CRC/Room 1-5750, Bethesda, MD 20892. Phone: 301-496-7387; Fax: 301-480-8871; E-mail: widemanb@mail.nih.gov

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Translational Relevance

Sorafenib is an orally bioavailable inhibitor of multiple kinases controlling tumor growth and angiogenesis. Sorafenib is U.S. Food and Drug Administration (FDA)-approved for adults with unresectable hepatocellular carcinoma and advanced renal cell carcinoma. We conducted a phase I study of single-agent sorafenib in children with refractory solid tumors or leukemias on a chronic dosing schedule. The maximum tolerated dose, toxicity profile, and pharmacokinetics of sorafenib in children are similar to adults. No objective responses were observed in solid tumors. Two children with acute myeloid leukemia (AML) and FLT3 internal tandem duplication (FLT3ITD) cleared their bone marrow blasts and proceeded to hematopoietic stem cell transplantation. On the basis of these findings and the reported activity of sorafenib in select solid tumors and AML and FLT3ITD in children and adults, the activity of single-agent sorafenib is currently being evaluated in a phase II study for children with select solid tumors and in children with AML and FLT3ITD. In addition, sorafenib has been incorporated into a phase III randomized trial for children with *de novo* AML with high allelic ratio FLT3ITD.

were the most common dose-limiting toxicities (DLT), and the recommended phase II doses were 90 mg/m^2/dose sorafenib twice daily, bevacizumab 15 mg/kg IV every 3 weeks, and cyclophosphamide 50 mg/m^2 once daily (8). In 12 children with refractory leukemias who received sorafenib combined with clofarabine and cytarabine (9), hand foot skin reaction and rash were prominent and dose limiting at the 200 mg/m^2/dose level, and a dose of 150 mg/m^2/dose was the maximum tolerated dose (MTD). Sorafenib decreased blast percentages in 10 of 12 patients by day 8, and after combination therapy, complete remission was observed in 6 patients [6 with FLT3 internal tandem duplication (FLT3ITD) and 3 with FLT3 wild-type acute myeloid leukemia (AML); ref. 9].

We conducted a phase I trial of single agent sorafenib on a continuous chronic dosing schedule to determine (i) the toxicity profile, DLTs, and MTD of sorafenib administered to children with refractory solid tumors (part A) and (ii) the tolerability of the solid tumor MTD in children with refractory leukemias (part B). Pharmacokinetics and pharmacodynamics of sorafenib were assessed during cycle 1.

Materials and Methods

Patient population

Patients $\geq$24 months and $\leq$21 years of age with treatment-refractory, histologically confirmed measurable, or evaluable solid extracranial tumors (part A) or with refractory leukemias with >25% leukemic blasts in the bone marrow (part B) were eligible. Other eligibility criteria included ability to swallow intact tablets; recovery from toxic effects of prior therapy; Karnofsky/Lansky performance score $\geq$ 50; interval from prior therapy $\geq$21 days for myelosuppressive chemotherapy or monoclonal antibody treatment; $\geq$7 days for hematopoietic growth factors, $\geq$2 weeks for local palliative radiation; $\geq$3 months from total body, craniospinal, or $\geq$50% radiation to the pelvis; $\geq$6 weeks from other substantial bone marrow radiation; $\geq$ 3 months from a stem cell transplant or rescue; and no evidence of active graft versus host disease; adequate renal function [age-adjusted normal serum creatinine, or GFR $\geq$ 70 mL/min/1.73 m^2); and adequate liver function [total bilirubin $\leq$1.5 $\times$ institutional upper limit of normal (ULN), albumin $\geq$ 2 g/dL, and alanine aminotransferase (ALT) $\leq$ 110 U/L]. Adequate bone marrow function was required and defined as an absolute neutrophil count (ANC) $\geq$ 1,000/μL, transfusion-independent platelet count $\geq$75,000/μL, and hemoglobin $\geq$8.0 g/dL for part A; and platelet count $\geq$ 20,000/μL and hemoglobin $\geq$ 8.0 g/dL for part B.

After dose-limiting serum, ALT/aspartate aminotransferase (AST) elevation was observed at the starting dose level in one patient with hepatic metastases and preexisting grade 1 elevation in AST/ALT, the eligibility criteria were revised to require a normal ALT ($\leq$45 U/L) at enrollment. Eligibility criteria were re-revised in part B due to allow for mild elevation in the ALT ($\leq$225 U/L) as many patients with leukemia have disease-related baseline elevations in serum transaminases. Additional eligibility criteria included normal serum lipase and amylase; diastolic blood pressure within the 95th percentile for age and gender and not receiving anti-hypertensive medication. Exclusion criteria included pregnancy or lactation; uncontrolled infection; concurrent use of other investigational agents, anticancer agents, agents to prevent organ rejection posttransplant, cytochrome P450 enzyme-inducing antiepileptic drugs, rifampin, grapefruit juice, St. Johns Wort, or therapeutic anticoagulants; evidence of bleeding diathesis; leptomeningeal disease; and Gilbert syndrome.

This trial was approved by the Institutional Review Boards of participating sites. All patients or their legal guardians signed a document of informed consent indicating their understanding of the investigational nature and risks of this study. Assent was obtained according to institutional guidelines.

Drug administration and study design

Sorafenib was supplied as 50- and 200-mg tablets by the Cancer Therapy Evaluation Program (NCI, Bethesda, MD) and administered orally, twice daily, continuously for 28-day cycles. The starting dose was 150 mg/m^2/d with planned escalations to 200, 250, and 325 mg/m^2/dose. Doses were prescribed using a dosing nomogram with a maximum dose of 600 mg/dose, as higher doses were intolerable in adults. Patients maintained a diary to document drug intake.

A traditional 3 + 3 phase I dose-escalation scheme was used. Intrapatient dose-escalation was not permitted. At the solid tumor MTD, the trial was expanded to enroll 12

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evaluable solid tumor patients (6 < 12 and 6 ≥ 12 years of age) to study steady-state pharmacokinetics and further define sorafenib toxicities (part A), and children with refractory leukemias to evaluate the tolerability, pharmacokinetics, and pharmacodynamics of sorafenib (part B).

Toxicity assessment and disease evaluations

Monitoring for sorafenib-related toxicity included physical examination with blood pressure measurement (weekly during cycle 1, then every other week); weekly serum chemistries including electrolytes, calcium, phosphate, magnesium, creatinine, ALT, bilirubin, lipase, and amylase; total protein and albumin before each cycle; and complete blood counts (twice weekly during cycle 1, then weekly). Clinical and laboratory adverse events, except hypertension, were graded according to the NCI Common Terminology Criteria for Adverse Events version 3 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Age- and gender-adjusted norms were used to determine whether the blood pressure was elevated (10) and a previously described algorithm for management of sorafenib-related hypertension was used (11).

As inhibition of VEGF has been previously shown to affect bone growth in juvenile animals by thickening of the growth plate and inhibition of trabecular bone formation (12–14), plain radiographs of tibial growth plates were conducted at baseline in patients <18 years of age, and then after every 3 cycles in patients with open growth plates.

Response was evaluated using Response Criteria in Solid Tumors (15) and published criteria for leukemias (16) at baseline and before every odd cycle in part A as well as at the end of cycles 1 and 2, and before every other cycle in part B.

Definition of DLT and MTD

Hematologic DLT was defined as any grade 4 neutropenia (<500/μL) or thrombocytopenia (<25,000/μL). For patients with leukemia, hematologic toxicity was monitored but not used to define the MTD or considered dose-limiting. Nonhematologic DLTs were any sorafenib-related grade 4 toxicity and any grade 3 toxicity with exception of the following: nausea and vomiting of less than 5 days duration, ALT or AST elevations that recovered to grade ≤1 within 7 days of stopping drug, fever, or infection <5 days, and electrolyte abnormalities responsive to oral supplementation. Persistent (≥7 days) grade 2 toxicities intolerable to the patient were also defined as DLTs. Dose-limiting hypertension was initially defined as grade ≥2 hypertension; however, this definition was redefined after dose level 1 accrual to include grade 4 hypertension, a confirmed diastolic blood pressure >25 mm Hg above the ULN, or an elevated diastolic blood pressure not controlled by anti-hypertensive medication within 14 days (11). Patients with a DLT who resolved within 14 days of sorafenib discontinuation were eligible for one dose reduction provided toxicity resolved to meet on study parameters within 14 days. Sorafenib was permanently discontinued for recurrent DLTs.

Patients were considered fully evaluable for toxicity and determination of the MTD provided they either developed a DLT at any time during cycle 1 or did not develop a DLT and received at least 85% of the prescribed sorafenib dose during cycle 1. Patients not meeting these criteria were replaced. The MTD was the dose level immediately below the dose level at which 2 or more patients in a dose level of up to 6 patients experienced a DLT.

Pharmacokinetics and pharmacodynamics

During the dose-escalation phase, pharmacokinetic sampling was conducted in consenting patients after the first dose of sorafenib (day 1). Three milliliters of heparinized blood was collected before and 0.5, 1, 2, 3, 5, 8, 10–12, 24, and 30–36 hours after dose 1 (doses 2 and 3 were held). Trough samples were obtained on days 5, 7, and 27–28 during cycle 1 in all patients. In the expanded solid tumor cohort and the leukemia cohort, sorafenib pharmacokinetics were evaluated at steady state. Blood was collected 12 hours after the last sorafenib dose, which was also used as the level immediately before the next dose, as well as 0.5, 1, 2, 3, 5, and 8 hours after the dose of sorafenib between days 14 and 28 of cycle 1. Sorafenib plasma concentrations were measured using the high-performance liquid chromatography tandem mass spectroscopic (HPLC/MS-MS) method adapted from an assay (17) with a lower limit of quantification of 5 ng/mL (18).

The sorafenib plasma concentration–time data were analyzed using noncompartmental methods. Peak sorafenib concentration (C_{max}) and time to peak concentration (T_{max}) were determined from each patient's concentration–time plot. For day 1, the sorafenib exposure [area under curve $(AUC)_{0-24h}$] was calculated using the linear trapezoidal method. For steady-state pharmacokinetics, the pre-sorafenib trough concentration was also used as the 12-hour after sorafenib concentration based on the assumption that at steady state the trough concentration should be constant. At steady state, the AUC over the dosing interval (AUC_{0-12h}) is equivalent to the $AUC_{0-\infty}$, if no time-dependent changes occur in exposure. Therefore, apparent clearance was calculated by dividing the sorafenib dose by the AUC_{0-12h}. The relationship between day 1 and steady-state drug exposure (normalized AUC_{0-24h} and AUC_{0-12h}, respectively) to gender, DLT, and response (<4 or ≥4 cycles received) were evaluated by the Mann–Whitney *U* test. The relationship between clearance and age was evaluated by linear regression.

Blood samples for plasma VEGF, soluble VEGFR2, endoglin, and placental growth factor (PlGF) were obtained in EDTA tubes and quantified at baseline and on days 27 and 28 of cycle 1 using a commercially available ELISA assay (Quantikine, R&D Systems; ref. 19). Total circulating endothelial cells (CEC) and circulating endothelial progenitor cells (CEPC) were analyzed from baseline and day 27 or 28 of cycle 1 blood samples using a 4-color fluorescence-activated cell sorter (19). The average paired values obtained before treatment and at steady state were compared (Student *t* test) and correlations were made to drug exposure for day 1 and steady-state pharmacokinetics and response for each growth factor analyzed (Spearman correlation).

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Table 1. Characteristics of all eligible patients ($N = 60$)

Patient strata	Solid tumor[a] ($n = 49$)	Leukemia ($n = 11$)
Age in years: Median (range)	14 (4–21)	14 (6–19)
Sex: Female: Male	22: 27	1: 10
Performance status: Median (range)	90 (50–100)	90 (80–100)
Karnofsky	90 (60–100)	90 (90–100)
Lansky	100 (50–100)	100 (80–100)
Prior chemotherapy regimens: Median (range)	2 (0–7)	1 (1–4)
Number with prior radiation	29	1
Number with prior BMT	5	4
Diagnosis		
Osteosarcoma	10	AML 8
Ewing's sarcoma	4	ALL 3
Alveolar rhabdomyosarcoma	4	
Synovial sarcoma	3	
Alveolar soft part sarcoma	2	
MPNST	2	
Sarcoma, other	7	
Hepatoblastoma	4	
Wilms tumor	4	
Adrenocortical carcinoma	3	
Renal cell carcinoma	2	
Other	4	

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; BMT, bone marrow transplant; MPNST, malignant peripheral nerve sheath tumor.

[a]Dose escalation cohort ($n = 34$), expanded solid tumor cohort at the maximum tolerated dose ($n = 15$).

Results

Patient characteristics

Of 65 patients enrolled from August 2006 to February 2010, 5 were ineligible [required pretreatment lipase not conducted ($n = 3$), preexisting organ dysfunction ($n = 2$)] and 10 were not fully evaluable for toxicity: disease progression during cycle 1 ($n = 4$), best patient interest ($n = 3$), acute death after 4 days of sorafenib in patient with numerous preexisting conditions ($n = 1$), non–dose-limiting grade 2 allergic reaction ($n = 1$), never received sorafenib ($n = 1$). Table 1 shows characteristics of the 60 eligible patients.

Toxicity and MTD

There were no patient deaths attributed to sorafenib toxicity. Table 2 summarizes cycle 1 DLTs. The MTD was exceeded at the first dose level (150 mg/m^2/dose) with DLT in 4 of 6 fully evaluable patients, one of whom developed grade 3 AST/ALT elevation in the presence of preexisting grade 1 transaminase elevation and hepatic metastases, and one of whom developed grade 2 hypertension. No DLTs were observed at the next lower dose (105 mg/m^2), which corresponds to a fixed dose of approximately 190 mg, approximately half of the adult recommended dose. The protocol was amended to require normal ALT and bilirubin at enrollment and to provide new guidelines for the grading and management of hypertension (11) as described in the Materials and Methods section. With these changes, sorafenib was re-escalated to an intermediate dose of 130 mg/m^2 with no DLT in 3 patients, and then to 150, 200, and 250 mg/m^2, at which dose the MTD was exceeded with DLT (rash/hand foot skin reaction and hyponatremia) in 2 of 2 evaluable patients. The 200 mg/m^2/dose was defined as the MTD with DLT (grade 3 ALT) in 1 of 7 patients. In the expanded solid tumor cohort, DLTs were similar to those previously observed and occurred in 1 of 6 patients $\geq$12 years, and in 2 of 6 patients <12 years old, for a combined DLT rate of 21% (4 of 19) in all evaluable solid tumor patients at the MTD. Four patients developed grade 3 DLTs during subsequent treatment cycles: at 200 mg/m^2, diarrhea ($n = 2$), hyponatremia (recurrent DLTs, $n = 1$); at 150 mg/m^2, hand foot skin reaction ($n = 1$). The solid tumor MTD was not tolerated in children with leukemias with DLT (anorexia and gastrointestinal hemorrhage) in 2 of 2 patients, and the 150 mg/m^2/dose was determined as the MTD. No dose-limiting ALT/AST elevation was observed in children with leukemia, 2 of whom had mild ALT elevation (62 and 65 U/L) at study entry. One DLT after completion of cycle 1 (150 mg/m^2) was observed (grade 4 hyperglycemia).

Sorafenib's most frequent non-DLTs were fatigue, rash, diarrhea, AST/ALT/bilirubin elevation, and predominantly mild myelosuppression (Table 3). No bony abnormalities

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Table 2. Cycle 1 dose-limiting toxicities of sorafenib by stratum and dose level

Stratum	Dose level mg/m^2/dose	Patients (*n*)		Dose-limiting toxicity	
		Entered	Evaluable	Pt. no.	CTC toxicity term (grade)
Solid tumor dose escalation	150[a]	6	6	1	Platelets (3)[b]
				4	Hypertension (2), back pain (3)
				6	Rash/desquamation (3), urticaria (3)
				5	ALT (3), AST (3)
	105	7	6	—	—
	130[c]	4	3	—	—
	150[c]	6	6	23	Lipase (3)
	200[c]	8	7	22	ALT (3)
	250[c]	3	2	35	Rash: Hand-foot skin reaction (3)
				34	Hyponatremia (3)
Solid tumor expansion	200[c]				
≥12 years		9	6	56	Rash/desquamation (3)
<12 years		6	6	41	Hypertension (3), pain - back and chest (3)
				44	Rash/desquamation (3)
Refractory leukemia	200[c]	2	2	49	Anorexia (3)
				42	GI hemorrhage – abdomen (4)
	150[c]	9	6	-	-

[a]Equivalent to an adult fixed dose of 270 mg based on adult body surface area of 1.8 m^2.
[b]Dose-limiting due to failure to recover to ≥75,000 within 2 weeks of holding sorafenib.
[c]Dose levels with modified eligibility criteria (see article).

were reported in 5 patients who underwent serial plain radiographs. Three patients required anti-hypertensive medication in reporting period 2 to 4 and were able to continue sorafenib at unchanged dosing.

Pharmacokinetics and pharmacodynamics

Twenty patients had pharmacokinetic sampling at day 1 and 17 patients at steady state.

There was substantial interpatient variability for day 1 and steady-state pharmacokinetic parameters (Table 4 and 5). Drug exposure increased only marginally when it was escalated from 150 to 200 mg/m^2 for day 1 pharmacokinetics (Table 4). The plasma concentration–time profile captured drug exposure incompletely (Fig. 1A). The terminal half-life appeared to be prolonged (≥24 hours) but could not be estimated. Sorafenib accumulated after multiple doses and steady state appeared to be achieved after 5 to 7 days (Table 4 and Fig. 1B) with the median accumulation ratio (day 27 trough/day 2 trough) ranging from 3.7 to 11.6. No statistically significant relationship between AUC_{0-24h} to DLTs or response was observed.

For steady-state pharmacokinetics, the accumulation ratio of sorafenib at the MTD [mean (SD) AUC_{0-12h} of 61.2 (18.2) steady state divided by mean (SD) calculated day 1 AUC_{0-12h} of 14.4 (8.9)] was 4.3. Steady-state sorafenib concentrations ($AUC_{0-12h}/12$) were 4.1 ± 2.1 μg/mL at the 150 mg/m^2 and 5.4 ± 1.8 μg/mL at 200 mg/m^2 dose levels, respectively. The median apparent sorafenib clearance at the MTD was 56.0 mL/min/m^2 (range, 19.2–72.8). The apparent sorafenib clearance increased with patient age ($P = 0.048$; Fig. 1C). No statistically significant relationship between AUC_{0-12h} and DLTs was observed.

In paired samples for plasma VEGF and endoglin concentrations ($n = 26$) and paired samples for CEC and CEPC number ($n = 21$), there was no change comparing baseline with end of cycle 1. A statistically significant decrease in soluble VEGFR2 ($P \leq 0.001$) and increase in PlGF ($P \leq 0.001$) was observed at steady state (Supplementary Fig. S2A and S2B). No correlations of the pharmacodynamic parameters to drug exposure or response were observed.

Response evaluation

The median number of sorafenib cycles for solid tumors was 2 (range, 1–22). There were no confirmed objective responses in patients with solid tumors but 1 patient (#24) with synovial sarcoma had more than 40% tumor shrinkage after cycle 1. This patient could not be considered a confirmed partial response, as disease progression was documented after cycle 2. Patients with leukemia received a median of 1 (range, 1–6) cycle. Two patients with AML and FLT3ITD achieved an M1 bone marrow (<5% blasts) after cycles 4 and 5, respectively, and were removed from sorafenib treatment to undergo hematopoietic stem cell transplantation.

Discussion

The MTD of single-agent sorafenib in children with refractory solid tumors is 200 mg/m^2/dose twice daily, given orally on a continuous dosing schedule, similar to the recommended 400-mg twice daily fixed dose in adults

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Table 3. Non–dose-limiting toxicities possibly, probably, and definitely related to sorafenib (maximum toxicity grade per patient) observed in more than 10% of evaluable patients

Solid tumor dose-escalation cohort	Course 1 ($n = 30$)[a]				Course ≥ 2 ($n = 66$)[a]			
Toxicity grade CTCv3	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Hematologic								
Hemoglobin	3	1	2		4	1	1	
Leukopenia	5	2	2		4	2	2	
Lymphopenia	2	1	2		2	2	1	
Neutropenia	5	1	2		3	1	2	
Thrombocytopenia	4				5	1		
Cardiovascular								
Hypertension	4	1			3		1	
Constitutional								
Fatigue	14				3	2		
Dermatologic								
Rash/Desquamation	11	3			4			
Hand-foot skin reaction	1	4				2		
Gastrointestinal								
Diarrhea	9	1			3	4		
Nausea	4				4			
Vomiting	4	1						
Metabolic/laboratory								
Increased ALT	4	1			4	1		
Increased AST	4	1			3	1		
Increased bilirubin	4	1				1		
Hyperglycemia	4				2			
Hypophosphatemia	3	2			3	1		
Pain								
Headache	3	1			1	1		
Solid tumor expanded PK cohort	**Course 1 ($n = 12$)[a]**				**Course ≥ 2 ($n = 31$)[a]**			
Toxicity grade CTCv3	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Hematologic								
Lymphopenia	1		1		2			
Thrombocytopenia	4	1			3	1		
Constitutional								
Fatigue	4	2			2	2		
Fever	2				1			
Dermatologic								
Alopecia	2				1			
Rash/Desquamation	3	1			2			
Hand-foot skin reaction	1	1						
Gastrointestinal								
Anorexia	4				3	1		
Diarrhea	8	1			3	2		
Mucositis/stomatitis	2							
Nausea	3	2			2		1	
Vomiting	1	3			1		1	
Metabolic/laboratory								
Hypoalbuminemia	1	1			1			
Increased ALT	5				4			

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Table 3. Non–dose-limiting toxicities possibly, probably, and definitely related to sorafenib (maximum toxicity grade per patient) observed in more than 10% of evaluable patients (Cont'd)

Solid tumor expanded PK cohort	Course 1 ($n = 12$)[a]				Course ≥ 2 ($n = 31$)[a]			
Toxicity grade CTCv3	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Increased AST	6				6			
Increased bilirubin	2				1			
Hypocalcemia	3				3			
Hyperglycemia	2				1			
Hypophosphatemia	2				4	1		
Hyponatremia	3				3			
Pain								
Other (forearm)	1							
Other (jaw)					1			
Refractory leukemia	**Course 1 ($n = 8$)[a]**				**Course ≥ 2 ($n = 12$)[a]**			
Toxicity grade CTCv3	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Constitutional								
Fatigue	1	2						
Dermatologic								
Rash/Desquamation	5				2			
Hand-foot skin reaction		2						
Gastrointestinal								
Anorexia	1	1				1		
Diarrhea	2	1			1			
Nausea	2				1			
Metabolic/laboratory								
Increased ALT	1	1			1			
Increased AST	3	1			1			
Increased bilirubin	2				1			
Hyperglycemia	2	1			1			
Hypophosphatemia		1	1			1		
Hypoalbuminemia	1	1						
Hyponatremia	2				1			
Hypocalcemia	1	1				1		
Hypomagnesemia	1		1		2			
Hypokalemia	2						1	
Proteinuria	1	1						
Pain								
Headache	1	1				1		

[a]Numbers indicate number of patient courses.

(5, 6). Children with refractory leukemias did not tolerate the solid tumor MTD, and the recommended dose for this population is 150 mg/m^2/dose, which is identical to the recommended dose in children with leukemia in combination with clofarabine and cytarabine (9) and similar to the recommended dose of 300 mg twice daily in adults with AMLs (20). Similar to adults, children with solid tumors and leukemias experienced rash, hand-foot skin reaction, hypertension, ALT/AST elevation, asymptomatic lipase elevation, diarrhea, and mild myelosuppression (5, 6). The DLTs, anorexia and gastrointestinal (GI) hemorrhage, in children with leukemia in our study were different from those with solid tumors (Table 2). In contrast to the toxicities observed in our study, children with leukemia or solid tumors who received sorafenib in combination with other agents, experienced grade 2 and 3 hand foot skin reactions and rashes with much greater incidence (8 of 12 children with leukemia, 5 of 19 children with solid tumors; refs. 8, 9).

In contrast to adults, fatigue in children was predominantly mild, and hypertension was infrequently observed. Up to a third of adults receiving sorafenib require dose reductions with chronic administration, mostly due to skin toxicity and diarrhea (2, 3, 21). While we could not

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Table 4. Sorafenib day 1 plasma pharmacokinetic parameters in children with solid tumors

Dose Level (mg/m^2)	Pt no.	Age (y)	BSA (m^2)	Dose (mg)	Actual dose/m^2	Deviation (%)	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-24h} (μg·h/mL)	C_{trough} (μg/mL)		
										D 5	D 7	D 27–28
105	7	19	1.98	200	101	−3.8	0.1	5.0	2.5	—	2.8	1.4
105	10	17	1.88	200	106	1.3	1.1	2.0	15.1	—	—	3.3
105	11	14	1.50	150	100	−4.8	1.2	8.0	20.4	—	10.0	3.4
105	13	21	1.86	200	108	2.4	0.4	5.1	9.2	5.0	2.6	6.2
Mean						−1.2	0.7	5.0	11.8		5.1	3.6
SD							0.5	2.5	7.7		4.2	2.0
Median							0.8	5.0	12.2		2.8	3.4
130	14	18	1.40	200	143	9.9	2.4	5.1	20.0	4.4	3.0	3.4
130	18	14	1.22	150	123	−5.4	0.6	7.9	9.1	3.5	4.2	3.6
Mean						−2.2	1.5	6.5	14.6	4.0	3.6	3.5
SD							1.3	2.0	7.7	0.6	0.8	0.1
Median							1.5	6.5	14.6	4.0	3.6	3.5
150	1[a]	12	1.26	200	159	5.8	1.0	23.5	15.5	4.9	4.2	8.1
150	2	14	1.62	250	154	2.9	1.6	5.0	29.2	—	4.9	3.4
150	3	13	1.22	200	164	9.3	1.0	8.0	12.2	—	—	—
150	6[a]	12	1.05	150	143	−4.8	1.1	5.5	18.3	—	—	—
150	19	21	1.83	250	137	−8.9	1.8	23.3	19.2		5.8	14.6
150	20	16	1.91	300	157	4.7	0.4	24.0	6.8	1.6	2.0	2.4
150	21	14	1.65	250	152	1.0	3.8	3.0	55.0	—	11.2	11.1
150	23[a]	6	0.74	100	135	−9.9	5.1	5.1	81.5	6.6	6.6	—
150	24	15	1.49	200	134	−10.5	1.1	5.0	16.9	3.2	2.8	1.9
Mean						−1.0	1.9	11.4	28.3	4.1	5.4	6.9
SD							1.6	9.2	24.4	2.2	3.0	5.2
Median							1.1	5.5	18.3	4.1	4.9	5.8
200	22[a]	7	1.80	350	194	−2.8	1.8	1.0	19.0	—	—	—
200	29	16	1.48	300	203	1.4	3.8	3.0	46.8	3.6	0.9	1.8
200	30	11	1.15	250	217	8.7	1.4	5.0	—	—	—	—
200	32	20	2	400	200	0	1.0	3.0	16.1	8.4	6.3	5.0
Mean						0.7	2.0	3.0	27.3	6.0	3.6	3.4
SD							1.3	1.6	17.0	3.4	3.8	2.3
Median							1.6	3.0	19.0	6.0	3.6	3.4
250	35[a]	11	1.43	350	245	−2.1	1.8	8.0	27.6	5.5	7.8	—

Abbreviations: BSA, body surface area; Deviation, percent deviation of actual dose from protocol prescribed dose; C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}; AUC, area under the plasma concentration time curve; C_{trough}, sorafenib concentration before administration of the day 5, 7, and 27–28 dose.

[a]Dose-limiting toxicity during cycle 1.

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Table 5. Sorafenib steady-state plasma pharmacokinetics

Dose Level (mg/m^2)	Pt no.	Age (years)	BSA (m^2)	Dose (mg)	Actual dose/m^2	Deviation (%)	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-12h} (μg·h/mL)	CL/F (mL/min/m^2)
Children less than 12 years with solid tumors										
200	39	7	0.82	150	183	−8.5	6.4	2	65.4	46.7
200	40	9	1.27	250	197	−1.6	11.3	2	96	34.2
200	41	11	1.3	250	192	−3.9	5.9	3	55.9	57.4
200	44[a]	7	0.83	100	120	20.5	10.4	5	104.6	19.2
200	45[a]	9	1.14	250	219	9.7	5.8	5	54.6	67
200	59	5	0.73	150	205	2.7	8.5	2.1	50.7	67.6
200	42[a]	6	0.9	200.0	225.0	12.4	5.0	2.0	51.4	72.8
Mean						4.5	7.2	2.7	62.3	57.6
SD							2.3	1.2	17.3	14.8
Median							6.2	2.0	55.2	62.2
Children ≥ 12 years with solid tumors										
200	38	15	1.65	350	212	6.1	5.7	5	53.9	54.7
200	43	17	2.2	400	182	−9.1	10.7	5	87.8	34.5
200	50	21	1.95	400	205	−2.6	2.5	8	26.3	130
200	51	19	1.64	350	213	6.7	7.7	0.6	70.7	50.3
200	52	12	1.57	300	191	−4.5	15.3	1	55.5	57.4
200	53	16	1.93	400	207	3.6	7.9	0.5	66.8	51.7
Mean						0	8.3	3.4	60.2	63.1
SD							4.4	3.1	20.6	33.7
Median							7.8	3.0	61.2	53.2
Children with refractory leukemias										
150	55	9	1.1	150.0	143.0	−4.8	12.2	3.0	97.8	24.4
150	58	19	1.7	250.0	147.0	−2.0	1.9	2.0	20.3	121.0
150	62	6	0.9	150.0	163.0	8.7	6.0	1.0	50.0	54.3
150	63	14	1.2	200.0	167.0	11.1	3.8	2.1	30.7	90.6
Mean						3.3	6.0	2.0	49.7	72.6
SD							4.5	2.0	34.4	42.2
Median							4.9	0.8	40.3	72.5

Abbreviations: BSA, body surface area; Deviation, percent deviation of actual dose from protocol prescribed dose; CL/F, apparent clearance.

[a]Dose-limiting toxicity during cycle 1. Pharmacokinetic sampling performed after dose reduction, and thus patient 44 was not included in any summary calculations.

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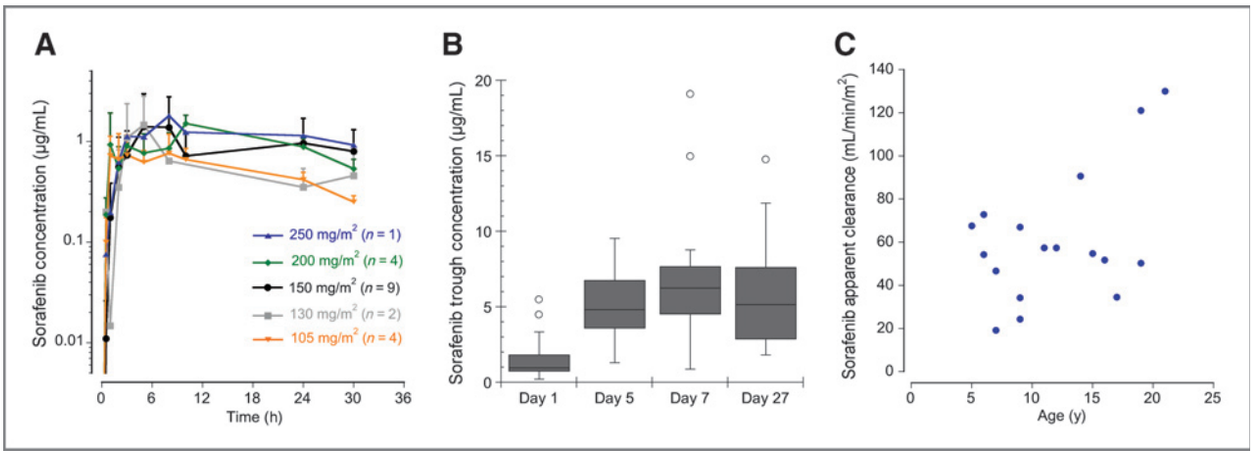

Figure 1. Pharmacokinetics of sorafenib. A, mean plasma concentration × time curves after a single day, 1 dose for each dose level. Error bars, SD of the concentrations. B, cycle 1 plasma sorafenib trough concentrations normalized to 200 mg/m^2/dose on days 1 (calculated 12-hour concentration; $n = 18$), 5 ($n = 10$), 7 ($n = 15$), and 27 ($n = 14$). C, relationship of sorafenib apparent clearance (Cl/F) at steady state to age. The Cl/F increases with patient age ($P = 0.048$).

comprehensively assess cumulative toxicity of sorafenib, after cycle 1, only 5 patients developed a DLT, and only 3 patients required initiation of anti-hypertensive medication.

The pharmacokinetics of sorafenib in children were similar to adults. There was substantial interpatient variability both after a single dose and at steady state (22–25). For day 1 pharmacokinetics, only marginal differences between AUC_{0-24h} from 150 to 200 mg/m^2/dose were observed. In adults, the AUC_{0-12h} increased only marginally beyond the recommended 400 mg twice daily dose and saturable sorafenib absorption has been described (26). The 400-mg dose is comparable with the pediatric 200 mg/m^2/dose twice daily. Sorafenib accumulated and steady state was reached by days 5 to 7, similar to adult studies (6, 23, 24). The median steady-state AUC_{0-12h} at the MTD of 200 mg/m^2 was 55.7 μg h/mL, which is within the range seen in adults (AUC_{0-12h} at 400-mg dose after multiple doses of sorafenib 47.8–76.5 μg h/mL; refs. 6, 23, 24). In 12 children with refractory leukemia, Inaba and colleagues (9) reported sorafenib steady-state (day 7) concentrations of 7.0 ± 1.8 μg/mL at 150 mg/m^2 and 6.5 ± 3.6 μg/mL at 200 mg/m^2, which is similar to the day 7 concentrations in our study (Table 4) and to the calculated steady-state concentrations of children in our study who had steady-state pharmacokinetics conducted.

In our analysis in 17 patients, the apparent sorafenib clearance at the MTD increased with age ($P = 0.048$). Additional pharmacokinetic data from young patients receiving sorafenib on other trials will be helpful to more completely analyze this relationship. If confirmed, an analysis of possible etiologies, such as differences in protein binding or drug metabolism, should be explored. Interestingly, the 2 patients (patients 23 and 44) with the highest AUC were the 2 youngest patients (6 and 7 years of age), and both had DLTs. A statistically significant change from baseline to steady-state pharmacodynamics was only observed for soluble VEGFR and PlGF, but there was no correlation to response or sorafenib exposure.

In solid tumor patients, no objective responses were observed; however, stable disease for ≥4 cycles was observed in 14 patients. The objective response of sorafenib has been low in adults with advanced HCCs (2%) and RCCs (10%), and sorafenib was FDA-approved for adults with these diseases based on improvement in progression-free and overall survival (2, 3). The development of sorafenib for pediatric solid tumors has therefore mostly focused on diseases with documented activity in adults. The ongoing Children's Oncology Group phase II trial of sorafenib includes strata for refractory HCCs and papillary thyroid carcinoma in addition to rhabdomyosarcoma and Wilms tumor. In addition, sorafenib has been evaluated in combination with standard chemotherapy in children with HCCs (27), a phase II study of sorafenib for children with refractory low-grade astrocytomas is ongoing, and sorafenib is undergoing phase I evaluation in combination with irinotecan in children with refractory solid tumors.

Activity of sorafenib in adult AMLs with FLT3ITD has been previously reported in adults (20, 28–30) and in children in combination with additional chemotherapy agents (9, 31). Pharmacokinetic studies showed a much higher rate of conversion of sorafenib to the active N-oxide metabolite than that reported in adult patients and more potent inhibition of FLT3ITD by the N-oxide metabolite providing possible explanations for the promising activity in AMLs (9, 32). In our study, preliminary activity of single-agent sorafenib was observed in 2 children with AMLs and FLT3ITD who cleared their bone marrow blasts and proceeded to hematopoietic stem cell transplantation. On the basis of these findings, our study was expanded to determine the activity and pharmacokinetics of sorafenib and of its active N-oxide metabolite in children with AMLs and FLT3ITD. In addition, a Children's Oncology Group phase III randomized trial for *de novo* AMLs

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incorporating bortezomib and sorafenib for patients with high allelic ratio FLT3ITD was developed and is ongoing (32).

Disclosure of Potential Conflicts of Interest

A. Kim is a consultant/advisory board member of the Nexavar Pediatric Advisory Board. No potential conflicts of interest were disclosed by the other authors.

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The views expressed do not necessarily represent views of the NIH or the U.S. government.

Authors' Contributions

Conception and design: B.C. Widemann, E. Fox, P.C. Adamson, J.G. Bender, F.M. Balis, S.M. Blaney
Development of methodology: B.C. Widemann, S. Baruchel, P.C. Adamson, F.M. Balis
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.C. Widemann, A. Kim, E. Fox, S. Baruchel, J.G. Bender, B. Weigel, F.M. Balis, S.M. Blaney
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.C. Widemann, A. Kim, E. Fox, S. Baruchel, A.M. Ingle, J.G. Bender, F.M. Balis, S.M. Blaney
Writing, review, and/or revision of the manuscript: B.C. Widemann, A. Kim, E. Fox, S. Baruchel, P.C. Adamson, A.M. Ingle, J.G. Bender, M. Burke, B. Weigel, D. Stempak, F.M. Balis, S.M. Blaney
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B.C. Widemann
Study supervision: B.C. Widemann, J.G. Bender, M. Burke, B. Weigel, F.M. Balis, S.M. Blaney
Protocol chair: B.C. Widemann

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