

Phase I Trial of Preoperative Chemoradiation plus Sorafenib for High-Risk Extremity Soft Tissue Sarcomas with Dynamic Contrast-Enhanced MRI Correlates

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Abstract

Purpose: We conducted a phase I trial of the addition of sorafenib to a chemoradiotherapy regimen in patients with high-risk (intermediate/high grade, >5 cm) extremity soft tissue sarcoma undergoing limb salvage surgery. We conducted a correlative study of quantitative dynamic contrast-enhanced MRI (DCE-MRI) to assess response to treatment.

Experimental Design: Patients were treated at increasing dose levels of sorafenib (200 mg daily, 400 mg daily, 400 mg twice daily) initiated 14 days before three preoperative and three postoperative cycles of epirubicin/ifosfamide. Radiation (28 Gy) was administered during cycle 2 with epirubicin omitted. The primary objective was to determine the maximum tolerated dose (MTD) of sorafenib. DCE-MRI was conducted at baseline, after 2 weeks of sorafenib, and before surgery. The imaging data were subjected to quantitative pharmacokinetic analyses.

Results: Eighteen subjects were enrolled, of which 16 were evaluable. The MTD of sorafenib was 400 mg daily. Common grade 3–4 adverse events included neutropenia (94%), hypophosphatemia (75%), anemia (69%), thrombocytopenia (50%), and neutropenic fever/infection (50%). Of note, 38% developed wound complications requiring surgical intervention. The rate of $\geq 95\%$ histopathologic tumor necrosis was 44%. Changes in DCE-MRI biomarker ΔK^{trans} after 2 weeks of sorafenib correlated with histologic response ($R^2 = 0.67$, $P = 0.012$) at surgery.

Conclusion: The addition of sorafenib to preoperative chemoradiotherapy is feasible and warrants further investigation in a larger trial. DCE-MRI detected changes in tumor perfusion after 2 weeks of sorafenib and may be a minimally invasive tool for rapid assessment of drug effect in soft tissue sarcoma. *Clin Cancer Res*; 19(24); 6902–11. ©2013 AACR.

Introduction

The optimal management of patients with high-risk (intermediate/high grade, >5 cm) extremity soft tissue sarcomas remains undefined. Although local control rates of 80% to 90% can be achieved with limb salvage surgery and radiation therapy, up to 50% of these patients will die from metastatic disease (1–5). The use of chemotherapy to address micrometastatic disease remains controversial, and the optimal regimen and timing of chemotherapy in rela-

tion to surgery and radiation is unknown. One strategy that has been investigated is combination preoperative chemotherapy and radiation. This approach has the theoretical advantages of early treatment of micrometastatic disease and radiation sensitization to decrease the chance of local recurrence. We have previously reported our results with a regimen of pre- and postoperative epirubicin and ifosfamide with preoperative hypofractionated radiotherapy (6). This hypofractionated radiotherapy plan (28 Gy over 8 fractions) was originally developed by the UCLA group to maximize efficacy while minimizing complications (7).

Overexpression of platelet-derived growth factor receptor (PDGFR), VEGF, and VEGF-R occurs in soft tissue sarcomas (8–10). VEGF-R tyrosine kinase inhibitors have shown activity against a variety of soft tissue sarcomas, with pazopanib receiving an U.S. Food and Drug Administration indication for soft tissue sarcoma treatment in 2012 (11). Sorafenib, an oral inhibitor of multiple tyrosine kinases including VEGF, PDGF, raf, flt-3, and c-kit, has likewise been studied in patients with refractory soft tissue sarcomas including 2 phase II studies that suggested clinical benefit

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Translational Relevance

Overexpression of platelet-derived growth factor receptor (PDGFR), VEGF, and VEGF-R is seen in soft tissue sarcomas, and VEGF-targeted therapies have shown some activity in the treatment of advanced disease. We hypothesized that the addition of sorafenib to a chemoradiotherapy regimen in conjunction with surgery is tolerable and could improve disease control. This phase I trial established a maximum tolerated dose of 400 mg of sorafenib daily in combination with this chemoradiotherapy regimen. Dynamic contrast-enhanced MRI (DCE-MRI) detects changes in blood flow and blood vessel wall permeability, making it an attractive imaging modality for assessing response to antiangiogenic agents. We observed that a DCE-MRI biomarker, ΔK^{trans} , measured after only 2 weeks of treatment with sorafenib alone correlated with histologic necrosis at surgery. These results have provided a rationale for investigating this novel imaging biomarker in future studies with antiangiogenic agents for early prediction of response.

particularly in patients with vascular sarcoma subtypes (12, 13). The addition of antiangiogenic drugs such as sorafenib to chemoradiotherapy has been found to be safe and has promising results in early clinical studies in various solid tumors (14–17). Blockade of VEGF signaling may help normalize tumor vasculature and enable better drug delivery to the tumor and oxygenation to enhance the effectiveness of radiation (15). We hypothesized that the addition of sorafenib to chemoradiotherapy would be safe and could improve outcomes by potentiating the effects on the local tumor and enhancing the effects on micrometastatic disease.

We conducted a phase I trial to determine the maximum tolerated dose (MTD) of sorafenib in combination with pre- and postoperative epirubicin and ifosfamide and 28 Gy of preoperative hypofractionated radiotherapy. DCE-MRI is a powerful imaging tool for evaluation of tumor microvascular properties. An additional exploratory objective was to use the quantitative DCE-MRI approach to assess preoperative therapy effects.

Materials and Methods

Eligibility

Eligible patients were ≥ 15 years of age with histologically confirmed intermediate or high grade (grade 2–3 on a 3-point scale or grade 2–4 on a 4-point scale) soft tissue sarcoma of the extremities or body wall. Excluded histologies were rhabdomyosarcoma (patients with pleomorphic rhabdomyosarcoma were eligible), Ewing sarcoma, primitive neuroectodermal tumor, osteosarcoma, or gastrointestinal stromal tumor. Tumors were superficial or deep and > 5 cm in greatest dimension. Patients had no contraindications

to limb sparing surgery. Patients with metastatic disease (excluding brain metastases) were allowed, if they were appropriate candidates for resection of the primary tumor. No prior chemotherapy, radiation, or biotherapy was permitted. Patients had Eastern Cooperative Group performance status of 0 or 1, adequate organ function, and left ventricular ejection fraction (LVEF) $\geq 50\%$. Patients with systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management, serious bleeding or major surgery within the previous 4 weeks, coagulopathy, severe peripheral vascular disease, or malabsorption problems were excluded. The protocol was approved by the local institutional review board, and all patients provided written informed consent.

Study design

Subjects were treated at escalating dose levels of sorafenib (200 mg daily, 400 mg daily, or 400 mg twice daily) and fixed doses of chemotherapy and hypofractionated radiation. MTD was defined as the dose that produced dose limiting toxicity (DLT) in no more than 33% of patients. At least 3 patients were enrolled at each dose level. If 1 of the first 3 patients experienced DLT, the dose level was expanded to a total of 6 patients. If no more than one DLT was observed among the 6 patients, enrollment proceeded to the next dose level. If 2 or more of 3 patients or 3 or more of 6 patients experienced DLT, the MTD was considered exceeded and the dose was reduced to the previous level. Dose escalation was determined on the basis of the DLTs observed through the first 8 weeks of therapy. DLT was defined as grade 4 anemia, grade 4 neutropenia > 7 days, grade 3–4 thrombocytopenia with bleeding or grade 4 thrombocytopenia > 5 days, and grade 3–4 nonhematologic toxicity. Exceptions to this definition included nausea/vomiting responsive to antiemetics, grade 3 neutropenic fever ≤ 5 days, grade 3 encephalopathy ≤ 2 days, grade 3–4 hypokalemia, hypophosphatemia, hypomagnesemia, hypocalcemia unless requiring hospitalization, grade 3 diarrhea controlled with medication within 2 days, and grade 3 hypertension controlled with medication.

Sorafenib was initiated 14 days before the first cycle of chemotherapy and administered orally at the assigned dose level. Sorafenib was discontinued 1 week before surgery and resumed 1 week after surgery and then continued until the completion of postoperative chemotherapy. Chemotherapy consisted of epirubicin 30 mg/m²/d for days 1–3 and ifosfamide 2.5 g/m²/d for days 1–3 every 21 days for 3 preoperative and 3 postoperative cycles. These doses were chosen to be 25% less than used in our previous trial as the average delivered dose intensity in that study was only 69% of planned (6). Intravenous hydration and mesna were administered with each cycle. Peg-filgrastim was administered after each cycle of chemotherapy. Epirubicin was omitted during cycle 2, which coincided with the start of external beam hypofractionated radiotherapy consisting of 28 Gy administered over 8 daily fractions. The biologic effective dose of the hypofractionated regimen is estimated to be slightly lower than that of a standard fractionation

regimen to maintain the same level of toxicity when the radiation is delivered concurrently with radiation-sensitizing chemotherapy. A postoperative radiotherapy boost of 12 Gy over 6 daily fractions was given only to patients with positive surgical margins and began approximately 2 weeks following resection. At week 11 of treatment, surgical resection with wide excision was planned with margins >1 cm where possible, without compromising function. Around vital structures, the margin removed was often <1 cm. Dissection was done through grossly normal tissue planes. If the tumor was close to or displaced major vessels, nerves, or bone; adventitia, perineurium, or periosteum was removed and frozen section was checked. If this margin was considered negative, the vessel, nerve, or bone remained. The use of pedicled muscle, myocutaneous flaps, or free flaps was encouraged to fill dead space and provide adequate soft tissue coverage for vital structures. Split thickness skin graft was used as necessary. Sorafenib and chemotherapy were resumed as soon as adequate wound healing was achieved.

The sorafenib dose was reduced for grade 4 or recurrent grade 3 nonhematologic toxicity and for grade 2 symptomatic/persistent or grade 3 hypertension. Grade 4 hypertension required discontinuation of sorafenib. A dose reduction could also be considered for grade 2 hand-foot skin reaction and was required for the second occurrence of grade 2 or for grade 3 hand-foot skin reaction. Re-escalation of sorafenib was permitted after improvement of hand-foot skin toxicity to grade 0 and 1.

Assessments

Safety. Safety evaluations including history and physical examinations, vital signs, and adverse event (AE) assessment were conducted at screening, before each cycle, before surgery, and at the end of treatment. Blood pressure was monitored weekly for the first 6 weeks of therapy. Laboratory tests including complete blood counts (CBC) and chemistries were checked weekly during treatment. MUGA or echocardiography was obtained before treatment and before cycle 5. Adverse event severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Efficacy. All specimens of the primary tumor were examined for histologic response at the time of surgery by the study pathologist who estimated the amount of viable tumor and reported the percentage of necrosis. For the purposes of this study, specimens were classified as either $\geq 95\%$ necrosis or $< 95\%$ necrosis. Radiographic response of the primary tumor was evaluated at baseline and before surgery per Response Evaluation Criteria in Solid Tumors (RECIST; ref. 18).

DCE-MRI

Subjects were given the opportunity to consent to a separate Institutional Review Board (IRB)-approved study evaluating the use of DCE-MRI biomarkers for evaluation of therapy response during the preoperative period. DCE-

MRI of the primary tumor was conducted within 7 days before the start of treatment with sorafenib, approximately 2 weeks after initiating sorafenib therapy but before receiving chemotherapy, and once more after the completion of preoperative therapy, before surgery. MRI data were acquired with a 3T Siemens Tim Trio whole-body system using the body coil as the transmitter and a body matrix phased array (combined with a spine matrix phased array) coil as the receiver. Following scout and axial T₂-weighted MRI, a 3D RF-spoiled gradient echo sequence was used to acquire sagittal DCE-MRI images covering the entire tumor, with 10° flip angle, TE/TR = 1.5/6.0 ms, 24–26 cm field of view (FOV), 5 mm slice thickness, and 320 × 160 matrix size. A parallel imaging acceleration factor of 2 was used for DCE-MRI, resulting in 7- to 16-second temporal resolutions depending on tumor size. The total DCE acquisition time was approximately 10 min with gadolinium contrast agent (Prohance) IV injection (0.1 mmol/kg at 2 mL/s) carried out following acquisition of 5 baseline image volumes.

For pharmacokinetic modeling of the DCE-MRI data, the arterial input function (AIF) was determined by direct measurement from a major artery within the image field of view, adjacent to the tumor: for example, femoral artery was used for AIF measurement for most tumors located in the thigh, knee, and calf. The DCE-MRI data set was subjected to pharmacokinetic analysis twice, once with the standard model (SM) or Tofts model (19) and once with the shutter-speed model (SSM; refs. 20, 21)—the former ignores whereas the latter takes into account the intercompartmental water exchange kinetics. DCE-MRI time course data fitting with the SM and SSM generated the values of K^{trans} (rate constant for contrast agent transfer between plasma and interstitium) and ν_e (extravascular and extracellular volume fraction) for each model, and ΔK^{trans} , defined as [$K^{\text{trans}}(\text{SSM}) - K^{\text{trans}}(\text{SM})$] (22–24), was calculated. As the only difference between the 2 models is that the SSM takes into account the finite water exchange kinetics whereas SM does not, ΔK^{trans} appraises the exchange effects on K^{trans} estimation (22–24). As a result of always assuming infinitely fast equilibrium transcytoleml and transendothelial water exchange kinetics, the SM generally underestimates tumor K^{trans} values (22–24). In a recent breast DCE-MRI study, we have shown that ΔK^{trans} is a more sensitive and specific imaging biomarker for breast cancer diagnosis than either $K^{\text{trans}}(\text{SSM})$ or $K^{\text{trans}}(\text{SM})$ (refs. 22, 23). The theory and mathematical formulations for the SM and SSM analyses of DCE-MRI data obtained with a gradient echo sequence have been described in detail (20–22). The whole tumor region of interest (ROI) DCE-MRI parameter values were calculated by averaging the ROI values from each of the image slices covering the entire tumor, weighted by the pixel numbers within the ROI in each image slice. Pixel parameter values were analyzed with histograms and the amplitude and median values were obtained. MRI tumor size changes were assessed with RECIST (18) using the post-contrast DCE images at or near the maxima of signal intensity time courses.

Statistical analysis

Descriptive statistics were used to summarize patient clinical characteristics, safety data, and the percentage of patients who achieved histologic or radiologic response. Progression-free survival (defined as the duration of time from registration to progressive disease, local recurrence, distant metastatic disease, or death, whichever occurs first) was estimated using Kaplan–Meier method. Linear regression analysis was used to test the association between percent necrosis in the pathology specimen at the time of surgical resection (dependent variable) and the changes in DCE-MRI parameters and RECIST after 2 weeks of treatment with sorafenib (independent variables).

Results

Patient characteristics

Eighteen patients were consented for this study from September 2009 through July 2011. One patient was found to be ineligible due to a history of a gastric bypass. Another patient withdrew consent before starting treatment leaving 16 patients who were eligible and received study treatment (Table 1). The median length of follow-up at the time of this report is 26 months (range, 19–40 months).

MTD and DLTs

A summary of DLTs is included in Table 2. Dose level 1 was expanded by 3 patients due to a DLT of grade 3 mucositis in 1 of the first 3 patients. One patient at dose level 2 developed grade 3 hypertension that was controlled with adjustment of antihypertensive medication but nonetheless required sorafenib dose reduction due to the prespecified dose modification guidelines. As this event did not meet the definition of DLT, an additional patient was enrolled at this dose level to adequately determine safety for dose escalation. At dose level 3, all patients experienced DLT. One patient developed grade 4 neutropenic sepsis with an associated catheter-related septic thrombus as well as grade 3 hand–foot syndrome. The remaining 2 patients developed grade 3 rash and hand–foot syndrome. The MTD was determined to be sorafenib 400 mg once daily. Dose level 2 was subsequently expanded by an additional 3 patients to further estimate safety. Of these 3 patients, one experienced a syncopal event and therefore one DLT in the dose level 2 cohort.

A summary of delivery of epirubicin and ifosfamide chemotherapy is detailed in Table 2. Twelve patients (75%) completed all 6 cycles of planned chemotherapy with epirubicin and ifosfamide and 6 (38%) completed all planned chemotherapy without dose reduction. Three of the 4 patients who did not complete all 6 cycles received 5 cycles of chemotherapy. The remaining one patient, who was treated in the dose level 3 cohort, withdrew consent after one cycle of chemotherapy because of toxicity (neutropenic sepsis, thrombosis, and hand–foot syndrome).

Six patients (38%) discontinued sorafenib before the end of treatment. Three patients (19%), 2 in dose level 2 and 1 in dose level 3, required discontinuation per protocol for

Table 1. Baseline patient demographics and clinical characteristics ($N = 16$)

Characteristic	n (%)
Age, y	
Median	54
Range	25–63
Sex	
Male	12 (75)
Female	4 (25)
ECOG performance status	
0	13 (81)
1	3 (19)
Largest tumor dimension, cm	
Median	11.7
Range	6.6–26.1
Grade	
Intermediate	9 (56)
High	7 (44)
Depth	
Superficial	0
Deep	16 (100)
Stage (AJCC 6th edition)	
III	14 (88)
IV	2 (12)
Histology	
Pleomorphic/NOS	7 (44)
Synovial	5 (31)
Liposarcoma	3 (19)
Leiomyosarcoma	1 (6)
Location	
Lower extremity	12 (75)
Upper extremity	4 (25)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

prolonged thrombocytopenia, decreased LVEF, and rash, respectively. One patient was removed from protocol treatment due to a greater than 3-week delay in treatment as the result of a wound complication. Two patients withdrew consent. Four patients (25%) required at least one dose reduction of sorafenib with 3 of the 4 patients being treated at dose level 3. The mean dose delivery of the planned sorafenib dose was 91%, 87%, and 38% for dose levels 1, 2, and 3, respectively.

Safety

The most common adverse events are shown in Table 3. Fourteen patients (88%) experienced grade 4 toxicity but only 2 patients (13%) experienced a grade 4 nonhematologic toxicity similar to 84% and 16% reported with our previous chemoradiotherapy regimen without sorafenib (6). Eight patients (50%) experienced a neutropenic fever or neutropenic infection despite the routine use of

Table 2. DLTs and dose intensity

	Dose level 1	Dose level 2	Dose level 3
Sorafenib dose	200 mg daily	400 mg daily	400 mg BID
Epirubicin dose per cycle	30 mg/m ² /d × 3 d	30 mg/m ² /d × 3 d	30 mg/m ² /d × 3 d
Ifosfamide dose per cycle	2,500 mg/m ² /d × 3 d	2,500 mg/m ² /d × 3 d	2,500 mg/m ² /d × 3 d
Radiation	350 cGy × 8 fractions	350 cGy × 8 fractions	350 cGy × 8 fractions
Subjects, n	6	7	3
DLTs, n	1	1	3
DLT (grade)	Mucositis (3)	Syncope (3)	1. Neutropenic sepsis (4), thrombosis (3), hand-foot syndrome (3) 2. Rash (3), hand-foot syndrome (3), 3. Rash (3)
Mean dose delivered of epirubicin (% of planned dose)	86%	86%	73%
Mean dose delivered of ifosfamide (% of planned dose)	94%	92%	73%

NOTE: DLTs during the first 8 weeks of treatment.

prophylactic colony-stimulating factor, similar to the 40% rate previously reported (6). Two patients (13%) had a grade 1 decline in LVEF. Two patients (13%) experienced grade 3 ifosfamide-induced neurotoxicity. There was a high rate of hypophosphatemia with 12 patients (75%) developing grade 3 hypophosphatemia compared with only 16% previously reported with the chemoradiation alone (6). No treatment-related deaths have occurred.

Nine postoperative wound complications that required surgical intervention occurred in 6 patients (38%). An expected 35% wound complication rate with preoperative radiation alone has been previously published (25). Most of the complications were infectious and required IV antibiotics and surgical debridement. Four of the 6 patients with wound complications had lower extremity tumors.

Efficacy

Limb salvage surgery was conducted on all 16 patients. One patient ultimately required amputation after falling and fracturing the tibia at the site of an infected wound. Only one patient had microscopically positive margins requiring postoperative boost radiotherapy. Seven patients (44%) had ≥95% histologic necrosis in the surgical specimen following preoperative chemoradiotherapy; we previously reported a 40% rate in our prior phase II trial without sorafenib (6). Three of these patients were treated in the dose level 1 cohort, and the remaining 4 patients were treated in the dose level 2 cohort. Histologic necrosis ranged from 10% to 100%. One patient (6%) had a partial response by RECIST. This patient was treated in the dose level 2 cohort and had <95% histologic necrosis in the surgical specimen. No patients had progressive disease by RECIST during the preoperative treatment period.

A Kaplan–Meier curve of progression-free survival is shown in Fig. 1. With a median follow-up of 26 months, none of the 14 subjects with stage III disease have recurred. Two subjects with metastatic disease at baseline progressed at 6 and 14 months, respectively, after the completion of study treatment. At the time of writing, there have been no local recurrences and no patients in this study have died.

DCE-MRI

Eleven of the 16 patients were enrolled in the correlative DCE-MRI study. Eight of these patients completed at least the first 2 of the 3 planned MRI studies. Tumors that showed a greater decrease in ΔK^{trans} (tumor ROI value or histographic median of the pixel values) after 2 weeks of sorafenib were generally found to have a higher percentage of histologic necrosis in the subsequent surgical specimen (Fig. 2), whereas changes in RECIST measurements of tumor size after 2 weeks of treatment with sorafenib were indeterminate in relation to necrosis percentage. The inverse relationship of percent change in tumor ΔK^{trans} after 2 weeks of sorafenib with necrosis percentage of surgical specimen is statistically significant ($R^2 = 0.67$, $P = 0.012$). On the basis of mean ROI and histographic median K^{trans} (SM), K^{trans} (SSM), and ΔK^{trans} values, the percentage change of ΔK^{trans} was able to differentiate 2 of 3 patients with optimal responses (≥95% necrosis in surgical specimen) from 5 with suboptimal responses (<95% necrosis; Fig. 2), whereas those of K^{trans} (SM) and K^{trans} (SSM) could only discriminate one optimal responder from the suboptimal responders. After completion of preoperative treatment, however, multiple MRI parameters were good biomarkers to completely differentiate the optimal from suboptimal responders, including RECIST, ROI,

Table 3. Most common and grade 3–4 adverse events

Adverse event	All grades and DLs (N = 16), n (%)	DL 1 (n = 6)		DL 2 (n = 7)		DL 3 (n = 3)	
		Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Hematologic							
Neutrophils	16 (100)		6		7	1	2
Lymphopenia	16 (100)		6	1	6	2	1
Hemoglobin	16 (100)	2	4	1	6	2	1
Platelets	16 (100)	2	4	4	3	2	1
Leukocytes	15 (94)	1	5		6	1	2
Nonhematologic							
Alopecia	16 (100)	6		7		3	
Nausea/vomiting	16 (100)	6		7		3	
Fatigue	15 (94)	5		5	2	3	
Constipation	12 (75)	4		6		2	
Diarrhea	11 (69)	4	1	4		2	
Rash	10 (63)	4		4			2
Rash/burn associated with radiation	10 (63)	4		5		1	
Mucositis	10 (63)	2	1	5		2	
Neutropenic fever/neutropenic infections	8 (50)		3		4		1
Hand-foot syndrome	8 (50)	1		4		1	2
Hiccoughs	8 (50)	3		4		1	
Anorexia	8 (50)	4		3		1	
Hypertension	7 (44)	1	3	1	1	1	
Headache	7 (44)	3		2		2	
Non-neutropenic infections	6 (38)	1	2	1	2		
Dyspnea	5 (31)	3		2			
Atrial/sinus tachycardia	5 (31)	4				1	
Taste alteration	5 (31)	3		2			
Voice changes	5 (31)	2		2		1	
Encephalopathy/memory impairment	4 (25)		2	2			
Vasovagal/syncope	3 (19)		1	1	1		
Fracture	2 (13)				2		
Thrombosis	2 (13)		1				1
Laboratory abnormalities							
Hypoalbuminemia	15 (94)	4	2	6		3	
Hypophosphatemia	14 (88)		5	2	4		3
Hyponatremia	14 (88)	5	1	4	1	3	
Transaminitis	11 (69)	6		4		1	
Alkaline phosphatase	9 (56)	5		3		1	
Hypokalemia	8 (50)	1	3	2		1	1
Hypomagnesemia	8 (50)	3		2		3	
Hypocalcemia	7 (44)	2	1	3		1	
Hyperglycemia	6 (38)	5		1			
Hyperbilirubinemia	3 (19)	2			1		
Hyperkalemia	1 (6)				1		

NOTE: All adverse events with frequency of >25% and all grade 3–4 adverse events, regardless of frequency. There were no grade 5 adverse events.

Abbreviation: DL, dose level.

and histographic median values of $K^{\text{trans}}(\text{SM})$, $K^{\text{trans}}(\text{SSM})$, and ΔK^{trans} (data not shown). v_e is not a good discriminator of the 2 responder groups at either time point (data not shown). Figure 3A shows tumor $K^{\text{trans}}(\text{SM})$, $K^{\text{trans}}(\text{SSM})$,

and ΔK^{trans} maps on one image slice at 3 time points in one patient with a good histologic response ($\geq 95\%$ necrosis). All 3 parameter values were substantially reduced after 2 weeks of sorafenib, with the decrease in ΔK^{trans} being the

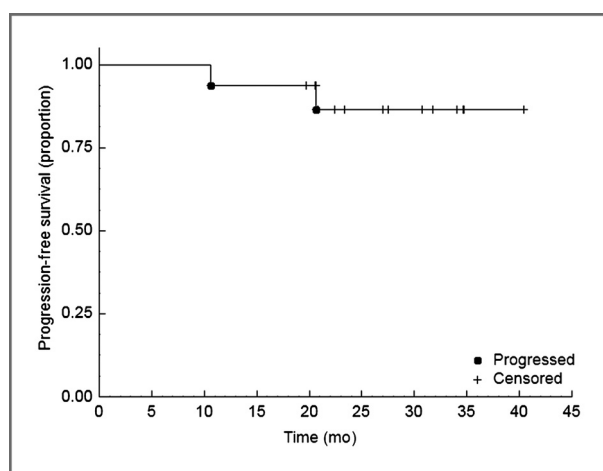


Figure 1. Kaplan-Meier curve of progression-free survival. With a median follow-up of 26 months, there have been no local recurrences and 2 of 16 subjects had progression of distant metastatic disease.

most dramatic. The percentage change in the mean ROI or histographic median ΔK^{trans} value, but not those of the corresponding K^{trans} (SM) and K^{trans} (SSM) values, was able to discriminate this patient from the suboptimal responders. After the completion of the entire treatment course, all 3 maps were essentially uniformly blue (close to values of zero), consistent with minimal perfusion and considerable necrosis. Figure 3B shows the same types of parametric maps at baseline and after 2 weeks of sorafenib treatment for a suboptimal (30% necrosis at surgery) and another optimal responder (99% necrosis at surgery). Again, the K^{trans} (SM and SSM) and ΔK^{trans} parameters were significantly decreased for the optimal responder—in this case, the percentage changes of all 3 parameters was able to discriminate this optimal responder from the suboptimal responders, whereas there were no noticeable changes for the suboptimal responder after 2 weeks of sorafenib.

Discussion

The addition of sorafenib to chemoradiotherapy for extremity soft tissue sarcomas is feasible without significant additional systemic toxicity compared with historical studies using pre- and postoperative chemoradiotherapy alone. We determined an MTD for sorafenib of 400 mg daily when combined with a regimen of preoperative hypofractionated radiation and pre- and postoperative epirubicin and ifosfamide and recommend this dose for phase II testing.

Sorafenib-associated toxicities including rash and hand-foot syndrome limited further dose escalation of sorafenib when administered with chemoradiotherapy. At the MTD of sorafenib, toxicity was similar to that seen with chemoradiotherapy alone (6). The most common grade 3–4 non-hematologic toxicity was hypophosphatemia, a known side effect of both sorafenib and ifosfamide, which was managed with phosphorus replacement and did not lead to any sequelae. Side effects were expected from the agents used, and there was no clear evidence of synergistic toxicity.

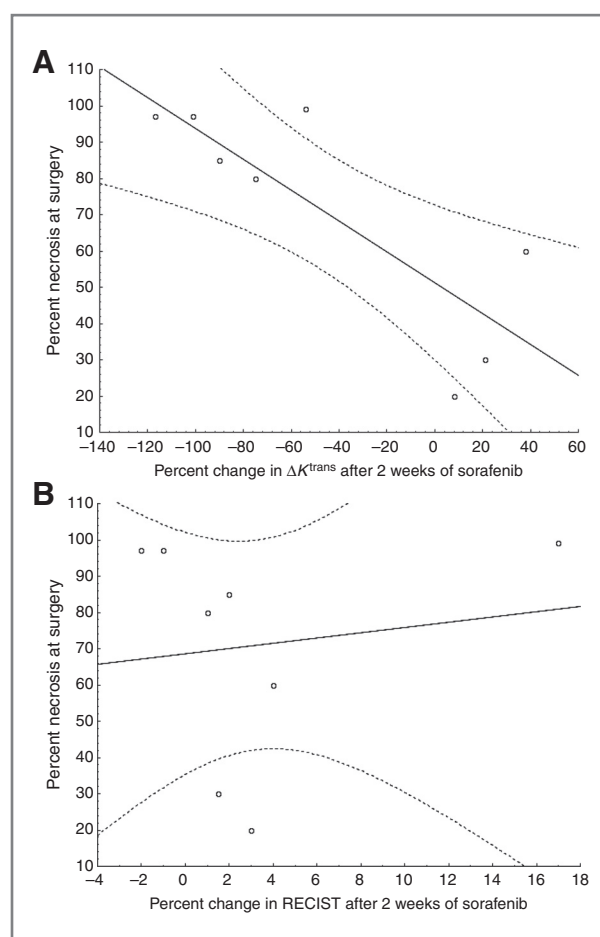


Figure 2. Scatter plots of percentage necrosis at the time of surgery versus percentage changes in tumor ROI ΔK^{trans} (A) and RECIST measure of tumor size (B) after 2 weeks treatment with sorafenib. The percentage change in ΔK^{trans} was significantly inversely associated with percent necrosis at surgery (A; $R^2 = 0.675$, $P = .012$), whereas percentage change in RECIST did not correlate with percent necrosis at surgery (B; $R^2 = 0.019$, $P = 0.747$). The solid lines indicate the predicted means from the linear regression model with 95% confidence bands shown by dashed lines.

Acute wound-healing complications are a potential disadvantage to the preoperative administration of radiotherapy in patients with extremity soft tissue sarcomas. The rate of wound complications of 38% in this study is similar to what has been reported with preoperative radiation alone, although greater than the 20% rate we previously reported with chemoradiation alone (6, 25). While acute wound complications associated with preoperative radiation is most commonly a phenomenon of lower extremity tumors, 2 of the 4 patients with upper extremity tumors in our study experienced wound complications. Further evaluation of the effect of sorafenib on wound healing in this setting should be carefully evaluated in future clinical trials.

The prescribed doses of epirubicin and ifosfamide were 25% less than used in our previous trial of chemoradiotherapy, in recognition that the previous study achieved only a 69% average delivered dose intensity (6). With the lower

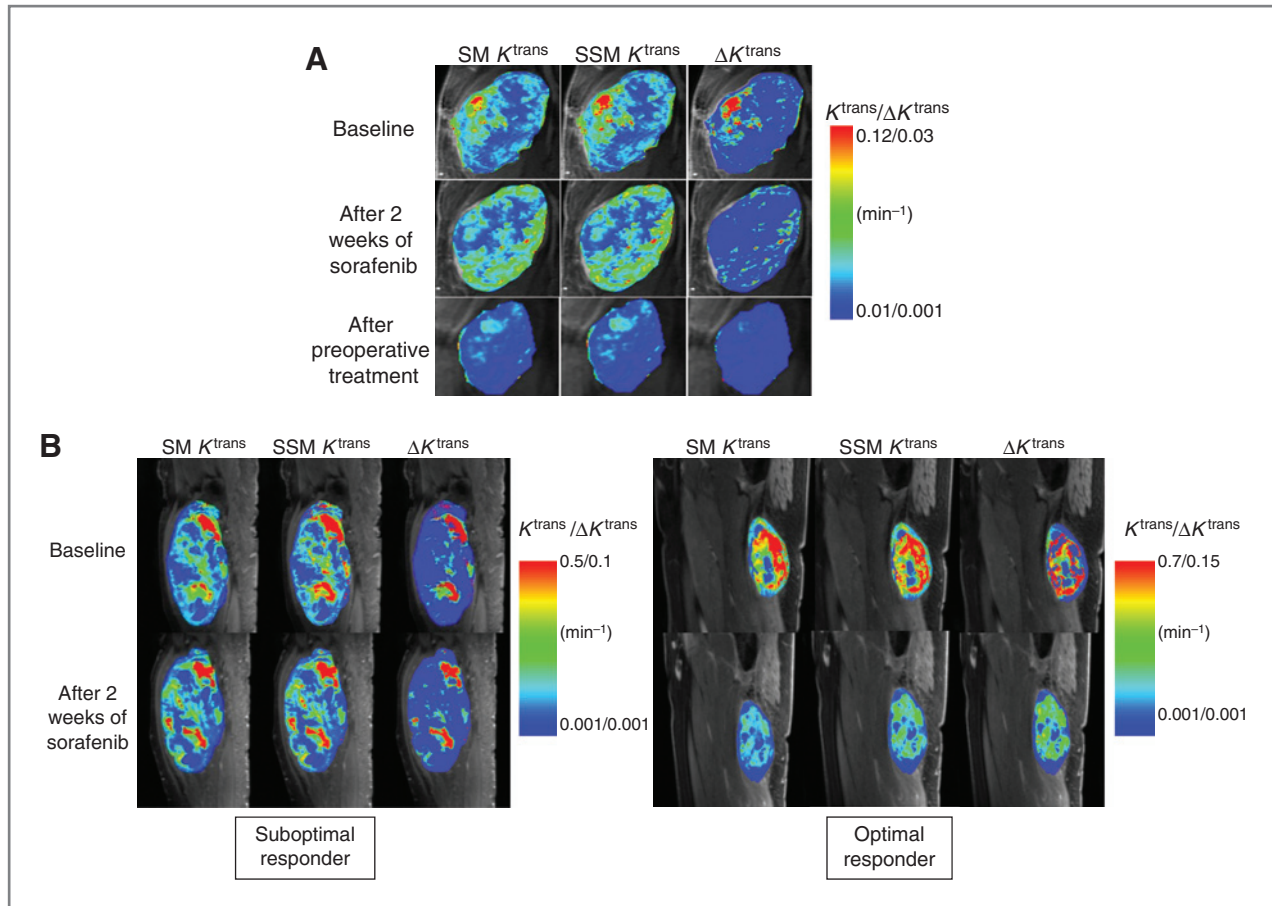


Figure 3. A, parametric color maps of tumor K^{trans} (SM), K^{trans} (SSM), and ΔK^{trans} before treatment (baseline), after 2 weeks of sorafenib, and after completion of preoperative treatment are overlaid on corresponding post-contrast DCE-MRI images. Substantial decreases in K^{trans} (SM and SSM) and especially ΔK^{trans} were observed after only 2 weeks of sorafenib in a myxoid round cell liposarcoma that showed good histologic response (>95% necrosis) at surgery. B, similar maps at baseline and after 2 weeks of sorafenib from a suboptimal responder (30% necrosis at surgery) and another optimal responder (99% necrosis at surgery). No noticeable changes were seen in K^{trans} (SM and SSM) and ΔK^{trans} maps of the suboptimal responder after 2 weeks of sorafenib.

doses of chemotherapy used in the current study, the mean dose delivered of epirubicin and ifosfamide ranged from 86% to 94% in dose levels 1 and 2 and was only 73% in dose level 3. Higher doses of sorafenib may have decreased the tolerability of the chemotherapy backbone, further supporting the choice of 400 mg sorafenib as the recommended phase II dose.

We found evidence of activity in this phase I study, with only 2 patients developing progressive disease and no deaths with a median follow-up of 26 months. Both progressing patients harbored low volume pulmonary metastatic disease at study entry and remained free of disease progression for 6 and 14 months. Of the remaining 14 patients with nonmetastatic disease at study entry, there have been no local or distant recurrences. The estimated 2-year disease-free survival in our previous trial using the chemotherapy backbone of epirubicin and ifosfamide was 62% (6). Evidence of significant treatment effect was seen in 44% of tumors that were found to have $\geq 95\%$ histologic necrosis in the operative specimen. Since the time that this study was initiated, VEGF-R tyrosine kinase inhibitors have

been established as active therapy for advanced soft tissue sarcomas (11). Data from a VEGF-overexpressing sarcoma mouse model showed that VEGF-R blockade can enhance chemotherapy responsiveness and decrease the development of pulmonary metastases (26), suggesting that the benefit of these agents could potentially be greatest in the low disease burden setting of earlier stage disease. The preliminary efficacy results from this phase I trial support further study in a larger trial.

One of the challenges to clinical trial design using antiangiogenic agents is that radiographic changes may be subtle. In this study, only one patient had a RECIST-defined partial response to preoperative chemoradiotherapy. However, primary soft tissue sarcomas are often heterogeneous tumors admixed with viable tumor, fibrosis, and hemorrhage, and radiographic tumor shrinkage to preoperative therapy often does not correlate with pathologic and clinical outcomes (27–30). DCE-MRI is a functional imaging modality that can detect changes in blood flow and blood vessel wall permeability and is being increasingly used as an imaging biomarker in studying the effect of antiangiogenic

agents. To our knowledge, this is the first study using DCE-MRI as an imaging biomarker for preoperative chemoradiotherapy in high-risk extremity soft tissue sarcomas in humans. While the SM (19) is frequently used to estimate kinetic parameters such as K^{trans} , the most reliable pharmacokinetic parameter for assessing the effect of antiangiogenic drugs remains undefined (31). The SSM is a comprehensive method for quantitative DCE-MRI data analysis and is probably more accurate in estimating pharmacokinetic parameters as it takes into account the fact that equilibrium intercompartmental (transcytolemmal and transendothelial) water exchange is not infinitely fast (20, 21). ΔK^{trans} , which is the difference between K^{trans} (SSM) and K^{trans} (SM) and appraises the exchange effects, is a DCE-MRI parameter that appears to be rather sensitive to angiogenesis in malignant tumors (23). It has also been shown to be an accurate diagnostic marker for breast (22, 23) and prostate cancers (24) and a potential biomarker for assessing breast cancer response to chemotherapy (32). Consistent with our findings in previous diagnostic studies (22–24), the ΔK^{trans} parameter seems to be more sensitive than either K^{trans} (SM) or K^{trans} (SSM) to antiangiogenic agent-induced vascular changes in soft tissue sarcoma. The results from this study suggest that the SSM DCE-MRI approach can detect clinically significant changes in perfusion of soft tissue sarcomas early in the course of treatment with an antiangiogenic agent. Such findings have future implications for modifying the treatment plan for an individual patient early in the course of therapy who is not likely to respond to current treatment based on functional imaging findings. In addition, screening novel agents for activity in the primary tumor with this methodology could be explored in future clinical trials.

In conclusion, the addition of sorafenib to perioperative chemoradiotherapy for high-risk soft tissue sarcomas is

feasible. A phase II study of this chemoradiotherapy regimen using the MTD of sorafenib of 400 mg daily is planned and will incorporate further investigation of ΔK^{trans} as an imaging biomarker for early response to therapy.

Disclosure of Potential Conflicts of Interest

W. Huang has ownership interest in a patent. C.W. Ryan has served as a paid consultant for ONYX and Bayer. He has also received research support from ONYX and Bayer. No potential conflicts of interest were disclosed by the other authors.

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References

- Suit HD, Russell WO, Martin RG. Sarcoma of soft tissue: clinical and histopathologic parameters and response to treatment. *Cancer* 1975;35:1478–83.
- Lindberg RD, Martin RG, Romsdahl MM, Barkley HT Jr. Conservative surgery and postoperative radiotherapy in 300 adults with soft tissue sarcomas. *Cancer* 1981;47:2391–7.
- Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998;16:197–203.
- Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. *J Clin Oncol* 2003;21:2719–25.
- Herbert SH, Corn BW, Solin LJ, Lanciano RM, Schultz DJ, McKenna WG, et al. Limb-preserving treatment for soft tissue sarcomas of the extremities. The significance of surgical margins. *Cancer* 1993;72:1230–8.
- Ryan CW, Montag AG, Hosenpud JR, Samuels B, Hayden JB, Hung AY, et al. Histologic response of dose-intense chemotherapy with preoperative hypofractionated radiotherapy for patients with high-risk soft tissue sarcomas. *Cancer* 2008;112:2432–9.
- Eilber F, Eckardt J, Rosen G, Forscher C, Selch M, Fu YS. Preoperative therapy for soft tissue sarcoma. *Hematol Oncol Clin North Am* 1995;9:817–23.
- Weiner TM, Liu ET, Craven RJ, Cance WG. Expression of growth factor receptors, the focal adhesion kinase, and other tyrosine kinases in human soft tissue tumors. *Ann Surg Oncol* 1994;1:18–27.
- Franklin WA, Christison WH, Colley M, Montag AG, Stephens JK, Hart CE. In situ distribution of the beta-subunit of platelet-derived growth factor receptor in nonneoplastic tissue and in soft tissue tumors. *Cancer Res* 1990;50:6344–8.
- Heymach JV. Angiogenesis and antiangiogenic approaches to sarcomas. *Curr Opin Oncol* 2001;13:261–9.
- van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879–86.
- Maki RG, D'Adamo DR, Keohan ML, Saule M, Schuetz SM, Undevia SD, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol* 2009;27:3133–40.
- von Mehren M, Rankin C, Goldblum JR, Demetri GD, Bramwell V, Ryan CW, et al. Phase 2 Southwest Oncology Group-directed intergroup trial (S0505) of sorafenib in advanced soft tissue sarcomas. *Cancer* 2012;118:770–6.
- Duda DG, Jain RK, Willett CG. Antiangiogenics: the potential role of integrating this novel treatment modality with chemoradiation for solid cancers. *J Clin Oncol* 2007;25:4033–42.

15. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;307:58–62.
16. Wadlow RC, Ryan DP. The role of targeted agents in preoperative chemoradiation for rectal cancer. *Cancer* 2010;116:3537–48.
17. Spigel DR, Bendell JC, McCleod M, Shipley DL, Arrowsmith E, Barnes EK, et al. Phase II study of bevacizumab and chemoradiation in the preoperative or adjuvant treatment of patients with stage II/III rectal cancer. *Clin Colorectal Cancer* 2012;11:45–52.
18. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
19. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. *J Magn Reson Imaging* 1999;10:223–32.
20. Li X, Rooney WD, Springer CS Jr. A unified magnetic resonance imaging pharmacokinetic theory: intravascular and extracellular contrast reagents. *Magn Reson Med* 2005;54:1351–9.
21. Yankeelov TE, Rooney WD, Li X, Springer CS Jr. Variation of the relaxographic "shutter-speed" for transcytolemmal water exchange affects the CR bolus-tracking curve shape. *Magn Reson Med* 2003;50:1151–69.
22. Huang W, Li X, Morris EA, Tudorica LA, Seshan VE, Rooney WD, et al. The magnetic resonance shutter speed discriminates vascular properties of malignant and benign breast tumors *in vivo*. *Proc Natl Acad Sci U S A* 2008;105:17943–8.
23. Huang W, Tudorica LA, Li X, Thakur SB, Chen Y, Morris EA, et al. Discrimination of benign and malignant breast lesions by using shutter-speed dynamic contrast-enhanced MR imaging. *Radiology* 2011;261:394–403.
24. Li X, Priest RA, Woodward WJ, Tagge IJ, Siddiqui F, Huang W, et al. Feasibility of shutter-speed DCE-MRI for improved prostate cancer detection. *Magn Reson Med* 2013;69:171–8.
25. O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002;359:2235–41.
26. Zhang L, Hannay JA, Liu J, Das P, Zhan M, Nguyen T, et al. Vascular endothelial growth factor overexpression by soft tissue sarcoma cells: implications for tumor growth, metastasis, and chemoresistance. *Cancer Res* 2006;66:8770–8.
27. DeLaney TF, Spiro IJ, Suit HD, Gebhardt MC, Hornicek FJ, Mankin HJ, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 2003;56:1117–27.
28. Meric F, Hess KR, Varma DG, Hunt KK, Pisters PW, Milas KM, et al. Radiographic response to neoadjuvant chemotherapy is a predictor of local control and survival in soft tissue sarcomas. *Cancer* 2002;95:1120–6.
29. Pisters PW, Patel SR, Varma DG, Cheng SC, Chen NP, Nguyen HT, et al. Preoperative chemotherapy for stage IIIB extremity soft tissue sarcoma: long-term results from a single institution. *J Clin Oncol* 1997;15:3481–7.
30. Pezzi CM, Pollock RE, Evans HL, Lorigan JG, Pezzi TA, Benjamin RS, et al. Preoperative chemotherapy for soft tissue sarcomas of the extremities. *Ann Surg* 1990;211:476–81.
31. O'Connor JP, Jackson A, Parker GJ, Roberts C, Jayson GC. Dynamic contrast-enhanced MRI in clinical trials of antivasular therapies. *Nat Rev Clin Oncol* 2012;9:167–77.
32. Tudorica A OK, Chui SYC, Roy N, Troxell ML, Chen Y, Naik A, et al. Early prediction of breast cancer therapeutic response and evaluation of residual disease using quantitative DCE-MRI. *Proc Intl Soc Magn Reson Med* 2013;21:504.