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A Phase II Study of Sorafenib in Advanced Uterine Carcinoma / Carcinosarcoma: A Trial of the Chicago, PMH, and California Phase II Consortia

Halla S. Nimeiri^{*,1}, Amit M. Oza², Robert J. Morgan³, Dezheng Huo¹, Laurie Elit⁴, James A. Knost⁵, James L. Wade III⁶, Edem Agamah⁷, Everett E. Vokes¹, and Gini F. Fleming¹

¹University of Chicago, Chicago, IL

²Princess Margaret Hospital, Toronto, ON, Canada

³City of Hope Comprehensive Cancer Center, Duarte, CA

⁴Juravinski Cancer Centre, Hamilton, Ontario, Canada

⁵Oncology/Hematology Associates, Peoria, IL

⁶Decatur Memorial Hospital, Decatur, IL

⁷Central Illinois Hematology/Oncology Center, Springfield, IL

Abstract

Objectives—To determine the efficacy and safety of single agent sorafenib, an oral multi-targeted tyrosine kinase inhibitor, in patients with advanced uterine carcinoma and carcinosarcoma.

Methods—This multi-institutional non-randomized phase II trial enrolled two cohorts: patients with uterine carcinoma (cohort A) and uterine carcinosarcoma (cohort B). Eligibility criteria included measurable disease, 0–1 prior chemotherapy regimens, and ECOG performance status ≤ 2 . Sorafenib at a dose of 400 mg was administered orally twice daily. A cycle was defined as 28 days. Objective tumor response was the primary endpoint and was assessed following every two cycles.

Results—Fifty-six patients (40 with carcinoma, 16 with carcinosarcoma) were enrolled between March 2005 and August 2007. Two (5%) patients with uterine carcinoma had a partial response (PR) and 17 (42.5%) achieved stable disease (SD). Five had SD lasting at least 4 months. The 6-month progression free survival rate for patients with carcinoma was 29%, and the median overall survival was 11.4 months. No patients with carcinosarcoma had an objective response. Four (25%) had SD, and one had SD lasting 18 months. The 6-month progression free survival rate was 13%, and the median overall survival was 5.0 months. Grade 3/4 drug related toxicities included: hypertension (13%), hand-foot syndrome (13%), hypophosphatemia (7%), anemia (5%), rash (5%), diarrhea (5%), thrombosis (5%), fatigue (5%) and bleeding (5%).

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Address Correspondence to: Gini F. Fleming, M.D, University of Chicago Hospitals, 5841 South Maryland, MC 2115, Chicago, IL 60637, gffleming@medicine.bsd.uchicago.edu, Phone 773-702-6712, Fax 773-702-0963.

*Currently at Northwestern University

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Conclusion—Sorafenib had minimal activity in patients with uterine carcinoma. Predictive factors for potential benefit are needed.

Introduction

Uterine cancer is the most common gynecologic malignancy in the United States with an estimated 40,100 new cases and 7,470 deaths in 2008.¹ The overall death rate is low as most endometrial cancer is diagnosed at an early stage when surgical resection is often curative. However, the median survival of women with recurrent or advanced endometrial carcinoma is only approximately one year,² and there is a substantial need for improved therapies in the treatment of advanced or recurrent disease. Although testing of conventional cytotoxics has been less exhaustive in endometrial cancer than in ovarian cancer, only taxanes have produced response rates over 20% in the setting of second-line systemic therapy, and these agents are now generally used in the first-line setting.^{3,4}

Uterine carcinosarcomas (also known as malignant mixed Mullerian tumors) are less common but more aggressive than typical (endometrioid) uterine carcinomas. In the past carcinosarcomas were treated as uterine sarcomas, but recent evidence suggests that these tumors are metaplastic carcinomas.⁵ It is not clear whether they respond differently to systemic therapy from uterine carcinomas, and we elected to evaluate them in a parallel cohort.

There is preclinical evidence that the Ras/Raf/Mek/MAP pathway has a role in uterine cancer.⁶ In addition, increased levels of VEGF and angiogenic markers are associated with poor outcomes in endometrioid endometrial carcinoma patients⁷, and antiangiogenic agents appear to have activity in preclinical models of endometrial cancer⁸. Sorafenib is an oral agent that inhibits Raf-1 wild-type and mutant B-Raf, and multiple receptor tyrosine kinases, including vascular endothelial growth factor receptors. It is currently FDA-approved for use in renal cell carcinoma and hepatocellular carcinoma. This multicenter phase II study investigated the clinical activity and safety of sorafenib in patients with advanced uterine carcinoma and carcinosarcoma.

Methods

Eligibility Criteria

The clinical trial was reviewed and approved by the Institutional Review Board (IRB) at the University of Chicago and those of all other participating institutions. All patients provided written informed consent before study participation according to institutional and federal guidelines. Eligible patients were at least 18 years old and had advanced or recurrent uterine carcinoma (cohort A), or uterine carcinosarcoma (cohort B). The two cohorts enrolled simultaneously. Central review of pathology was not performed.

Patients were required to have: measurable disease, ECOG performance status of 0 to 2, absolute neutrophil count $\geq 1500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, serum bilirubin less than or equal to the institutional upper limits of normal (ULN), AST/ALT ≤ 2.5 times ULN, and serum creatinine ≤ 1.5 mg/dL. No more than one prior cytotoxic chemotherapy regimen was allowed. Previous radiation therapy was permitted. Patients were excluded if they had prior treatment with VEGF or VEGFR-directed therapy, known brain metastases, uncontrolled hypertension, bleeding diathesis, clinical or radiologic evidence of bowel obstruction or perforation, or were taking cytochrome P450 enzyme-inducing anti-epileptic drugs.

Treatment and Monitoring

Sorafenib was supplied by the National Cancer Institute/ Cancer Therapy Evaluation Program as 200 mg tablets.

Radiologic assessment of measurable disease was performed by computed tomography scan (CT) or magnetic resonance imaging (MRI) within 28 days prior to registration. Baseline laboratory testing included a complete blood count (CBC) with differential and platelets, serum chemistries including creatinine, AST/ALT and bilirubin, and PT/INR. All patients received a starting dose of 400 mg sorafenib orally twice daily on a continuous basis. A treatment cycle was defined as 28 days. Compliance was monitored with a patient medication diary. Toxicity was evaluated using NCI Common Toxicity Criteria Version 3.0. Sorafenib was to be held for most grade 3 toxicities, including uncontrolled hypertension, rash, diarrhea, and hand-foot syndrome until resolution to grade 0 or 1, and then restarted at a dose of 200 mg twice daily. Grade 2 toxicities were generally managed with dose interruption; the drug was restarted at the same dose and then dose-reduced if the toxicity recurred. CBC/differential and serum chemistries were repeated every four weeks. Patients were evaluated for response every two cycles (eight weeks). Response was defined using the by the Response Evaluation Criteria in Solid Tumors (RECIST),⁹ and treatment was continued until unacceptable toxicity or progression of disease.

Statistical Design

The primary end point of this phase II study was objective response rate (complete and partial responses). Secondary endpoints included overall survival, time to tumor progression, and duration of response. Separate analyses were performed for patients in cohort A (uterine carcinoma) and cohort B (uterine carcinosarcoma). A Simon optimal two-stage design was employed for each arm. A $\leq 5\%$ response rate was to preclude further study (null hypothesis), whereas a $\geq 20\%$ response rate would suggest that further study would be warranted (alternative hypothesis). Using α and β errors of 0.05 and 0.10, respectively, twelve assessable patients were to be enrolled in each arm in the first stage and if ≥ 1 response was observed, an additional 25 patients would be enrolled, for a total of 37 patients. If ≥ 4 responses were observed among the 37 patients the treatment would be considered sufficiently active to warrant further testing. This design had a 0.54 probability of stopping at the first stage if the true response rate was 5%. An exact 95% confidence interval (CI) was calculated for the response rate based on the binomial distribution. Overall and progression-free survival rates were estimated using the Kaplan–Meier method. Median progression-free and overall survival times and their respective 95% CIs were constructed using the method of Brookmeyer and Crowley.¹⁰

Results

Between March 2005 and August 2007, fifty-six patients were accrued to the study (40 with carcinoma – cohort A, 16 with carcinosarcoma – cohort B). Subjects came from ten total participating institutions within the University of Chicago, Princess Margaret Hospital and the California Cancer Phase II Consortia. Clinical characteristics of cohorts A and B are shown in Table 1. One patient in cohort A signed the informed consent but withdrew before starting treatment and this patient was excluded from the survival and toxicity analyses below. Two additional patients with carcinoma and two patients with carcinosarcoma were not evaluable for response because they discontinued treatment before completing the second cycle of treatment. Neither had evidence of disease progression. In two of these cases the stated reason for withdrawal was rash, in one fistula formation (this patient had a 19% decrease in tumor measurements on a CT scan performed early) and in one “patient choice”. These four are included in the response statistics as nonresponders, but the trial size was expanded to ensure that there were sufficient patients with adequate response assessments in the first stage of each cohort before deciding whether or not to continue to the second stage of accrual. Two further additional patients were treated on the carcinosarcoma cohort in administrative error. The median number of 28-day sorafenib cycles administered was 3 in cohort A (range 1 to 46); and 2 in cohort B (range 1 to 22).

Toxicity

Toxicity data are shown in Table 2. Grade 3 or higher adverse events included hypertension (13%), hand–foot syndrome (13%), hypophosphatemia (7%), hyponatremia (7%), anemia (5%), rash (5%), diarrhea (5%), fatigue (5%), bleeding (5%), and thrombosis (4%). Twenty-two patients (40%) required dose reductions.

Response and Survival

Uterine Carcinoma

Two patients with uterine carcinoma (5%), both with prior systemic therapy (one with prior carboplatin/paclitaxel completed 3 1/2 months prior to study entry, and one with prior temsirolimus completed 3 1/2 months prior to study entry, had confirmed partial responses. The histologic subtypes of these two patients included one with grade one endometrioid adenocarcinoma, and the other with serous carcinoma. The response in the patient with serous carcinoma lasted more than 40 months. Seventeen patients with carcinoma had stable disease as their best response and five of them had stable disease lasting more than four months. One of these was a patient with a chemotherapy-naïve poorly differentiated carcinoma who achieved a minor response (26% shrinkage from baseline) lasting 20 months.

At a median follow-up of 23 months, 26 patients had died. The median overall survival time was 11.4 months (95% CI: 6.9 – 17.7 months), with 6 and 12 month survival rates of 73% and 45%, respectively (Figure 1). The median progression-free survival was 3.2 months (95% CI: 1.9–4.0 months) and the 6-month progression free survival was 29% (Figure 2).

The median overall survival time was 7.0 months (95% CI: 4.5–44.0 months) in women with uterine carcinoma and prior chemo/biologic therapy, which was not statistically significantly different from that in women without prior chemo/biologic therapy.

Uterine Carcinosarcoma

No patient had an objective response rate in cohort B. Four patients (25%) had stable disease; one patient remained on study for 18 months discontinuing study treatment for an attempt at resection of the pelvic recurrence. Tumor slides from this subject were reviewed and the diagnosis of carcinosarcoma confirmed.

Fourteen patients had died with a median follow-up of 15 months. The median overall survival time was 5.0 months (95% CI: 1.4–14.0 months) with 6 and 12 month survival rates of 44% and 29%, respectively (Figure 1). The median progression-free survival time was 1.8 months (95% CI: 1.4–3.5 months) and the 6 month progression-free survival rate was 13% (Figure 2).

Discussion

Sorafenib was relatively well tolerated in this relatively elderly population although many (40%) patients eventually required a dose reduction. This appears to be a higher rate of dose reductions than reported in phase III trials using a similar starting dose of renal cell carcinoma (13%) or hepatocellular carcinoma (26%)^{11,12}, perhaps reflecting the effects of prior chemotherapy and pelvic radiotherapy. Many publications of phase II trials do not report on “eventual” dose reductions, but only dose reductions in the first couple of cycles, making these data difficult to compare with the reports on patients with more prior therapy. A recent publication regarding use of sorafenib and sunitinib in renal cell carcinoma concludes that the toxicity in the literature is under-reported, and a significant percentage of patients do require drug discontinuation or dose reduction.¹³

Objective response rates in our trial were low. However there appeared to be some minimal anti-tumor activity in advanced uterine carcinoma, with a couple of patients clearly deriving benefit. The median overall survival of 11.4 months in women with uterine carcinoma is similar to the 12–15 months usually seen in phase III trials of chemotherapy-naïve patients with advanced or recurrent endometrial carcinoma.^{4,14,15} More than half of the patients with carcinoma in this study had prior therapy.

The results in women with carcinosarcoma appear less promising, although this may simply reflect the fact that carcinosarcomas are more aggressive tumors. Cohort B did not continue to the second stage of accrual. Only one patient with carcinosarcoma had prolonged stable disease, although this response persisted for 18 months. The median overall survival for patients treated on cohort B was only 5.0 months, which is lower than that reported in front-line trials of cytotoxic therapy such as ifosfamide-containing combinations (7–13 months).^{16,17} However, most of the patients with carcinosarcoma on our trial were pretreated.

It is clear that sorafenib benefits some patient populations without producing a dramatic response rate. Sorafenib is FDA-approved for use in hepatocellular carcinoma and renal cell carcinoma, diseases in which it prolongs survival despite producing response rates of only 3% and 5.2%, respectively.^{11,12} Other antiangiogenic agents are currently being investigated in the treatment of endometrial carcinoma. A phase II trial of bevacizumab in women with one or two prior chemotherapy regimens for endometrial carcinoma has been completed by the Gynecologic Oncology Group (GOG), and preliminary results suggest a 15.1% response rate with a median survival of 10.5 months.¹⁸ Phase II trials of sunitinib and aflibercept (VEGF-trap), are ongoing. If these agents, similar to sorafenib, appear to promote disease stability, randomized trial designs will be needed to establish their levels of benefit. Placebo-controlled trials will be more difficult to conduct than was the case with sorafenib in patients with hepatocellular and renal cell carcinoma, tumors for which few other agents with potential benefit to patients are available.

Randomized phase II trials of potentially active agents may be an option. This could take the form of randomly assigning subjects to a chemotherapy agent versus a chemotherapy agent plus targeted agent, as has been done with sorafenib for breast cancer. Single agent sorafenib has generally shown minimal activity in terms of major clinical responses in the treatment of women with metastatic breast cancer; the North Central Cancer Treatment Group, for example, reported no CR or PR with 10% (2 pts) achieving stable disease lasting longer than six months.^{19,20} Four separate randomized phase IIb trials comparing single agent chemotherapy to the combination of sorafenib with chemotherapy (one trial each using capecitabine, paclitaxel, docetaxel, and gemcitabine) have been launched.²¹ To date the combination with paclitaxel has been reported to produce no significant additional benefit²² while the addition sorafenib to capecitabine produced a statistically significant improvement in progression free survival (6.4 months vs 4.1 months, $p=0.0006$).^{23,24} However combinations of chemotherapy plus sorafenib are toxic (for example, 45% grade 3 hand-foot skin reactions with the combination of sorafenib plus capecitabine), and randomization between chemotherapy and a combination of chemotherapy plus targeted agent does not address the ability of the single targeted agent to achieve meaningful disease stabilization. One attractive option is the randomized discontinuation design, in which all subjects are given a run-in of 8–12 weeks of active agent. Those who progress at the end of this time are removed from study, those who have a major response are permitted to continue taking active agent, and those with stable disease are randomized to continue active agent or receive placebo until the time of progression (when crossover to active agent is generally permitted) This design has the advantage of enriching for patients who may be benefit in situations where a bioassay to select patients with a relevant molecular target is not available.²⁵

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Figure 1.
Overall survival

Figure 2.
Progression-free survival

Table 1**Patient Characteristics (N=56)**

Characteristic	Carcinoma (N=40)	Carcinosarcoma (N=16)
Age in years, median (range)	64 (44–83)	64 (40–87)
Race/ethnicity, no.		
Non-Hispanic white	29	10
Hispanic	4	1
African-American	2	3
Asian	5	2
ECOG performance status, no.		
0	17	7
1	20	8
2	3	1
Histology, n (%)		
Adenocarcinoma (unspecified)	12	0
Serous	3	0
Clear cell	1	0
Endometrioid	24	0
Carcinosarcoma	0	16
Prior therapy, n (%)		
Surgery	28	9
Radiation	20	7
Chemo/ biologic Therapy	28	10

Table 2**Most Frequent Adverse Events Related to Sorafenib**

Toxicity	All grades No.	Grade 3 No.	Grade 4 No.
Skin Toxicity			
Hand foot skin reaction	20	7	0
Rash/desquamation	27	4	0
Alopecia	16	0	0
Constitutional			
Fatigue	27	3	0
Hematological			
Anemia	19	3	1
Leukopenia	12	0	0
Thrombocytopenia	7	0	0
Gastrointestinal			
Diarrhea	23	3	0
Nausea	20	0	0
Vascular			
Hypertension	17	7	0
Thrombosis	2	1	1
Bleeding	16	3	0
Fistula	2	1	0
Metabolic			
Hypophosphatemia	12	4	0
Hyperglycemia	9	0	1
Hyponatremia	14	4	0
Hypokalemia	15	4	2
Hypomagnesemia	1	1	0