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A Phase II Evaluation of Pazopanib in the Treatment of Recurrent or Persistent Carcinosarcoma of the Uterus: A Gynecologic Oncology Group Study

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Abstract

INTRODUCTION—Carcinosarcomas of the female genital tract, also called malignant mixed müllerian tumors, are aggressive biphasic tumors. Second-line treatment options in the recurrent/persistent setting have yielded marginal responses. Given the potential role of angiogenesis in the gynecological carcinomas, pazopanib, a VEGFR inhibitor, was investigated in the management of patients with recurrent carcinosarcoma of the uterus.

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CONFLICT OF INTEREST

The co-authors have no conflicts of interest to declare.

METHODS—Eligible patients had histologically confirmed carcinosarcoma of the uterus, a maximum of two prior lines of therapy, adequate renal, hepatic and hematologic function and a performance status of 0-2. Pazopanib was administered orally at 800 mg. Two dose reductions were allowed. The primary objective was to ascertain the activity of pazopanib as measured by the proportion of patients who survive progression-free for at least six months and the proportion of patients that have objective tumor responses. Secondary objectives included the frequency and severity of adverse events as assessed by CTCAE v4.0.

RESULTS—Of the 22 enrolled patients, 19 were eligible and evaluable for toxicity and survival. No patients had a partial or complete response (90% confidence interval [CI]: 0%, 14.6%). Three patients (15.8%) had PFS ≥ 6 months (90% CI: 4.4%, 35.9%). The median PFS was 2.0 months (first and third quartiles were 1.6 and 4.0 months, respectively). The median overall survival was 8.7 months (first and third quartiles were 2.6 and 14.0 months, respectively).

CONCLUSION—Pazopanib demonstrated minimal activity as a second or third line treatment for advanced uterine carcinosarcoma. Potential clinical trial participation should be discussed with the patients.

Keywords

Carcinosarcoma; uterus; VEGFR inhibitors; angiogenesis

INTRODUCTION

Malignant uterine neoplasms that contain both carcinomatous and sarcomatous elements are designated carcinosarcomas. These neoplasms arise most commonly in the uterus, and with a lesser frequency in the ovary, fallopian tube, cervix or peritoneum. They are regarded as rare aggressive malignancies with a high potential to develop distant metastases and are associated with an overall poor survival.

The histogenesis of this neoplasm has been debated. A number of studies have accumulated evidence suggesting that most of these neoplasms, but not all, are monoclonal in origin rather than true collision tumors [1-8]. Schipf et al investigated the molecular genetic aberrations of both ovarian and uterine carcinosarcoma using comparative genomic hybridization and fluorescence in situ hybridization. In the 30 cases studied, the molecular cytogenetic analysis revealed a high level of homology of chromosomal aberrations between the different tumor components suggesting a monoclonal origin of these tumors [9].

Evidence suggests that the carcinomatous component of carcinosarcomas is the more aggressive element of the cancer. Proliferation indices in both the carcinomatous and sarcomatous tumor component (immunohistochemical Ki-67 staining) revealed a significantly higher proliferation index in the carcinomatous tumor element (mean 70 %) compared to the sarcomatous tumor element (mean 28 %; $p < 0.001$) [9]. Data highlight that the carcinomatous component may be the driving force and that the sarcomatous component is derived from the carcinoma or from a stem cell that undergoes divergent differentiation.

Five-year survival figures for patients with carcinosarcoma are poor [10]. First line treatment of patients with advanced uterine carcinosarcoma with paclitaxel plus carboplatin

achieved an objective response rate of 54 % of patients. Progression-free survival (PFS) and overall survival (OS) for the entire cohort was 7.6 months and 14.7 months, respectively [11]. Response rates to second line therapy have been limited. [12-17]. Despite several studies suggesting the activity of various cytotoxic agents, enthusiasm for cytotoxic chemotherapy has been tempered by the rapid emergence of resistance [10, 12-16]. The aggressive nature of this malignancy coupled with a high relapse rate defines a poor clinical course for most patients. As such, a focus on alternative targeted therapeutics has emerged. Huh et al initiated a multi-institutional phase II trial to assess the activity and toxicity of imatinib mesylate in recurrent or persistent uterine carcinosarcoma [18]. Imatinib mesylate had minimal activity as a single agent in unscreened patients.

Independent studies have reported an increase in microvessel density with the progression of a benign to a malignant endometrium [19-22]. These studies have also reported the association of microvessel density with PFS and OS. Wright et al reported a retrospective analysis of patients (n=11) with recurrent uterine neoplasms treated with bevacizumab [23]. Two partial responses were noted in this heavily pretreated cohort and their median progression free intervals were 5.4 months and 8.7 months. Aghajanian et al investigated the role of bevacizumab in the treatment of patients with recurrent/persistent endometrial carcinoma [24]. The median PFS was 4.2 months while the median OS was 10.5 months. Twenty one patients (40.4%) survived progression free for at least 6 months. Nimeiri studied the role of sorafenib, a multi-targeted kinase inhibitor with anti-angiogenic activity, in advanced recurrent endometrial carcinomas and carcinosarcomas. In a group of 39 patients, 5% were reported as having a partial response while 50% had stable disease after two months [25].

Angiogenesis in uterine carcinosarcomas is less well characterized than in endometrial carcinomas. Emoto et al described the localization of the vascular endothelial growth factor (VEGF) and angiopoietin genes in uterine carcinosarcoma [26]. The microvessel density in the epithelial element was found to be higher than that of the mesenchymal element. Ang-2 mRNA was also seen in the vasculature adjacent to the periphery of carcinoma cells. Giatromanolaki et al explored the expression of phosphorylated kinase domain receptor (KDR / VEGFR-2) in endometrial cells utilizing a novel monoclonal antibody that recognized the activated (phosphorylated) form of the KDR (VEGFR-2) receptor [27]. Approximately one-third of patients with endometrial cancer exhibited intense cytoplasmic and nuclear pKDR expression in both cancer cells and peritumoral vessels. This reactivity in the cancer cells was related directly to VEGF and VEGF/KDR complexes. In addition, pKDR expression was associated with poor prognosis. A Phase II GOG study of thalidomide in this patient cohort reported an association between high pre-treatment VEGF-serum levels and poor prognosis in this population [28].

Pazopanib, is a potent competitive, small molecule inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)- α , - β - and c-kit. In preclinical models pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation and was 3- to 400-fold selective for VEGFRs. Pazopanib is approved by the Food and Drug Administration (FDA) for the treatment of soft tissue sarcomas and renal cell carcinoma, and has been evaluated in the management of gynecological cancers [29-32].

Based on the following rationale: (1) the lack of standard second line therapy in patients with advanced carcinosarcoma; (2) the expression of VEGF-mRNA in carcinosarcomas; (3) evidence that angiogenesis plays a role in endometrial carcinomas; and (4) the expression of phosphorylated KDR (VEGFR-2) in endometrial cells, the GOG initiated a phase II study of pazopanib, as second or third-line treatment for patients with recurrent uterine carcinosarcomas.

METHODS

Eligibility

Eligible patients had histologically confirmed recurrent or persistent uterine carcinosarcoma and measurable disease defined by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) [33]. All patients must have received one prior chemotherapeutic regimen administered after surgical or non-surgical assessment. Patients were allowed to have received one additional cytotoxic regimen for management for recurrent or persistent disease. Patients were not allowed to have received any prior non-cytotoxic or biological therapy. Additional requirements included a GOG performance status of 0-2, adequate bone marrow, renal, hepatic and neurologic function. Patients signed an approved informed consent. The protocol was approved by the Institutional Review Board of each of the participating GOG institutions. Central Pathology review by the GOG Pathology Committee was required. Patients with clinically significant cardiovascular disease, uncontrolled CNS disease, active bleeding and an increased risk of gastrointestinal bleeding or gastrointestinal perforation were considered ineligible.

Pazopanib was administered at 800 mg daily as an oral dose and a cycle was defined as a period of four weeks (28 days). Pazopanib therapy was continued until progressive disease or adverse effects prohibited further therapy. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria Version 4.0 (CTCAE v4) [34]. Hematologic treatment decisions were based on the absolute neutrophil count (ANC) and subsequent cycles of therapy were initiated when the ANC was 1500 cells/mcl and the platelet count was 100,000/mcl. Therapy could be delayed for a maximum of two weeks. Patients who failed to recover adequate counts within this two week period were removed from study. Non-hematologic toxicity assessment for hypertension, peripheral neuropathy, metabolic, endocrine, gastrointestinal disturbances, and cardiac function were reviewed prior to each cycle. Two dose reductions were permitted while on trial. LVEF testing was required prior to enrollment for patients who had received prior anthracycline therapy. Thyroid function tests were also assessed prior to enrollment.

Response assessments were performed by CT imaging every eight weeks. Response and progression were based on RECIST v 1.1.

Statistical methods

The primary objective of this study was to assess the activity of pazopanib in patients with persistent or recurrent carcinosarcoma of the uterus as measured by the proportion of patients achieving a six-month PFS and the proportion of patients who had objective tumor

response (complete or partial). Time at risk was assessed from the date of registration onto the study and included all eligible patients who received the drug. The null hypothesis (H0) relating to uninteresting levels of activity was determined from an analysis of a historical dataset based on a similar population of patients where the levels of activity were believed to be inactive to modestly active. The null hypothesis jointly specified that the probability of a patient experiencing a tumor response would be less than or equal to 5% and the probability of a patient experiencing PFS for at least six months would be less than or equal to 15%. Clinically significant differences were a 20% increase in the probability of response (to 25%) or a 20% increase in PFS at six months (to 35%).

To evaluate these hypotheses, a two-stage study design was performed to determine if the study should continue to a second stage of accrual or if the drug should be deemed unworthy of further investigation [35]. The targeted accrual for the first stage was 20 eligible and evaluable patients with a permitted range of 16-23 patients. The cumulative targeted accrual for the second stage was 35 (range from 31-38). With 19 eligible patients, the study required more than one patient with a complete or partial response or more than three patients having PFS for at least six months. The frequency and the severity of adverse events as assessed by CTCAE v4.0 and were tabulated by system affected. Secondary endpoints used to characterize drug efficacy were OS and PFS.

RESULTS

Patients and eligibility

Twenty-two patients were enrolled over the period of 12 months. Of these 19 were evaluable and eligible (two patients were ineligible due to the wrong cell type; one patient was enrolled but never treated).

Patient characteristics are listed in Table 1. The median age was 69 years (range, 50-79). Fourteen patients (74%) had a performance status of 0 while two (11%) and three (16%) had a performance status of 1 and 2, respectively. Ten patients (53%) had received one prior line of therapy and nine patients (47%) had received two prior lines of treatment. Chemotherapy regimens utilized as prior therapy included carboplatin and paclitaxel, ifosfamide and paclitaxel, ixabepilone, and a combination of liposomal doxorubicin, carboplatin and docetaxel. Fifty-seven percent of patients had been previously treated with radiation. The majority of patient receiving radiation therapy underwent pelvic radiation therapy +/- brachytherapy. Two patients received brachytherapy alone.

Treatment responses

The median number of pazopanib cycles delivered was two (range 1 to 9). No patients (0%) had a partial or complete response (90% confidence interval [CI]: 0%, 14.6%). Three patients (15.8%) had a PFS of ≥ 6 months (90% CI: 4.4%, 35.9%). The median PFS was 2.0 months (first and third quartiles were 1.6 and 4.0 months, respectively). The objective response rate and the six-month PFS failed to meet the pre-study criteria at completion of the first stage of study accrual; therefore the study was not re-opened to a second stage of

accrual. The median OS was 8.7 months (first and third quartiles were 2.6 and 14.0 months, respectively).

Adverse events

Adverse events are listed in Table 2. Six patients (32%) experienced grade 3 toxicities which included anemia, diarrhea, rectal hemorrhage, fatigue, changes in liver function tests, dehydration, hyperglycemia, hyponatremia, headache, memory impairment and hypertension. Grade 2 hypertension was observed in three patients (16 %). Two patients experienced grade 4 toxicities which included including anemia, proctitis, and metabolic abnormalities. Two patients were removed from trial due to toxicity and five patients required dose reductions due to toxicity.

DISCUSSION

Pazopanib is a potent and selective, orally bioavailable, adenosine triphosphate competitive, small molecule inhibitor of VEGFR-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)- α , - β , and c-kit. The rationale for evaluating this drug in recurrent carcinosarcomas was based on the strong association of VEGF-mRNA in carcinosarcomas, evidence that angiogenesis plays a role in endometrial cancer, the expression of phosphorylated KDR (VEGFR-2) in endometrial cells, a recent report of thalidomide noting an association between pre-treatment VEGFA and prognosis in this population and the positive expression of c-kit or PDGFR- β in 88% of patients studied with recurrent or persistent carcinosarcoma of the uterus [18,26,27,28].

Pazopanib demonstrated minimal clinical activity with no objective responses observed and only 15.8% of patients' progression free at six months. Despite the disappointing performance of this agent, the role of angiogenesis inhibitors in uterine carcinosarcoma remains undefined. Other anti-angiogenic agents therapeutics such angiopoietin inhibitors and vascular disrupting agents have not been explored in carcinosarcoma. Central to the success of these agents may be the identification of a marker that predicts response. Angiogenic signatures identifying high-risk patients or those that may benefit from the addition of anti-angiogenic therapies in other diseases such as high-grade serous ovarian carcinoma have been published and are currently being explored prospectively in clinical trials [36, 37]. A predictive biomarker for anti-vascular treatment in uterine carcinosarcoma has not been identified. In recent years, focus has shifted to understanding the molecular aberrations that drive the pathogenesis of various tumors. In carcinosarcoma this disease is made difficult by the rare and heterogenous nature of the disease. Previous studies exploring genetic aberrations have highlighted characteristic and frequent chromosomal amplifications observed on chromosomes 8q and 20q [9]. Other amplifications have been noted in the MDM2 and ERBB2 gene [9]. Growdon and colleagues recently identified mutational profiles that may be potential drivers of disease [38]. The authors identified in a cohort of 52 patients several gene mutations including TP53 (23%), PI3KCA (19%), KRAS (15%), CTNNB1 (4%) and NRAS (2%). Recently reported by the Cancer Genome Atlas Research Network was an integrated genomic characterization of 373 endometrial carcinomas using array- and sequencing-based technologies [39]. This resulted in classification of endometrial

cancers into four categories: POLE ultra mutated, microsatellite instability hyper mutated, copy-number low, and copy-number high. A similar analysis is planned specifically for patients with carcinosarcoma of the uterus.

Identification of mutation(s) that drive tumorigenesis coupled with the identification of signaling pathway cross-talks confer the greatest potential for a successful targeted approach to treatment. In light of the Growdon data, the MAPK and PI3K/AKT/mTOR pathway may be a logical target in the study of carcinosarcoma [39-42].

In this phase II study, pazopanib failed to achieve objective responses or disease stabilization in a sufficient number of patients to be considered a potentially active agent in uterine carcinosarcoma. The overall goal remains to target this uncommon disease early in its evolution utilizing agents that target potential driver mutations. Potential clinical trial participation should be discussed with the patients.

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HIGHLIGHTS

- Clinical evidence suggests that angiogenesis plays a role in endometrial cancer
- Pazopanib, a small molecule inhibitor of VEGFR, has limited activity in the management of carcinosarcoma of the uterus
- Mutational Profiles and Chromosomal amplifications may profile potential driver of disease

Overall and Progression-Free Survival

Figure 1. Overall and Progression-Free Survival

Kaplan – Meier estimate of progression free survival (PFS) and overall survival (OS) for all eligible and evaluable patients on the study

Table 1

Patient Characteristics

Characteristic	Category	No. of Cases	% of Cases
Age	50-59	1	5.3
	60-69	11	57.9
	70-79	7	36.8
Race	African American	2	10.5
	American Indian	1	5.3
	White	16	84.2
Performance Status	0	14	73.7
	1	2	10.5
	2	3	15.8
Cell Type	Carcinosarcoma-homologous	8	42.1
	Carcinosarcoma-heterologous	7	36.8
	Carcinosarcoma, unspecified: MMT	4	21.1
Grade	Poorly differentiated	2	10.5
	Not graded	17	89.5
Prior Chemotherapy			
	1	10	52.6
	2	9	47.4
Prior Radiation	No	10	52.6
	Yes	9	47.4
Prior Surgery	Yes	19	100.0

Table 2

Adverse Events possibly related to study drug

Adverse Event	1	2	3	4	Total
Leukopenia	8	1	0	0	19
Thrombocytopenia	2	0	0	0	19
Neutropenia	9	1	0	0	19
Anemia	4	1	2	1	19
Other Investigations: (LFTs elevation, creatinine)	4	5	1	0	19
Cardiac	1	0	0	0	19
Gastrointestinal	11	3	1	1	19
General (constitutional)	9	3	1	0	19
Metabolism/nutrition	3	2	3	1	19
Musculoskeletal/connective tissue	3	0	0	0	19
Nervous system	4	1	2	0	19
Psychiatric	1	0	0	0	19
Renal/urinary Gynecological	0	1	0	0	19
	1	1	0	0	19
Respiratory/thoracic/mediastinal	4	0	0	0	19
Skin/subcutaneous	3	3	0	0	19
Vascular disorders (hypertension)	2	3	3	0	19

* Gynecological: Pelvic pain: grade 1; Vaginal fistula grade 2

Table 3

Objective Responses (OR) and Progression Free Survival (PFS) at 6 months

Characteristic	Category	No. of Cases	% of Cases
Response	Increasing Disease	10	52.6
	Stable Disease	7	36.8
	Indeterminate	2	10.5
PFS > 6 Months	No	16	84.2
	Yes	3	15.8
Numebr of cycles of Treatment	1	1	5.3
	2	11	57.9
	3	1	5.3
	4	3	15.8
	8	1	5.3
	9	2	10.5
Alive	Without progression	1	5.3
	With progression	5	26.3
Dead	From disease	12	63.2
	From neither treatment nor disease	1	5.3