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Phase 2 trial of Sorafenib in Children and Young Adults with Refractory Solid Tumors: A Report from the Children's Oncology Group

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Abstract

Background—Sorafenib is an oral small molecule inhibitor of multiple kinases controlling tumor growth and angiogenesis. The purpose of this phase 2 study was to determine the response rate of sorafenib and gain further information on the associated toxicities, pharmacokinetics, and pharmacodynamics of sorafenib in children and young adults with relapsed or refractory tumors including rhabdomyosarcoma, Wilms tumor, hepatocellular carcinoma (HCC) and papillary thyroid carcinoma (PTC).

Procedure—Sorafenib, 200 mg/m²/dose, was administered every 12 hours continuously for 28 day cycles using a two-stage design in two primary strata (rhabdomyosarcoma and Wilms tumor) and two secondary strata (HCC and PTC). Correlative studies in consenting patients included determination of sorafenib steady state trough concentrations and assessments of VEGF and sVEGFR2.

Results—Twenty patients (median age of 11 years; range, 5–21) enrolled. No objective responses (RECIST) were observed in the 10 evaluable patients enrolled in each of the two primary disease strata of rhabdomyosarcoma and Wilms tumor. No patients with HCC or PTC were enrolled. Sorafenib was not associated with an excessive rate of DLT. The mean $\pm$ SD steady state concentration during cycle 1 day 15 was 6.5 ± 3.9 μ g/mL (n=10).

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CONFLICT OF INTEREST STATEMENT

Nothing to declare

Conclusions—Sorafenib was well tolerated in children at 200 mg/m²/dose twice daily on a continuous regimen with toxicity profile and steady state drug concentrations similar to those previously reported. Single agent sorafenib was inactive in children with recurrent or refractory rhabdomyosarcoma or Wilms tumor.

Keywords

sorafenib; pediatrics; solid tumors

INTRODUCTION

Sorafenib (Nexavar, Bayer, Onyx) is an orally bioavailable small molecule inhibitor of multiple kinases that are components of signaling pathways that control tumor growth and angiogenesis including C-, B-RAF, VEGFR-2,3, PDGFR- β , FLT3, and c-KIT [1]. Sorafenib has been relatively well tolerated in adults with manageable toxicities [2], and responses have been reported in a variety of adult tumors, including those that have not traditionally been described to harbor BRAF mutations. Sorafenib is approved by the United States Food and Drug Administration for adults with advanced renal cell carcinoma (RCC), unresectable hepatocellular carcinoma (HCC), or recurrent or progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment [3].

A phase 1 study of sorafenib in children with refractory solid tumors and leukemia (ADV0413) conducted by the Children's Oncology Group (COG) Phase 1 and Pilot Consortium recommended a phase 2 dose of 200 mg/m²/dose every 12 hours continuously for children and adolescents with solid tumors and 150 mg/m²/dose for children with leukemia [4]. Similar to adults, common toxicities observed were rash, palmar-plantar erythrodysesthesia, hypertension, elevated serum transaminases, lipase elevation, diarrhea, and mild myelosuppression. In children and adolescents with refractory or recurrent solid tumors, no objective responses were observed; however, stable disease 4 cycles was observed in 14 patients.

Further evaluation of the activity of sorafenib in pediatric solid tumors has focused on clinical experience in adults with cancer, limited clinical reports of sorafenib administration in children with rare tumors, and preclinical testing in animal models of pediatric cancers. Although the objective response rate of single agent sorafenib in adults was low, sorafenib was FDA-approved based on improvements in progression free survival for patients with RCC and DTC, and overall survival in HCC [3,5,6]. Multiple clinical trials in adults have evaluated the activity of sorafenib in soft tissue sarcomas [7–10]. As a single agent, sorafenib had evidence of disease activity as defined by tumor regression against some sarcoma subtypes such as angiosarcoma and leiomyosarcoma. These trials did not include patients with rhabdomyosarcoma, a disease primarily of childhood, adolescence and young adults. Sorafenib has demonstrated biologic anti-tumor activity in adults with metastatic PTC [11,12], and case report of successful use in a pediatric patient with progressive radioactive iodine resistant PTC [13].

Evaluation of sorafenib in the National Cancer Institute's pediatric pre-clinical testing program (PTPP) showed *in vitro* cytotoxicity with a median IC(50) of 4.3 μ M as well as

growth inhibition in multiple tumor types *in vivo* [14]. Xenograft models in the PPTP did not have objective responses, but sorafenib induced tumor growth inhibition meeting criteria for intermediate activity in 44% of solid tumor xenografts. Sorafenib inhibited rhabdomyosarcoma cell growth in a dose dependent manner and *in vivo* studies demonstrated significant inhibitory effect on tumor growth associated with inhibited vascularization and enhanced necrosis in adjacent stroma [15]. Sorafenib was not evaluated in Wilms tumor xenografts in the PPTP; however, PPTP investigators and others have demonstrated activity of anti-angiogenic agents in Wilms tumors [16–19]. In an orthotopic mouse model for papillary thyroid carcinoma (PTC), sorafenib dramatically reduced tumor growth in PTC with RET/PTC1 mutation to a greater extent than in PTC with BRAF mutation [20]. This was compelling since children with PTC are more likely to have RET/PTC rearrangements and less likely to harbor somatic BRAF mutations [21,22].

In this report we describe the results of a phase 2 single agent trial of sorafenib in children with relapsed/refractory rhabdomyosarcoma, Wilms Tumor, HCC or PTC.

METHODS

Patient eligibility

At study enrollment, patients with rhabdomyosarcoma or Wilms tumor must have been 24 months and 30 years of age; patients with HCC <18 years; and those with PTC 21 years. All patients were required to have histologically confirmed, measurable, refractory or relapsed disease with no known curative treatment options. Standard performance status and organ function, as well as normal blood pressure without antihypertensive agents were also required.

The trial was approved by the National Cancer Institute Pediatric Central IRB or local institutional IRBs. All patients or their legal guardians signed a document of informed consent and assent was obtained as appropriate according to individual institutional guidelines.

Drug Administration

Sorafenib was supplied as 50- and 200-mg tablets by the Cancer Therapy Evaluation Program (NCI, Bethesda, MD). All patients received 200mg/m²/dose administered orally, twice daily, continuously for 28-day cycles. [4].

Cycles were repeated without interruption for up to 24 cycles if the patient had at least stable disease and had again met the hematologic and organ function criteria required at enrollment. A single dose reduction was allowed for subjects who experienced a reversible dose limiting toxicity (DLT).

Study Design

A two-stage design was used to evaluate sorafenib in the disease strata: rhabdomyosarcoma, Wilms tumor, HCC and PTC. The two-stage design applied if sufficient patients were enrolled to the respective stratum. The study was designed to include a futility rule to end enrollment to all strata if the rhabdomyosarcoma and Wilms tumor primary strata were

complete and if the agent was considered inactive in those strata and no responses had been observed to that point in the secondary strata for patients with HCC or PTC.

At the first stage for each stratum, 10 patients were enrolled. If no patient experienced an objective response, sorafenib was considered inactive in that stratum, and enrollment to that stratum was terminated. If more than one patient achieved a partial response or complete response by RECIST criteria, 10 additional patients would be enrolled to that stratum. Sorafenib would be considered active if 3 of 20 patients in an expanded stratum experienced a partial or complete response. With this design, sorafenib would be identified as inactive if the true response rate was 5% with a probability of 0.93, and would be identified as active if the true response rate was 30% with a probability of 0.95. The point estimate of the response rate was calculated as the maximum likelihood estimate. Confidence intervals for the response rates were calculated using the method of Jung and Kim [23].

Any eligible patient who received at least one dose of sorafenib was considered evaluable for response provided: (1) the patient demonstrated progressive disease or died while on protocol therapy; or (2) the patient was observed on protocol therapy for at least one cycle and the tumor was not removed surgically prior to the time a complete or partial response was confirmed; or (3) the patient demonstrated a complete or partial response as confirmed by central review of radiographic images. All other patients were considered non-responders. The evaluation period for determination of the overall best response was six treatment cycles.

Response evaluation

Tumor disease evaluations including standard anatomic imaging for measurable disease (CT or MRI scan) were conducted at baseline and prior to every odd numbered cycle (cycle 3, 5, 7 etc.). Response evaluation criteria for solid tumors (RECIST v 1.1) were used to categorize objective response, stable disease and progression of disease. Central radiology review was planned for any patient with objective response or prolonged stable disease.

Toxicity evaluation

Each cycle in which sorafenib was administered to an eligible patient was considered in the analysis of toxicity. Physical and laboratory exams including blood pressure monitoring, complete blood count with differential, serum chemistries, hepatic function tests, amylase and lipase were performed weekly during cycle 1 and then prior to each subsequent cycle. Bone age and lower extremity x-ray for growth plate assessments were obtained at baseline and prior to odd numbered cycles in patients who had open growth plates at the time of enrollment.

The treating physician assigned an attribution for each CTCAE version 4 gradable adverse event (AE) as unrelated, unlikely, possibly, probably, or definitely related to sorafenib. The relative frequency of each AE considered possibly, probably, or likely related to sorafenib was estimated as the proportion of all toxicity-evaluable cycles in which such toxicity was observed.

Each AE was categorized as hematologic or non-hematologic. Hematologic DLT was defined as grade 4 neutropenia or thrombocytopenia. Non-hematologic DLT was defined as any grade 4 non-hematologic; any grade 3 event (excluding nausea/vomiting < 5 days duration; AST/ALT elevation that returned to eligibility within 7 days; fever or infection < 5 days duration; hypophosphatemia, hypokalemia, hypocalcemia, and/or hypomagnesemia that responded to oral supplementation); and grade 2 that persisted for 7 days and is considered sufficiently medically significant or sufficiently intolerable by patient that it required treatment interruption. Dose limiting hypertension was defined as any grade 4 hypertension, confirmed systolic or diastolic blood pressure 25mmHg above the 95th percentile for age [24], or an elevated blood pressure not controlled by anti-hypertensive medication within 14 days according to a previously described algorithm [25]. Grade 2 allergic reactions or urticaria that necessitated discontinuation of sorafenib was not considered dose limiting.

Each cycle received by a patient was considered for DLT assessment if (1) 24 or greater days of protocol therapy was received (approximately 85% of planned therapy) and no DLT occurred during the cycle; or 2) an incident of DLT occurred during the cycle if any DLT as described above was noted. The per-cycle rate of DLT was monitoring using a Bayesian rule. A beta prior distribution with $\alpha=0.6$ and $\beta=1.4$ was employed. The analytic unit for analysis was the patient cycle; all cycles were considered independent. If at any time the posterior probability that the per-cycle DLT probability exceeded 30% was greater than 0.80, the trial was to be identified for possible termination because of an excessive DLT rate.

Pharmacokinetic and Pharmacodynamic Studies

For pharmacokinetic studies, blood samples were collected at baseline prior to sorafenib administration and 12 hours after a dose on day 15 ± 2 days in cycle 1. During subsequent cycles, blood samples for sorafenib trough concentrations were drawn prior to every odd numbered cycle. Sorafenib plasma concentrations were measured using a high performance liquid chromatography tandem mass spectroscopic method previously described [4,26].

Angiogenic cytokines VEGF and soluble VEGFR2 (sVEGFR2) were measured in plasma and quantified at baseline and on day 15 ± 2 days of cycle 1 using a human VEGF immunoassay (Quantikine, R&D Systems, Minneapolis, MN). Changes in VEGF and sVEGFR2 were compared using matched Wilcoxon signed rank test for non-parametric data.

RESULTS

Patient Characteristics

This study (study code: ADVL1121; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01502410) identifier: NCT01502410) was opened in January 2012 and closed in August 2013. Data as of June 2014 were used in the analyses. Twenty (20) patients, 10 with recurrent rhabdomyosarcoma and 10 with recurrent Wilms tumor, were enrolled. No patients were enrolled in the HCC or PTC strata. All subjects were eligible and evaluable for the primary study endpoint. The characteristics of

all eligible patients in the analytic cohort are described in Table I. At the time of the analyses all patients had completed protocol therapy.

Antitumor Activity

No objective responses were observed in the 10 evaluable patients enrolled in the rhabdomyosarcoma and Wilms tumor disease primary strata.

The median number of treatment cycles for all evaluable patients was 2 (range, 1–8). Two patients, both with Wilms tumor, had stable disease of 6 and 8 cycles duration.

According to the protocol design, sorafenib was not considered to have sufficient efficacy for further development in rhabdomyosarcoma or Wilms tumor. In each stratum, the point estimate of the response rate was 0% with associated 95% confidence interval 0%–26%.

Toxicity Evaluation

The grade 2 or higher CTC AE version 4 adverse events considered possibly, probably or likely related to sorafenib are displayed in Table II. All DLTs were grade 3 events considered possibly or probably related to sorafenib. Seven patients demonstrated dose-limiting toxicity (DLT) during the first cycle of therapy. The cycle 1 DLTs included: palmar-plantar erythrodysesthesia (1 patient); pain (2 patients); maculo-papular rash (2 patients); anorexia (1 patient); fatigue (1 patient); dyspnea (1 patient); increased serum alkaline phosphatase (1 patient); and hypoalbuminemia (1 patient). Two patients who experienced DLT during cycle 1 experienced recurrence of the same DLT again in cycle 2, which were pain (1 patient) and increased serum alkaline phosphatase (1 patient) who also had increased bilirubin. Among the seven patients with DLT, five patients restarted sorafenib with dose reduction. Among those who restarted, sorafenib was tolerable but discontinued by two patients due to progressive disease. Only one patient discontinued therapy due to adverse effect; however, one patient discontinued by patient choice and another by physician choice. The posterior probability that the probability of DLT exceeds 30% was less than 0.07. Sorafenib was not associated with an excessive rate of DLT.

Pharmacokinetics and Pharmacodynamics

A total of 10 patients consented and had sufficient samples to analyze the sorafenib steady state trough concentrations. Four patients had additional post cycle 2 trough samples measured, and one patient had post cycles 4 and 6 samples measured. The mean $\pm$ SD steady state concentration during cycle 1 day 15 was 6.5 ± 3.9 $\mu\text{g/mL}$ ($n=10$). This was consistent post cycle 2 with a mean $\pm$ SD concentration of 7.0 ± 2.9 $\mu\text{g/mL}$ ($n=4$). For the one patient with multiple troughs sampled, sorafenib concentrations were relatively stable across 6 cycles with values ranging from 4.1 to 7.0 $\mu\text{g/mL}$.

VEGF concentrations generally increased during sorafenib: mean $\pm$ SD at baseline 161 ± 137 pg/mL versus at steady state 208 ± 114 pg/mL ($n=9$) ($p=0.2$). sVEGFR2 concentrations generally decreased with the mean $\pm$ SD baseline sVEGFR2 of 9458 ± 2419 pg/mL compared to a steady state of 7612 ± 1660 pg/mL ($n=9$) ($p<0.01$). When pharmacodynamic parameters were evaluated in relationship to steady state trough sorafenib concentrations,

there was not a relationship between the change in VEGF or VEGFR2 and the trough concentration (Figure 1).

DISCUSSION

Sorafenib administered continuously at the recommended solid tumor pediatric phase 2 dose of 200 mg/m²/dose twice daily was well tolerated and the toxicity profile similar to that reported in the phase 1 trial. In contrast to adults, hypertension was not an observed toxicity in this trial. Prolonged administration of sorafenib has been associated with cumulative toxicities of rash or hypertension [27–29], however, as the median number of cycles received was only 2, we were unable to assess cumulative toxicity.

Sorafenib steady-state concentrations obtained are similar to those reported in the COG single agent phase 1 trial [4] as well as the phase 1 pediatric leukemia trial in which sorafenib was administered with clofarabine and cytarabine [30]. Similar to other kinase inhibitors of angiogenesis evaluated in children and adults [25,31,32], baseline serum VEGF was high and increased with treatment, while baseline sVEGFR2 levels were high and decreased with treatment. The magnitude of these changes from baseline was not correlated with outcome in the large prospective study of sorafenib in adults with RCC [32]. Similarly, sVEGFR2 changes did not correlate with anti-tumor activity in our study.

Sorafenib as a single agent was found to be inactive in the two solid tumor strata, rhabdomyosarcoma and Wilms tumor, as defined by protocol design. We did not use prolonged stable disease as criteria for clinical efficacy on this trial. Although a small number of patients were enrolled on this study, prolonged stable disease was only observed in two patients with Wilms tumor.

Advanced or refractory HCC and PTC are very rare in the pediatric population. Therefore, this trial was designed with a futility rule for closure if the rhabdomyosarcoma or Wilms tumor strata completed enrollment and no enrollment or no responses were observed in these secondary strata. All strata were open during the duration of the study, but no patients with HCC or PTC were enrolled onto this trial. Reasons for lack of enrollment are likely multifactorial and may include commercial availability of sorafenib and very small numbers of children and adolescents with PTC and HCC. Sorafenib capsules are FDA approved and commercially available. However, formulations for dosing of small children including the 50 mg capsules used in this trial, are not commercially available.

The role of sorafenib in the treatment of children and adolescents with rare tumors is uncertain. A retrospective study in children with primary HCC concluded that sorafenib with cisplatin and doxorubicin may be a promising approach in children with HCC [33]. The subset of children with PTC and progressive distant metastasis that is no longer responsive to radioactive iodine and is not amenable to surgery is likely to be very small, however, there is no known effective therapy for patients who develop refractory PTC [13]. Successful use of sorafenib to treat a child with progressive metastatic resistant PTC has been reported [13].

Despite challenges, enrollment of children and adolescents with very rare pediatric tumors on clinical trials remains a priority for the Children's Oncology Group. Collaboration, novel trial designs, careful consideration of endpoints and appropriate drug formulations are required as genomic subtyping of tumors for the evaluation of targeted therapies further defines and restricts eligibility criteria for clinical trials.

In summary, sorafenib is well tolerated in children at 200 mg/m²/dose twice daily on a continuous regimen. Single agent sorafenib was determined inactive in the rhabdomyosarcoma and Wilms tumor cohorts. The lack of objective responses in this study suggests that combination studies may be warranted. Sorafenib is currently undergoing evaluation in combination with irinotecan (NCT01518413) and in combination with topotecan (NCT01683149) in children with refractory solid tumors.

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Figure 1. Pharmacokinetic- Pharmacodynamic Relationship

The percent change (baseline to day 15) in pharmacodynamic markers (VEGF, closed circles; VEGFR2, open squares) is plotted as a function of the individual patient's day 15 steady state sorafenib trough (Cmin, µg/mL). Nine subjects had sufficient data for inclusion in this analysis. In the small range of steady state trough concentrations, there was no relationship between sorafenib concentration and change in VEGF or VEGFR2.

Table I

Characteristics of Eligible Patients

Characteristic	Diagnosis		
	RMS* (n=10)	Wilms (n=10)	All (n=20)
Age (years)			
Median	12	11	11
Range	5–21	7–18	5–21
Gender			
Male:female	6:4	5:5	11:9
Race			
White	7	7	14
African American	3	0	3
Asian	0	1	1
Other	0	1	1
Unknown	0	1	1

* RMS, rhabdomyosarcoma; Wilms, Wilms tumor

Table II

Grade 2 and Higher Toxicities Possibly, Probably, or Likely Related to Protocol Therapy

	Maximum grade of toxicity (total number of patient cycles =48)	
Toxicity Type	Grade 2	Grade 3
Hematologic		
Lymphocyte count decreased		1
Neutrophil count decreased		2
Platelet count decreased		1
Constitutional		
Fatigue		1
Dermatologic		
Palmar-plantar erythrodysesthesia		1
Rash maculo-papular		2
Gastrointestinal		
Anorexia		1
Metabolic/laboratory		
Alkaline phosphatase increased		2
Blood bilirubin increased		1
Hypoalbuminemia		1
Hypocalcemia		1
Hypokalemia		1
Hypophosphatemia		1
Musculoskeletal /connective tissue		
Other, not specified	1	
Pain		
Abdominal pain		1
Back pain		1
Neck pain	1	
Pain in extremity		1
Pain (not specified)	1	
Renal and Urinary		
Proteinuria	1	
Respiratory		
Dyspnea	1	1
Pleural effusion	1	
Upper respiratory infection	1	