Phase I Study of Neoadjuvant Chemoradiation Plus Sorafenib for High Risk Extremity Soft Tissue Sarcomas

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Background and Objectives

Phase I Neoadjuvant Chemoradiation Plus Sorafenib Background

- Previously, we have studied a neoadjuvant chemoradiation regimen of 3 cycles of preoperative epirubicin/ifosfamide and hypofractionated radiation followed by 3 cycles of postoperative epirubicin/ifosfamide in high risk extremity soft tissue sarcomas[1].
  - Rate of ≥95% necrosis was 40%.
  - Estimated 2-year rate for overall disease-free survival was 62%.
- Phase II studies of sorafenib in metastatic soft tissue sarcoma have shown response and favorable progression-free survival, especially in vascular sarcoma subtypes[2,3].
- The addition of antiangiogenic drugs to chemoradiotherapy has been found to be safe with promising results in pre-clinical and clinical studies in various solid tumors[4].
- We hypothesized that the addition of sorafenib to our chemoradiotherapy regimen is safe and will improve outcomes by potentiating the effects of chemoradiotherapy.

DCE-MRI Background

- DCE-MRI is a functional imaging modality that can detect changes in blood flow and vessel wall permeability within a tumor. The standard model (SM) or Tofts' model[5] has historically been used to estimate gadolinium contrast kinetic parameters such as K^{trans}.
- The "Shutter-Speed" Model (SSM) is a unique method of quantitative DCE-MRI data analysis that may be more accurate in estimating pharmacokinetic (PK) parameters as it takes into account the fact that equilibrium transcytolemmal water exchange is not infinitely fast[6,7].
- ΔK^{trans}(defined as [K^{trans} (SSM) – K^{trans} (SM)]) is a new DCE-MRI pharmacokinetic parameter that appears to be very sensitive to vascular changes[8].
- We performed a correlative study of SSM DCE-MRI in patients participating in the Phase I study.

Primary Objective

- To determine the safety and maximum tolerated dose (MTD) of sorafenib when combined with neoadjuvant chemoradiotherapy in high risk extremity soft tissue sarcomas of the extremities or body wall.

Methods

Eligibility Criteria

- Histologically confirmed soft tissue sarcoma (excluding rhabdomyosarcoma, Ewing's, PNET, osteosarcoma, or GIST)
  - > 5 cm in size
  - Intermediate or high grade
  - Located in the extremities or trunk
- Candidate for limb-sparing surgery
- LVEF ≥ 50%, BP ≤ 150/90
- Adequate organ function
- Age ≥ 15
- ECOG 0-1

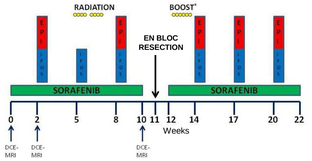
Study Design

- Increasing sorafenib dose using a 3+3 cohort design with dose level escalation based on dose limiting toxicities (DLTs) observed during the first 8 weeks.
- MTD was defined as the dose that produces DLT in 33% of patients.
- Percent histopathologic necrosis was estimated in the resection specimen by study pathologist.

MRI Methods

- MRI data were acquired with a 3T Siemens system using body coil transmit and a body matrix phased array (combined with spine matrix phased array) coil receive.
- MRI tumor size changes were assessed with RECIST and WHO criteria. The SM and SSM were used for DCE-MRI data PK modeling on tumor region of interest (ROI) and on a pixel-by-pixel basis. Arterial input function was measured from a major artery within the image field of view, adjacent to the tumor. Percent changes in PK biomarkers were calculated at week 2 and week 10 relative to baseline.

Treatment Schema



*Boost: postoperative boost of 12 Gy (200 cGy x 6 fractions) for patients with positive surgical margins only.

Dose Level	Sorafenib	Epirubicin	Ifosfamide	Radiation
1	200 mg once daily	30 mg/m²/day x 3 days	2500 mg/m²/day x 3 days	350 cGy x 8 fractions
2	400 mg once daily	30 mg/m²/day x 3 days	2500 mg/m²/day x 3 days	350 cGy x 8 fractions
3	400 mg twice daily	30 mg/m²/day x 3 days	2500 mg/m²/day x 3 days	350 cGy x 8 fractions

Peg-filgrastim or filgrastim was administered after each cycle of chemotherapy.

Results

Baseline Characteristics (N=16)

Median age , years	54 (25-63)
Median size, cm	11.7 (6.6-26.1)
Grade Intermediate High	 9 7
Histology Pleomorphic Synovial Liposarcoma Leiomyosarcoma Other	 5 5 3 1 2
Location Lower extremity Upper extremity	 12 4

Dose Limiting Toxicities During First 8 Weeks of Treatment*

Dose Level	Sorafenib Dose	# Subjects	# DLTs	DLTs	CTCAE Grade
1	200 mg daily	6	1	Mucositis	3
2	400 mg daily	7**	1	Syncope	3
3	400 mg BID	3	3	-Neutropenic sepsis, Thrombosis, Hand-foot syndrome -Rash, Hand-foot syndrome -Rash	4,3,3 3,3 3

* 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 non-hematologic toxicity (except: nausea/vomiting responding 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, grade 3 hypertension that is controlled with medication).

** Cohort expanded after MTD determined to further estimate safety.

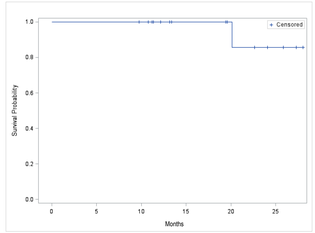
Delivery of Chemotherapy

	Epirubicin			Ifosfamide		
	DL1	DL2	DL3	DL1	DL2	DL3
Mean # cycles delivered (out of 6 planned cycles)	6	5.6	4.3	6	5.6	4.3
Mean dose delivered (percentage of planned dose)	86%	86%	73%	94%	92%	73%

Surgical Outcome and Response (N=16)

Surgical procedure Limb-sparing Amputation	 15 (94%) 1 (6%)
Microscopic margins R0 (negative) R1 (positive)	 15 (94%) 1 (6%)
Pathologic response ≥95% necrosis <95% necrosis	 7 (44%) 9 (56%)

Disease-Free Survival



Kaplan-Meier curve of disease-free survival. With a median follow-up of 19.5 months, there have been no local recurrences and 1 of 16 subjects has developed distant metastatic disease.

Grade 3-4 Toxicities

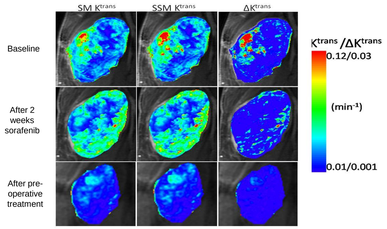
Worst Overall Grade per Patient

	CTCAE Grade 3-4 Toxicities			
	No.			No. (%)
Adverse Event	DL 1 (N=6)	DL 2 (N=7)	DL 3 (N=3)	Total (N=16)
Hematologic				
Neutrophils	6	7	2	15 (94%)
Hemoglobin	4	6	2	12 (75%)
Platelets	4	3	2	9 (56%)
Non-Hematologic				
Hypophosphatemia	5	4	3	12 (75%)
Neutropenic fever and neutropenic infections	3	4	1	8 (50%)
Hypertension	3	1	-	4 (25%)
Non-neutropenic infections	2	2	-	4 (25%)
Hypokalemia	3	-	1	4 (25%)
Hyponatremia	1	2	-	3 (19%)
Fatigue	-	2	-	2 (13%)
Hypoalbuminemia	2	-	-	2 (13%)
Encephalopathy	2	-	-	2 (13%)
Vasovagal/Syncope	1	1	-	2 (13%)
Fracture	-	2	-	2 (13%)
Thrombosis	1	-	1	2 (13%)
Hand-foot syndrome	-	-	2	2 (13%)
Rash	-	-	2	2 (13%)
Diarrhea	1	-	-	1 (6%)
Hyperbilirubinemia	-	1	-	1 (6%)
Hyperkalemia	-	1	-	1 (6%)
Hypocalcemia	1	-	-	1 (6%)
Mucositis	1	-	-	1 (6%)

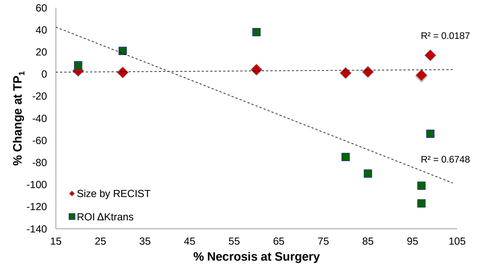
9 Wound Complications Occurred in 6 (38%) Subjects

Subject	Complication	Treatment	Tumor Location	Tumor Size	Outcome
1	Neutropenic wound infection	I&D and IV antibiotics	Right lower extremity	11.9 cm	Completely healed
2	Non-neutropenic wound infection	I&D and IV antibiotics	Left lower extremity	13.1 cm	Completely healed
3	-Neutropenic wound infection -Wound dehiscence -Non-neutropenic wound infection	-I&D and IV antibiotics -Wound vac placement -IV antibiotics and wound vac placement	Right upper extremity	8.7 cm	Completely healed
4	-Neutropenic wound infection	I&D, IV antibiotics, and wound vac placement	Right upper extremity	13.1 cm	Completely healed
5	-Non-neutropenic wound infection	-I&D x3, IV antibiotics, wound vac placement, and skin graft	Left lower extremity	23.0 cm	Completely healed
6	-Non-neutropenic wound infection -Pathologic tibia fracture in setting of continued wound infection	-I&D x2, IV antibiotics, wound vac, and skin graft -I&D, open reduction with external fixation, IV antibiotics, wound vac, and ultimately amputation	Right lower extremity	9.5 cm	Required a below knee amputation, completely healed

Early DCE-MRI changes detected in myxoid round cell liposarcoma with good histologic response (>95% necrosis)



After 2 weeks sorafenib, change in ΔK^{trans} but not RECIST correlated with pathologic necrosis



Discussion

- The addition of sorafenib to chemoradiotherapy is feasible with a MTD of 400 mg PO daily. Results are promising with only one recurrence with a median follow-up of 19.5 months. A phase II study is planned.
- Sorafenib-associated toxicities including rash and hand-foot syndrome limited full dose sorafenib when administered with chemoradiotherapy.
- At the MTD of sorafenib, toxicity is similar to that seen with chemoradiotherapy alone in the study by Ryan, et al[1].
- The rate of wound complications of 38% is similar to the 35% reported with preoperative radiation alone[9].
- ΔK^{trans} appears to be a sensitive biomarker for detecting early therapy-induced tumor vascular changes in patients treated with a VEGF-R inhibitor.

References

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