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Unacceptable Toxicity in Phase I Trial Adding Pazopanib to Chemotherapy for Sarcoma: A Precautionary Tale

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Abstract

Purpose: To determine the optimal dose (Phase II Recommended Dose (P2RD)) of pazopanib in combination with a biweekly gemcitabine and docetaxel regimen in patients with high risk Soft Tissue Sarcomas (STS) treated in the neoadjuvant setting.

Methods: Chemotherapy naïve patients with high risk STS, greater than 5cm and amenable to definitive resection were treated with gemcitabine 1500mg/m2 and docetaxel 50mg/m2 every 2 weeks for up to 8 doses. Pazopanib at an initial dose of 400mg daily was added on Days 4 to 13 of each 2 week-dosing period. Patients received definitive therapy with surgery and radiation therapy, as indicated. Primary endpoint and secondary endpoints were P2RD and safety, pathologic response, and progression-free survival, respectively.

Results: The trial was stopped for treatment intolerance after accruing 6 patients in the initial cohort. Only one patient received all 8 planned doses without reductions or delays. In the first cycle, 2 patients had a DLT of diarrhea with neutropenic fever and diverticulitis from C. *Difficile* infection, each. Elevated aminotransferase led to pazopanib discontinuation in 2 cases. Grade 2 and 3 adverse events and leading to a dose modification were infection in 4 patients, diarrhea in 3, liver anomalies in 3, neutropenia in 2, and pulmonary embolism in 1. There were 1 complete and 1 partial pathologic responses. Five patients recurred with a median PFS of 10.4 months (range, 6.2 to 26 months), 2 patients died. Only 1 patient remains alive and free of disease.

Conclusion: Pazopanib should not be combined with chemotherapy. There is no evidence of added benefits and the observed toxicity is not warranted in the neoadjuvant setting. They should rather be used sequentially in patients with progressive STS.

Keywords: Soft tissue sarcomas; Phase I trial; Gemcitabine; Docetaxel; Pazopanib

Introduction

Soft Tissue Sarcomas (STS) represent a very heterogeneous family of tumors derived from mesenchymal cells. Despite a variety of cells of origin, most STS are treated with the same chemotherapy regimens, although there are some exceptions. For example alveolar, soft part sarcoma is now treated with tyrosine kinase inhibitor in first line. Treatment of sarcomas is multidisciplinary, but the approach to the management of high risk primary STS remains controversial. While the combination of surgery and radiotherapy prevents local recurrence, the role of adjuvant or neoadjuvant chemotherapy to reduce the risk of metastatic disease or to reduce tumor size to facilitate an R0 resection is not established. Over 50% of patients with very high risk STS will eventually develop metastatic disease. Additional curative options must be identified in appropriate patients. The definition of high risk STS is also somewhat controversial. For the purpose of this clinical trial, we considered any high grade STS greater than 5cm in the greatest dimension, for which chemotherapy could be indicated in the first line setting. Although doxorubicin-based regimens are favored in first line for metastatic disease, the new combination of docetaxel and gemcitabine might have greater activity in some STS subtypes [1] with less long term toxicity [2], especially when administered on an every two-week schedule [3].

Vascular Endothelial Growth Factor (VEGF) is a potent tumor-produced angiogenic factor whose overexpression is usually associated with an adverse outcome in most STS [4]. Median pretreatment serum VEGF levels are significantly raised in patients with grade 2 and grade 3 sarcomas compared with concentrations in patients with benign lesions. Serum VEGF expression correlates with grade in soft tissue sarcoma and reflects response to treatment [5]. The tyrosine kinase inhibitor, pazopanib, is now approved for recurrent or metastatic STS, with good clinical benefit [6]. Health-related quality of life does not improve with pazopanib, but the improvement in progression-free survival without impairment of quality of life was considered meaningful. When administered as a single agent, side effects are manageable and include hypertension, diarrhea, nausea, liver inflammation, mild myelosuppression, and hair de-pigmentation [7]. In combination with chemotherapy, however, there is a synergistic effect on the toxicity profile and combination with multi-agent chemotherapy is not tolerable (Table 1) [8-14]. This study proposes to combine the least toxic chemotherapy regimen [3] with intermittent

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Table 1: Combinations of pazopanib with chemotherapy.

Chemotherapy (Intravenous, unless other stated)	Pazopanib MTD oral daily dose (mg)	DLTs, SAEs, or grade ≥ 3AES	Pharmacologic Outcome	References
Paclitaxel, 175mg/m^2 Carboplatin, AUC5	200	Neutropenia Thrombocytopenia Oral infection Hypertension	Pazopanib at 200mg increased paclitaxel C_{max} by 43% and carboplatin C_{max} by 54%.	[8]
Paclitaxel, 150 mg/m^2, q 21 days	800	Elevated liver transaminases	Pazopanib increases systemic exposure to paclitaxel by 38%.	[33]
Paclitaxel, 80 mg/m^2, weekly	800	Grade 4 neutropenia Fatigue Hypertension Elevated liver transaminases Ileal perforation	Feasible.	[34]
Paclitaxel, 80 mg/m^2, weekly	800	Neutropenia Diarrhea Elevated liver transaminases Hypertension	Better response rate in triple-negative breast tumors. High discontinuation rate related to toxicity. Not recommended	[14]
Paclitaxel, 80 mg/m^2, weekly	800	Neutropenia Abscess Elevated liver transaminases Diarrhea Hypertension Peripheral neuropathy	Pazopanib lowers paclitaxel clearance by 14%. Pazopanib increases maximal concentration by 31% with a 26% higher geometric mean paclitaxel AUC.	[35]
Docetaxel, 50 mg/m^2, q3 weeks Docetaxel, 20 mg/m^2, days 1, 8, and 15, q28 days	400	Neutropenia Diarrhea Elevated liver transaminases	Pazopanib lowers docetaxel clearance by 33% [mean 31.5 *vs* 21.1 L/h/m(2); P = 0.019]. Pazopanib increases AUC >50% [AUC(0-∞) (mean 1,602 *vs* 2,414 ng*h/mL; P = 0.029)].	[27]
Gemcitabine, 1,250 mg/m^2, days 1 and 8, q21 days	800	Fatigue, Neutropenia Thrombocytopenia Nausea Anorexia	No pharmacokinetic interaction.	[17]
Topotecan, oral, 8mg weekly or oral 2.5mg daily x 5, q21 days	800	Hand-foot syndrome Myelosuppression Diarrhea Liver failure Tumor hemorrhage	Topotecan does not affect pazopanib pharmacokinetics. Pazopanib increases exposure to total topotecan by 1.7 fold.	[36]
Irinotecan, 150 mg/m^2, q2 weeks & Cetuximab, 250 mg/m^2, weekly	400	Neutropenia Diarrhea	Pazopanib increased overall systemic exposure to SN-38.	[37]
Liposomal doxorubicin, 30 mg/m^2, q21 days	400	Neutropenia Rash/desquamation Hypertension Hand-foot syndrome	Too toxic, not recommended.	[9]
Pemetrexed, 500mg/m^2, q21 days	800	Fatigue, Neutropenia, Diarrhea Thrombocytopenia	Pazopanib did not affect pemetrexed clearance. Pazopanib increased pemetrexed maximal concentration by 22%.	[11]
Pemetrexed ,500mg/m^2, q21 days	800	Fatal ileus Tumor embolism Bronchopneumonia Sepsis	Combination too toxic, study stopped early.	[13]
Ifosfamide, 9g/m^2, CIV over 72 hours	800	Anemia Thrombocytopenia Neutropenia Fatigue Nausea Vomiting Anorexia Diarrhea Hypertension Encephalopathy Elevated liver transaminases Hypophosphatemia Proteinuria	Tolerability of pazopanib and ifosfamide is dependent on the infusion schedule. PKs do not explain these differences. Ifosfamide lowers pazopanib levels. Despite lower levels, pazopanib exerts a biological activity/toxicity. Combination with bolus ifosfamide is not feasible.	[10]

Highlighted rows: Combination not feasible.

Abbreviations: MTD: Maximum Tolerated Dose; DLT: Dose Limiting Toxicity; AE: Adverse Event; SAE: Serious Adverse Event; AUC: Area Under the Curve; C_{max}: Maximal Concentration; CIV: Continuous Intravenous Infusion.

pazopanib administration to avoid pharmacokinetics synergy, to be tested in the neoadjuvant setting for patients with high risk STS.

Patients and Methods

The study (NCT 01719302) was approved by the University of Vermont Institutional Review Board and all patients provided informed written consent in accordance with institutional and federal guidelines. The primary objective was to determine the recommended phase II dose for pazopanib in combination with gemcitabine and docetaxel. Secondary objectives included the assessment of side

Table 2: Patient & Treatment Characteristics.

Patient #	Sex	Age	Treatments Prior to Study Entry	STS Type	Anatomical Site	Tumor Size (cm)	Mitoses per 10 HPF	% Necrosis	FNCLCC Grade	Stage	TNM
1	M	59	Initial primary lesion confused for a hematoma and not resected en bloc. Adjuvant radiation with 66 Gy/33 fractions	Locally recurrent myxofibrosarcoma (outside of radiation field)	Back	7	20	10	3	III	pT2a N0 M0
2	F	78	None	Leiomyosarcoma	Right pelvis	10	3	40	2	IIB	T2b N0 M0
3	F	73	None	Pleomorphic sarcoma, NOS	Right thigh	22	10	None	2	IIB	T2b, N0, M0
4	F	47	None	Synovial sarcoma	Right pleura	19	N/A	N/A	Monophasic, positive for SS18-SSX1 fusion	III	T2b, N0, M0
5	F	59	En block resection, neo adjuvant XRT 50Gy	Leiomyosarcoma recurrent, oligometastatic in lungs	Left thigh	Primary tumor 7.4	34	30	3	III	T2b, N0, M0
6	F	73	None	Pleomorphic sarcoma with focal myoid differentiation	Right thigh	15.8	13	40	3	III	T2b, N0, M0

*All pazopanib studies were on hold per GSK (GlaxoSmithKline) sponsor for almost one year.
Abbreviations: HPF: High Power Field; PD: Progressive Disease; NOS: Not Otherwise Specified; FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer; N/A = Not Applicable; M = Male; F = Female; RT = Radiation Therapy.

effects, overall response rate and survival outcomes by RECIST version 1.1 criteria and the pathologic assessment of necrosis at surgery. No pharmacokinetics was planned. Eligible patients were ≥18 years old, had a life expectancy of ≥6 months, and a Zubrod performance status of 0-2. Patients with dermatofibrosarcoma protuberans, embryonal rhabdomyosarcoma, and alveolar soft part sarcoma were not eligible. All patients with another histologically high grade primary soft tissue sarcoma > 5cm in greatest diameter or with oligo-metastases (≤5 resectable metastases in the absence of a primary lesion) were eligible, if they were chemotherapy naïve. Patients with multiple metastatic sites were excluded from this study. Concurrent radiation was not allowed. Patients must have had adequate bone marrow function with an absolute peripheral granulocyte count of >1,500 or cells/mm^3, hemoglobin >8.0g/dL, and platelet count >100,000/mm^3, a total bilirubin ≤1.5mg/dL, liver transaminases and alkaline phosphatase ≤2.5 times the upper limit of normal, serum creatinine ≤1.5 times the upper limit of normal. Men and women of childbearing potential were required to consent to using effective contraception while on treatment and for at least 3 months thereafter.

Treatment consisted of a single-arm, non-randomized Phase I trial of gemcitabine, docetaxel, and pazopanib, administered in the neoadjuvant setting. Patients were enrolled in cohorts following the standard 3+3 Phase I design. The determination of the Phase II Recommended Dose (P2RD) was planned on the toxicity observed during the first cycle of treatment only (i.e., the first 2 doses of chemotherapy). A cohort of 10 additional patients was planned at the P2RD, if found. Chemotherapy consisted of docetaxel 50mg/m^2 followed by gemcitabine 1500mg/m^2 administered on day 1 and day 15 of each 28 day cycle for a total of 4 cycles. Both drugs were injected over 30 minutes each. In case of toxicity, doses of docetaxel and gemcitabine could be reduced to 40mg/m^2 and 1250mg/m^2, respectively. Pazopanib was started 72 hours after chemotherapy administration at an initial dose of 400 mg/day for 10 consecutive days (days 4-13 and 18-27 of each cycle). This schedule left a 48 hour window to decrease pharmacokinetics interactions. If 2 of 3 patients experienced a DLT, another 3 patients were enrolled in the cohort. If only 1 of 3 or 2 of 6 patients experienced a Dose Limiting Toxicity (DLT) at a dose level, the dose of pazopanib was increased by 200mg per cohort. Three cohorts of pazopanib, at 400mg, 600mg, and 800mg, were planned. A premedication of dexamethasone, 4mg orally and one 0.01% eye drop bilaterally was administered every 12 hours for six doses, starting 24 hours prior to each docetaxel administration. Non-pegylated filgrastim could be used at physician discretion, to obtain a white blood cell count in the acceptable range on the planned chemotherapy day. Patients who needed a delay >1 week were taken off study. Other supportive care was administered at physician discretion. Assessment of treatment efficacy was done with appropriate imaging after cycles 2 and 4 and compared to baseline. Assessment of toxicity was done prior to each chemotherapy administration and graded with the NCI CTCAE version 4.0. The primary endpoint was to determine the P2RD for this combination. Descriptive statistics of adverse events and outcomes were used. DLT was defined as the dose of drug that produces any grade 4 hematological toxicity lasting >7 days, or grade >3 (grade 2 for neurotoxicity) non-myelosuppressive toxicity. Only toxicity labeled possible, probable or definite were considered for DLT. The P2RD was defined as the highest dose for which no more than two patients per cohort develops a DLT.

Results

Six patients with high risk STS were enrolled in the first cohort at 400mg of pazopanib. Patients were 47 to 78 years old, 1 male and 5 females, with high-grade sarcomas > 5cm. Two patients had recurrent disease after local therapy, with oligometastases (Table 2). This new TKI/chemotherapy treatment, designed to minimize toxicity, induced 2 DLTs during the first cycle in two of 6 patients and one serious adverse event of pulmonary embolism in another patient

Table 3: Grading of Adverse Events on Active Study Treatment.

Patient #	1		2		3		4		5		6	
EVENTS on pazopanib	Cycle1	Next Cycles	Cycle1	Next Cycles	Cycle 1	Next Cycles	Cycle1	Next Cycles	Cycle1	Next Cycles	Cycle 1	Next Cycles
Grade												
Fatigue			1		1		1	2	1			
Hypertension							1		1			
Myalgia							2					
Infection				2 (Bladder infectio)	DLT - Grade 3 (Neutropenic fever)			2 (Bronchitis)			DLT – Grade 3 (Diverticulitis with C. Difficile)	
Mucositis				1			1					
Conjunctivitis								1				
Epistaxis									1			
Nausea					1		1	1				
Emesis					1			1				
Heartburn					1							
Diarrhea					DLT - Grade 3				1	1	DLT- Grade 3	
Elevation Transaminases					Grade 2 at dose 1 - Off Pazopanib			Grade 2 at dose 5 - Off pazopanib		1 Docetaxel dose reduced at dose 4		
Rash							1		2	2		
Alopecia							1		1			
Neutropenia					3			3 Docetaxel dose reduced at dose 5	1			
Anemia				3, but grade 1 change (Baseline Hb 8.3g/dL to 7.3g/dL)				1				
Pulmonary Embolism		Grade 3 at dose 7 - Off pazopanib										

Abbreviations: DLT: Dose Limiting Toxicity; Hb: Hemoglobin.

during cycle 4 (Table 3). Patient #2 received all 8 planned doses (completed neoadjuvant chemotherapy and RT, had a pCR) and patient #5 received 4 doses, had a 60-70% therapeutic effect but then progressed on treatment and was taken off study. Four patients had to discontinue pazopanib for side effects: at the 7th dose for pulmonary embolism, at the first dose for grade 2 transaminitis, at the 5th dose for grade 2 transaminitis, and at the second dose for diverticulitis. Three patients had a docetaxel dose reduction for increased transaminases (one grade 1 and two grade 2). Hypertension was not an adverse event of this combination. The addition of pazopanib, 400mg daily for 10 days every 2 weeks, to a biweekly docetaxel and gemcitabine chemotherapy regimen that is less toxic than the standard every schedule [3], was not deemed feasible for patients with STS. Interestingly, patient #4 had >50% necrosis, without prior RT, patient #5 had 60-70% therapeutic effect and patient #6 had 80% therapeutic effect, though required dose reduction of neoadjuvant chemotherapy due to toxicity.

Patients were then followed off study long term. Pazopanib activity was seen not only with the combination (patient #1), but notably for pazopanib as a single agent in the recurrent setting (Table 4). Re-induction with chemotherapy did not yield clinical responses in the recurrent setting. Three patients were re-induced with pazopanib and all had a partial remission. The length of single agent pazopanib treatment was 4 months in one patient, with another two still continuing the medication currently at 12+, and 16+ months. While patients started pazopanib at the prescribed dose of 800mg daily, all had to be dose-reduced to 600mg (2 patients) and 400mg (1 patient). Adverse events consisted of; in patient #1, hyponatremia (grade 3), macrocytosis (grade 2), dysgeusia (grade 2), bronchopleural fistula (grade 5) (this patient had moderate emphysema and previous thoracotomy for resection of metastases); in patient #4, hypertension (grade 2), nausea (grade 1), diarrhea (grade 1), fatigue (grade 1), and wound dehiscence of port (grade 3); and in patient #6, increased blood pressure (grade 3), headaches (grade 2), transaminase elevation (grade 1), renal failure (grade 2), right heart failure (grade 3), diarrhea (grade 2), whitening hair and eyebrows (grade 1), conjunctivitis (grade 1), hypothyroidism (grade 2), anemia (grade 2), and low platelet count (grade 1).

Table 4: Patient Treatment and Outcomes.

Patient	Number of cycles	Clinical Course following systemic treatment	PFS (months)	Recurrence	Subsequent treatments	–OS (months)	Status
1	7 with pazopanib 1 without - Taken off for pulmonary embolism after 7 doses	Complete response by MRI	10.6	Distant metastases in lung	· Gemcitabine and docetaxel q2w x 4 Outcome: PD · Doxorubicin q3w x 6 (NCT02049905 study) Outcome: SD · Metastatectomy · Pazopanib with anticoagulation, 800 then 600 mg daily x 4 months Outcome: PR	30.5	Dead of disease
2	8 with pazopanib with no modifications	SD by MRI • Neoadjuvant radiotherapy • Surgical resection with complete necrosis and negative margins - Treatment effect not measurable	Lost to follow-up	N/A		Lost to follow-up	Dead of disease
3	1 with pazopanib 3 without (Filgrastim used) - Taken off for DLT of neutropenic fever and diarrhea	SD by MRI • Surgical resection with positive margins - • ypT2b with minimal treatment effect; <5% tumor necrosis on excision. Tumor size at resection 12.8 x 12 x 6cm with positive deep, superficial, lateral, and proximal margins, Adjuvant radiation with 7000 cGy in 35 fractions	10.4	Local recurrence	· Re-resection Complicated by necrotizing fasciitis,with *C. Perfringens*, *S. Epidermidis* and *Corynebacterium*. Treated with debridements, vancomycin, metronidazole, clindamycin.	29.8	Alive, NED
4	5 with pazopanib 2 cycles without (dose reduction for docetaxel at dose 5) - Taken off for liver toxicity	SD by MRI, but more necrotic appearing images • Surgical resection with positive margins (tumor ruptured in pleural cavity during resection) One dose of Doxil® (30mg) was given intrapleurally prior to removing chest tube - High grade synovial sarcoma Mitotic count, 14/10 HPF, LVI present Treatment effect: >50% tumor necrosis	6.2	Local recurrence with new pleural nodules	· Pazopanib 800mg daily then 600mg daily Outcome PR	22.1	Alive, with disease, on pazopanib
5 At first recurrence Patient is oligometastatic and eligible for trial	4 (dose reduction for docetaxel at dose 4) - Taken off for PD	PD by CT chest • Lung resection 6/27/14 and 8/6/14 with positive pleural margin on second resection—Metastatic foci exhibited both treatment-type effect with 60-70% hyalinized necrosis, as well as one metastatic focus exhibiting >50% abrupt tumor cell necrosis with minimal treatment effect	2	Distant recurrence	· Doxorubicin q3w x 6 (NCT02049905 study) Outcome: PD · Radiotherapy on lung lesion Outcome: local PR · Eribulin x 2 Outcome: PD	18.0	Dead of disease
6	1 with pazopanib 3 without (dose reduction for docetaxel at dose 2) - Taken off for DLT of colitis	PD by MRI • Neoadjuvant radiation to 5000 cGy • Surgery: Margins negative for tumor with radiation induced changes. ypT2b with treatment effect; 80% hyalinized-type tumor necrosis • Adjuvant RT to total dose 7000 cGy - Treatment effect not measurable	18.9	Distant metastases: 2 new lung metastases; 2 and 0.7cm, one in each lung	· Pazopanib 800 mg daily then 400 mg M-F Outcome: PR · SABR in 4 sessions done every other day on biggest lung lesion	20.0	Alive with disease, on pazopanib

Abbreviations: PFS: Progression-Free Survival; OS: Overall Survival; PR: Partial Response; SD: Stable Disease; PD: Progression of Disease; MRI: Magnetic Resonance Imaging; LVI: Lymphovascular Invasion; N/A: Not Applicable; $_{c}$G: Centigray; HPF: High Power Filed; SABR: Stereotactic ablative radiation therapy.

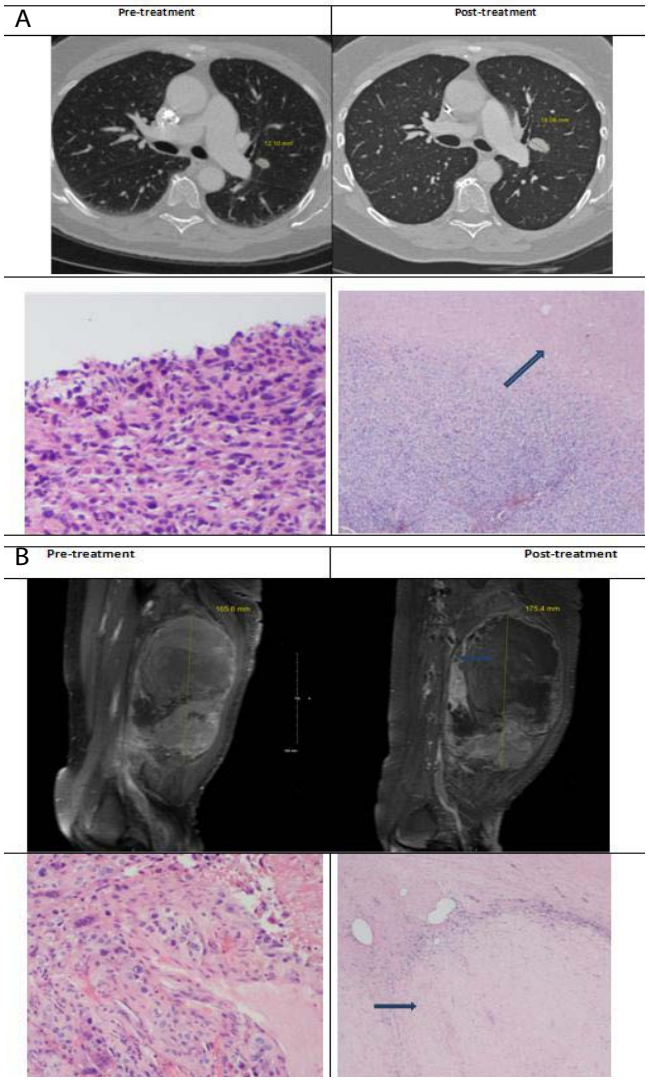

Figure 1: Responses by recist criteria and histology. **A:** Non responder: Leiomyosarcoma with oligometastases in the lungs with progression by RECIST criteria, but showing some necrosis (arrow) - Patient died of disease without a clinical remission. **B:** Stable Disease: Sarcoma NOS with stable disease by RECIST criteria, but showing >90% necrosis (arrows) - Patient remains NED on pazopanib.

Discussion

The combination regimen of gemcitabine and docetaxel is active in many STS with an initial report of a 53% overall remission rate with 20% Stable Disease (SD) and an Overall Survival (OS) of 17.9 months in patients with LMS [1] and an 18.4% overall remission rate (24.2% for the leiomyosarcoma subtype) and an overall survival of 12.1 months in another study [15]. In this combination, gemcitabine was administered intravenously on days 1 and 8 at 900mg/m^2 over 90 min and docetaxel on day 8 at 100mg/m^2 every 3 weeks. Grade 3 and 4 adverse events are common and filgrastim necessary to alleviate side-effects of neutropenia. In our previous study of the combination of gemcitabine and docetaxel with bevacizumab [3], drugs were administered every 2 weeks at doses of 1500mg/m^2, 50mg/m^2, and 5mg/kg, respectively, and no significant toxicity was observed. Most adverse events were the consequence of bevacizumab administration. The regimen was active with a 31% response rate. While bevacizumab has not been proven active in STS, pazopanib has been FDA approved for the treatment of recurrent STS. Pazopanib is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, Fibroblast Growth Factor Receptor (FGFR) -1 and -3, cytokine receptor (c-Kit), interleukin-2 receptor Inducible T-Cell Kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). *In vitro*, pazopanib inhibits ligand-induced autophosphorylation of VEGFR-2, Kit and PDGFR-β receptors.

Pazopanib in combination with chemotherapy has been difficult to administer because of significantly increased toxicity (Table 1). Unexpected hepatotoxicity of Pazopanib has been observed when combined with radiation therapy, however, whether this side effect is truly related to the combination is difficult to ascertain [16]. Pazopanib can be combined with camptothecins and gemcitabine, although all pazopanib investigator initiated studies were on hold for one year (2013-14) for inquiry into a grade 5 SAE in Japan related to the combination with gemcitabine. Gemcitabine does not interact with pazopanib [17] and so this issue is no longer of concern and will not be discussed further. The combinations with taxanes yield mixed results, with the main side effect being on liver tolerance. Pazopanib has not been tolerated with multi-agent chemotherapy combinations. A recent trial of neoadjuvant chemotherapy and pazopanib with 900mg/m^2 gemcitabine on days 1 and 8, 75mg/m^2 docetaxel on day 8, every 21 days, with 400mg of daily pazopanib, was halted early because 3 patients discontinued treatment for toxicity and none had a complete or partial response, despite one 90% pathologic response [12].

Pazopanib, as an intact pill [18], is absorbed under fasting conditions [19] with a median time to peak concentrations of 2 to 4 hours. Daily dosing at 800mg results in geometric mean AUC and C_{max} of 1,037hr•μg/mL and 58.1μg/mL (equivalent to 132 μM), respectively, with no consistent increase in AUC or C_{max} at doses above 800mg. Binding of pazopanib to human plasma protein *in vivo* is greater than 99% with no concentration dependence over the range of 10 to 100μg/mL. Pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8. Pazopanib has a mean half-life of 30.9 hours after administration of the recommended dose of 800mg [20]. Elimination is primarily via feces with renal elimination accounting for <4% of the administered dose. There are wide intrapatient variations in pazopanib exposure, thus target exposure within a predefined window is difficult [21]. A meta-analysis of nine prospective trials (patients = 2080) characterized liver chemistry abnormalities associated with pazopanib. Twenty percent of patients developed liver anomalies. Incidences of grade 2, grade 3, and grade 4 were 8%, 10% and 1%, respectively with a median time to anomaly of 42 days. Recovery is faster with dose interruption. Over 90% with grade less than 4 will recover, while about 65% with grade 4 will. Upon rechallenge, recurrence is possible in about 40% of patients [22]. Pazopanib clearance is decreased by 50% in patients with moderate hepatic impairment, with a maximum tolerated dose of 200mg once daily [23], but there is no correlation between hypertension and transaminitis [22].

The dose limiting toxicity of docetaxel is neutropenia. Liver is the organ with the highest binding capacity for docetaxel, with an intracellular binding capacity of about 15,000 nmol/kg tissue [24]. Patients with transaminases greater than 1.5 times the upper limit of normal (grade 1) and alkaline phosphatase greater than 2.5 times the upper limit of normal (grade 2) have decreased docetaxel clearance and will develop more toxicity. However, docetaxel can be administered at a reduced dose in patients with hepatic impairment [25]. Thus high binding capacity in the setting of decreased clearance induced by pazopanib makes the liver most susceptible to taxane toxicity. Pazopanib substantially increases docetaxel exposure through CYP3A4 and CYP3A5 of the cytochrome P 450 system [26], and Organic Anion Transporting Polypeptide (OATP) 1B1 inhibition [27,28]. While it is feasible to combine docetaxel with pazopanib, lower doses than the recommended single-agent doses are required. Docetaxel is mainly bound to α_1-acid glycoprotein (AAG), lipoproteins and albumin. AAG is an acute phase reactant protein which has intra- and inter-variations in cancer patients that causes difference in docetaxel AUC [29]. Docetaxel is detectable in plasma at 72 hours after weekly administration of 20mg/m^2 with a median concentration 3.0nM (range, 0.7-6.5nM). Taxane are retained in cancer cells for 1 week [30]. In our study, pazopanib was administered while docetaxel was still present in cells and circulation, perhaps explaining the increased in toxicity we observed [31].

Conclusions

We did not pursue a cohort of pazopanib at 200mg daily, mainly because our observation of pazopanib benefit as a single agent for STS recurrence made us question the utility of the combination of chemotherapy and pazopanib as a neoadjuvant therapy in the face of poor tolerance. The next question we would rather answer is whether pazopanib single agent is a viable neoadjuvant therapy for high risk STS. An analysis of pooled data from EORTC trials of pazopanib for recurrent STS (patients = 344) demonstrated that about 22% of patients had a progression-free survival greater than 6 months and an overall survival longer than 18 months. Prognostic factors included performance status, tumor grade, and absence of anemia at diagnosis. There were 3.5% of very long term survivors with a median time on pazopanib treatment of 2.4 years [32]. Onset of response is usually rapid and could lead to down staging for surgical purposes. Whether it could decrease the rate of metastatic recurrence remains to be studied.

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