

Double-Blind, Randomized, Phase 2 Trial of Maintenance Sunitinib Versus Placebo After Response to Chemotherapy in Patients With Advanced Urothelial Carcinoma

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BACKGROUND: Angiogenesis contributes to the progression of urothelial carcinoma (UC). In the current study, the authors investigated the role of maintenance sunitinib in patients with advanced UC. **METHODS:** Patients with locally recurrent/metastatic UC and adequate organ function who achieved stable disease or a partial or complete response after 4 to 6 chemotherapy cycles were randomized to sunitinib at a dose of 50 mg/day (28 days on and 14 days off) or placebo. The primary endpoint was the 6-month progression rate. Secondary endpoints were safety, survival, change in serum vascular endothelial growth factor (VEGF)/soluble VEGF receptor-2 (sVEGFR2), and the activity of sunitinib in patients who developed disease progression while receiving placebo. A total of 38 eligible patients per treatment arm were required to select better therapy with 90% probability ($\alpha = .05$). **RESULTS:** A total of 54 eligible patients were randomized to either the sunitinib arm (26 patients) or the placebo arm (28 patients). The median number of cycles received was 2 cycles per treatment arm. The most common grade 3 to 4 adverse events (graded according to version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events) among patients receiving sunitinib were thrombocytopenia, diarrhea, mucositis, fatigue, and hypertension. There were no grade 3 or 4 adverse events noted among >5% of patients receiving placebo. The 6-month progression rate was 72% versus 64%. The median progression-free survival (PFS) was 2.9 months (range, 0.5 months–32.5 months) versus 2.7 months (range, 0.8 months–65 months) for the sunitinib versus placebo arms, respectively. Patients receiving placebo were found to have no changes in their serum VEGF/sVEGFR2 levels over time. Patients treated with sunitinib had no significant change in their VEGF level, but the sVEGFR2 level significantly decreased after cycles 1 and 2 ($P < .0001$) and at the time of disease progression ($P = .0002$). A baseline VEGF level that was at or greater than the median was found to be correlated with a longer PFS. Sixteen patients who were receiving placebo received sunitinib at the time of disease progression, with the best responses being 1 partial response (6.3%), 6 cases of stable disease (37.5%), and 5 cases of progressive disease (31.3%); 4 patients were not evaluable for response. The median PFS was 3.7 months (range, 0.1 months–22 months). **CONCLUSIONS:** The current multicenter study was limited by premature closure and a small sample size. Maintenance sunitinib did not appear to improve the 6-month progression rate. Open-label sunitinib was found to have only modest activity. The sVEGFR2 level decreased among patients receiving sunitinib. *Cancer* 2014;120:692–701. © 2013 American Cancer Society.

KEYWORDS: urothelial carcinoma, bladder cancer, chemotherapy, angiogenesis, sunitinib, maintenance therapy.

INTRODUCTION

Metastatic urothelial cancer (UC) is lethal, with 15,210 estimated deaths expected in the United States in 2013.¹ Cisplatin-based chemotherapy continues to be the standard first-line treatment, resulting in a median progression-free survival (PFS) of 7 months to 8 months and a median survival of 14 months to 15 months.^{2,3} Considering that chemotherapy cannot be given in the long term and that disease progression invariably occurs after discontinuing chemotherapy,

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even in responding patients, strategies that can help to prolong the chemotherapy-induced disease response are critical to the management of this malignancy.

Angiogenesis appears to play a major role in the growth and metastasis of UC.⁴ Microvascular density, a measure of tumor angiogenesis, has been correlated with a higher incidence of metastasis and worse prognosis in patients with UC.⁵ Of the angiogenic factors, vascular endothelial growth factor (VEGF) has been identified as a crucial regulator of both normal and pathologic angiogenesis. Increased VEGF expression has been reported in patients with UC and has been correlated with a higher stage/grade of disease, disease progression, and poor prognosis.⁶⁻⁸ Preclinical data have supported the role of therapeutic targeting of VEGF in patients with UC; however, clinical data have shown only modest activity, especially when VEGF inhibitors are used as single agents.⁹⁻¹¹

Sunitinib (SU11248) is an oral inhibitor of multiple receptor tyrosine kinases, including VEGF receptors (VEGFRs), platelet-derived growth factor receptors, stem cell factor receptor (KIT), colony-stimulating factor 1 receptor, RET, and Flt-3. It is approved by the US Food and Drug Administration for the treatment of several solid tumors.¹²⁻¹⁷ Sunitinib has antitumor activity in human bladder cancer models both in vitro and in vivo.^{18,19} Based on the critical role of angiogenesis in disease progression and the preclinical activity of sunitinib in bladder cancer models, we hypothesized that VEGF pathway-directed therapy would maintain disease response and would therefore decrease the progression rate in patients with advanced UC who had achieved at least stable disease (SD) after chemotherapy.

MATERIALS AND METHODS

Key Eligibility Criteria

Eligible patients had a pathologic diagnosis of UC (pure or mixed histology); an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; a life expectancy > 6 months; adequate hematologic, renal, hepatic, and cardiovascular function; and had achieved SD or a partial (PR) or complete (CR) response after 4 to 6 cycles of standard first-line chemotherapy for locally recurrent or metastatic UC. Prior adjuvant or neoadjuvant chemotherapy was allowed, but no prior antiangiogenic agents were permitted for the current disease stage. Patients were registered within 42 days after their last chemotherapy dose and were excluded if they had undergone any major surgery or experienced a \geq grade 3 hemorrhage (according to version 3.0 of the National Cancer

Institute Common Toxicity Criteria for Adverse Events) within 4 weeks of starting study treatment, had active central nervous system disease, were pregnant or breastfeeding, were positive for the human immunodeficiency virus, had an unresolved bacterial infection, or experienced a serious medical condition within 6 months before study treatment that would impact on patient safety. All patients signed Institutional Review Board-approved consent forms and were registered with the University of Michigan Cancer Center Clinical Trials Office before the initiation of therapy.

Patient Evaluation

Baseline evaluation included a complete history and physical examination, complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, a pregnancy test in women of childbearing age, electrocardiogram, multigated acquisition scan, and chest/abdomen/bone imaging.

Adverse events (AEs) were graded according to version 3.0 of the National Cancer Institute Common Toxicity Criteria for Adverse Events. Disease status was assessed at baseline and then every 12 weeks (\pm 1 week) regardless of dose delays until disease progression. Response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0) and was confirmed by repeat assessment at least once at a minimum interval of 12 weeks. Response duration was measured from the time of objective response until the first date of disease recurrence or progression (based on the smallest measurements recorded since treatment started).

The current study is available at ClinicalTrials.gov (NCT00393796).

Treatment Plan

Patients were stratified by prior response to first-line chemotherapy (SD vs PR vs CR) and randomized to receive either sunitinib or placebo (1:1). The blinded study drug (sunitinib at a dose of 50 mg or placebo) was administered orally daily for 4 consecutive weeks, followed by a 2-week rest period (1 cycle). In the absence of disease progression or toxicity, patients were required to remain on the study for at least 12 weeks (2 cycles) to be regarded as having an adequate therapeutic trial. The study drug dose was reduced to 37.5 mg (-1 dose level) and 25 mg (-2 dose level) according to prespecified criteria. In the event of any drug-related (grade 2) nonurgent ventricular paroxysmal dysrhythmia requiring intervention or grade 3 to 4 nonhematologic or grade 4 hematologic AEs, the drug was held until resolution to less than

or equal to grade 1 and the drug was restarted at a -1 dose level. Therapy was continued until evidence of objective or clinical disease progression or unacceptable toxicity. At the time of disease progression, the blind was broken and patients receiving placebo were offered open-label sunitinib if they were otherwise eligible, whereas those patients whose disease progressed during treatment with sunitinib were removed from the study.

Correlative Studies

Circulating VEGF and soluble VEGFR2 (sVEGFR2) were evaluated as potential predictors of outcome based on data from patients with renal cell carcinoma (RCC) who were treated with sunitinib that suggested a correlation between changes in circulating marker levels and response to sunitinib.²⁰ We hypothesized that patients with advanced UC would have increased serum VEGF and decreased sVEGFR2 levels in response to sunitinib and that patients with an objective response would demonstrate larger proportional changes. Serum was collected at baseline and at the end of each cycle (for the first 3 cycles) to measure the VEGF and sVEGFR2 levels, in both the blinded and open-label study phases. Blood was collected in serum separator tubes and was immediately centrifuged at a cold temperature for 10 to 12 minutes or until the serum separated from the cell pellet. If immediate centrifugation was not feasible, the blood sample was spun and stored at 4°C for up to 6 hours. Serum VEGF and sVEGFR2 were measured by an enzyme-linked immunoadsorbent assay (R&D Systems, Minneapolis, Minn), according to the manufacturer's instructions.

Statistical Analysis

The primary endpoint was to compare the 6-month disease progression rate between patients randomized to receive either sunitinib or placebo. Based on published data with first-line chemotherapy,^{2,3} it was estimated that patients would have a median time to disease progression (TTP) of 4 months from the end of their last treatment cycle; it was hypothesized that sunitinib would increase this by 50% to 6 months. Assuming exponential survival rates, these median TTP values can be converted into 6-month progression rates of approximately 65% and 50%, respectively. Using these rates in the randomized selection design,²¹ a total of 38 subjects per treatment arm would allow for the selection of the superior treatment arm with a 90% probability ($\alpha = .05$). To account for patient dropouts before reaching the 6-month progression assessment, 4 additional subjects would be accrued to each arm, with an accrual goal of 42 subjects per treatment arm.

The 6-month progression rate was reported by treatment arm using product-limit estimates from the Kaplan-Meier method and the associated 95% confidence intervals (95% CIs). Progression events in this intent-to-treat analysis included documented disease progression or death, whichever occurred first. Patients who were lost to follow-up for disease progression were censored at the time of their last assessment for disease progression. The protocol was written with TTP as the secondary endpoint of the analysis. However, an early death while receiving treatment indicated PFS to be the more appropriate endpoint to report in this randomized trial to avoid introducing bias in the sunitinib arm inappropriately. A subset analysis was completed to determine whether an effect between treatments was found among patients who adhered to the treatment plan. This analysis censored 3 patients on the placebo arm at the date they were inadvertently given sunitinib. Secondary endpoints reported included the objective response rate in patients with SD after chemotherapy, median PFS, and median overall survival (OS). OS was assessed using product-limit estimates from the Kaplan-Meier method.

Changes in serum VEGF and sVEGFR2 levels after cycle 1 (days 27-35) and cycle 2 (days 69-84) were compared with baseline within each treatment arm using a Student *t* test for paired data. Kaplan-Meier methods were used to assess the association between baseline VEGF and sVEGFR2 levels and PFS and OS and changes from baseline at cycle 1 for each measure. Cox models were used to investigate biomarker association with PFS and OS controlling for the clinical and demographic covariates. The objective response rate, median PFS, median OS, and progression rates with 95% CIs for patients receiving open-label sunitinib were reported.

RESULTS

Baseline Characteristics and Treatment Summary

The study closed early due to slow accrual, with 54 eligible patients from 9 institutions enrolled between November 2006 and January 2011. The median age of the patients was 69 years, the median ECOG PS was 1, and 70% of patients had a primary tumor of the bladder. At the time of study entry, 28 patients had SD, 22 patients had achieved a PR, and 4 had achieved a CR after chemotherapy. Twenty-six patients were randomized to treatment with sunitinib and 28 were randomized to receive placebo (Table 1) (Fig. 1). Three patients randomized to receive placebo inadvertently received sunitinib during their treatment course (2 patients for 4 weeks and 1 patient for

TABLE 1. Baseline Patient Characteristics (N=54)

Characteristic	Sunitinib	Placebo
No. of patients	26	28
Men	20 (77%)	19 (68%)
Women	6 (23%)	9 (32%)
Median age (range)	69 (48-84)	69 (53-81)
ECOG PS		
0	10 (38.5%)	11 (39.3%)
1	15 (57.6%)	17 (60.7%)
2	1 (3.9%)	0
Visceral metastasis	9 (34.6%)	12 (42.9%)
Bladder primary tumor	20 (77%)	18 (64.3%)
Mixed histology	2 (7.7%)	4 (14.3%)
Median no. prior chemotherapy cycles (range)	6 (4-6)	6 (4-6)
Prior chemotherapy regimen		
Cisplatin and gemcitabine	10 (38.5%)	14 (50%)
MVAC	3 (11.5%)	2 (7.1%)
Non-cisplatin-containing	13 (50%)	12 (42.9%)
Response to prior chemotherapy		
CR	3 (11.5%)	1 (3.5%)
PR	10 (38.5%)	12 (42.9%)
SD	13 (50%)	15 (53.6%)

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PR, partial response; SD, stable disease.

1 week); however, they were included in the placebo arm until the time of disease progression or death, whichever occurred first (intent-to-treat analysis). Baseline demographic and clinical characteristics, including response to prior chemotherapy, were relatively well balanced. The median number of cycles (sunitinib or placebo) was 2 per treatment arm (range, 1 cycle-25 cycles). The median duration of therapy in the open-label sunitinib arm was 9.5 weeks (range, 0.3 weeks-96 weeks).

Safety and Tolerability

Table 2 summarizes the most frequent (occurring in > 5% of patients) grade 3 to grade 5 AEs in the blinded and open phases of the study. The most common grade 3/4 AEs in patients randomized to treatment with sunitinib were thrombocytopenia (23.1%/7.7%), diarrhea and mucositis (15.4%/0%), fatigue (15.4%/3.8%), and hypertension (11.5%/0%). Seven patients who were receiving sunitinib came off therapy due to toxicity and another patient withdrew consent during sunitinib therapy. There were 10 dose delays in 6 patients and 13 dose reductions; 9 patients had 1 dose reduction and 2 patients had 2 dose reductions while receiving sunitinib. One patient who developed liver metastasis while receiving sunitinib died of nonneutropenic septic shock related to a urinary tract infection and subsequent liver/renal failure, which were deemed unlikely to be related to treatment. In

the placebo arm, no high-grade AEs were noted to occur in > 5% of patients. Of the 16 patients who received open-label sunitinib, 5 patients discontinued sunitinib due to AEs (4 of which were related to treatment and 1 that was unrelated).

Efficacy Analysis

With a median follow-up of 10.3 months (range, 1 month-65 months), the 6-month progression rate from the time of study registration was not different between patients receiving sunitinib (71.7% [95% CI, 54%-87%]) and those receiving placebo (64.3% [95% CI, 47%-81%]). The median PFS was 2.9 months (95% CI, 2.4 months-6.3 months) for sunitinib versus 2.7 months (95% CI, 2.5 months-7.2 months) for placebo, and the median OS was 10.5 months for sunitinib (95% CI, 8.1 months-13.8 months) versus 10.3 months for placebo (95% CI, 6.8 months-18.1 months) (Figs. 2 and 3). Subset analysis including only those patients who received a minimum of 12 weeks of treatment resulted in similar 6-month progression rates. There was no confirmed response noted among patients with SD after chemotherapy who received sunitinib. Sixteen patients who received placebo were treated with sunitinib at the time of disease progression, with a best response of 1 PR (6.3%) that lasted 15 months (occurring in a female patient with a primary tumor of the bladder and hepatic metastasis who had achieved a PR after 6 cycles of chemotherapy with carboplatin, paclitaxel, and gemcitabine and developed disease progression on the placebo arm and then received open-label sunitinib, achieving SD for 8 months followed by a PR for 15 months), 6 cases of SD (37.5%), and 5 cases of progressive disease (31.25%); 4 patients were not considered to be evaluable for response. The median PFS was 3.7 months (range, 0.07 months-22.5 months; 95% CI, 1.6 months-5.5 months), and the median OS was 5.6 months (range, 0.9 months-31 months; 95% CI, 3.5 months-12.6 months). At the time of last follow-up, 1 patient continued to receive sunitinib (a female patient with ureteral UC who achieved a CR after 5 cycles of gemcitabine chemotherapy and continued in CR while receiving sunitinib, which she had tolerated well for 33 months at the time of last follow-up).

VEGF and sVEGFR2

There was no significant change in serum VEGF and sVEGFR2 levels in patients randomized to receive placebo. Patients treated with sunitinib were found to have no significant change in their serum VEGF level; however, the serum sVEGFR2 level significantly decreased after 1

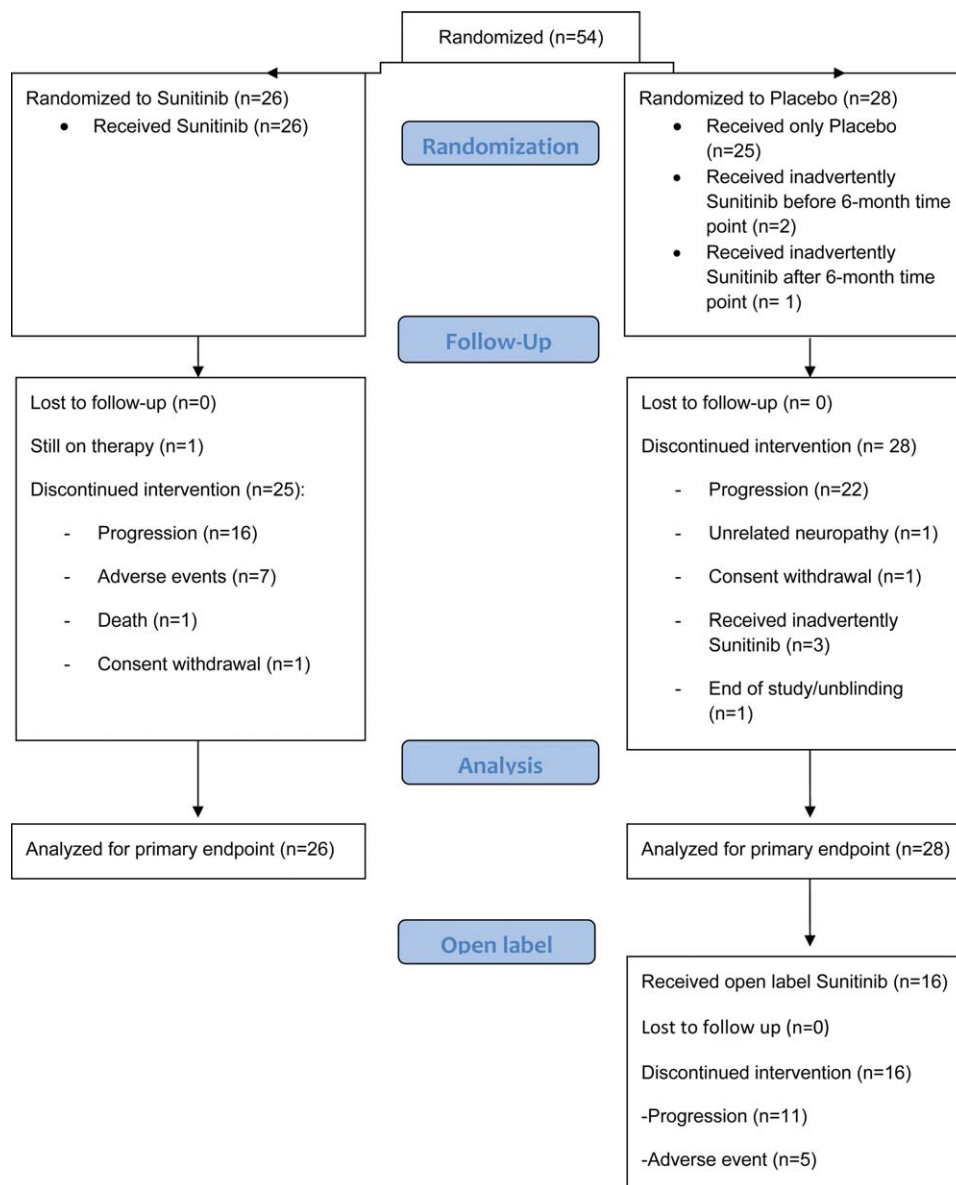


Figure 1. CONSORT (Consolidated Standards Of Reporting Trials) flow diagram is shown.

cycle ($P < .0001$), 2 cycles ($P < .0001$), and at the time of disease progression ($P = .0002$) (Fig. 4A and 4B). Baseline serum sVEGFR2 levels did not correlate with PFS or OS. It is interesting to note that the baseline serum VEGF was significantly associated with PFS even after controlling for treatment arm, patient age, tumor histology (pure UC vs mixed), ECOG PS, disease location (bladder vs other), and response to chemotherapy at the time of study entry. Patients with a baseline serum VEGF level ≥ 350 pg/mL (the median in the current study population) had a lower hazards ratio of disease progression or death compared with patients with a baseline VEGF level that was less than the median (hazards ratio, 0.27; 95% CI,

0.12-0.61 [$P = .001$]) (Fig. 5). However, the association between baseline serum VEGF and PFS did not appear to differ significantly by treatment arm ($P = .61$). The magnitude of the VEGF and sVEGFR2 level changes at cycle 1 compared with baseline did not correlate with PFS or OS. In the open-label cohort, the magnitude of change in the level of sVEGFR2 and the lack of change in VEGF level were similar to those of the blinded sunitinib cohort (Fig. 4C). In the open-label cohort, no levels were available at the time of disease progression, and no analysis regarding a correlation between levels and PFS or OS was performed due to the low number of patients and samples.

TABLE 2. Grade 3 to Grade 5 Adverse Events (>5%)^{a,b} Among Patients Randomized to Sunitinib or Receiving Open-Label Sunitinib

Adverse Event	Patients Randomized to Sunitinib (N=26) Grade 3/4, % ^c	Patients Receiving Open-Label Sunitinib (N=16) Grade 3/4 % ^c
Thrombocytopenia	23.1/7.7	6.3/6.3
Fatigue	15.4/3.8	12.5/0
Diarrhea	15.4/0	0/0
Mucositis	15.4/0	0/0
Neutropenia	3.8/0	12.5 /0
Hypertension	11.5/0	6.3/0
Dehydration	3.8/0	0/0
Hand-and-foot syndrome	7.7/0	6.3/0
Hyponatremia	7.7/0	0/0
Urinary tract infection	7.7/0	0/0
Lymphopenia	7.7/0	0/0
Anorexia	0/0	6.3/0
Bladder hemorrhage	0/0	6.3/0
Confusion	0/0	6.3/0
Elevated ALK	0/0	6.3/0
Elevated creatinine	0/0	6.3/0
GI hemorrhage	3.8/0	6.3/0
Heart failure	0/0	0/6.3
Muscle weakness	0/0	6.3/0
Pancytopenia	0/0	6.3/0
Thromboembolism	0/0	0/6.3

Abbreviations: ALK, alkaline phosphatase; GI, gastrointestinal.

^aPossibly, probably, or definitely related to treatment.

^bAdverse events were graded according to version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events.

^cNo grade 5 adverse event was reported.

DISCUSSION

In the current study, we evaluated maintenance sunitinib to consolidate tumor response to chemotherapy and delay disease progression. Although this approach is attractive in principle, its feasibility was compromised by the slow accrual related to the need for patients to have had at least SD or a response to prior chemotherapy and suboptimal tolerability to sunitinib due to adverse events. Sunitinib did not improve the progression rate at 6 months, had modest activity at the time of disease progression, and increased the rate of AEs. Its toxicity profile was notable and consistent with previous reports.^{14,15,22,23} In the context of expected treatment-related toxicity, the relative value of prolonging the median TTP by 2 months may be questioned; therefore, a favorable benefit-to-risk ratio is critical in the determination of endpoints for future trials.

There are several potential reasons to account for the lack of a significant effect with maintenance sunitinib. Factors include the modest efficacy of sunitinib as a single agent and the relative importance of the VEGF pathway

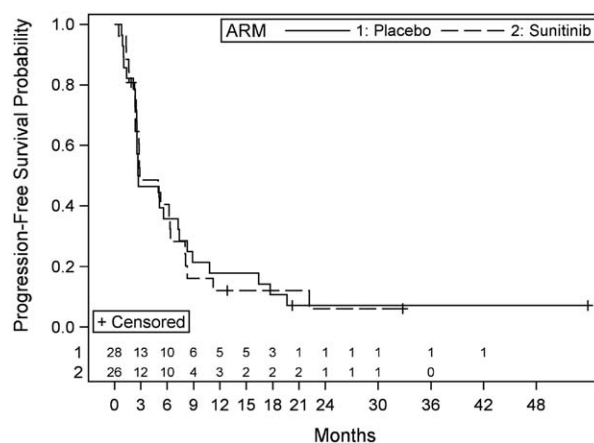


Figure 2. Kaplan-Meier plots of progression-free survival (PFS) are shown. The median PFS for patients treated with sunitinib was 2.9 months (95% confidence interval [95% CI], 2.4 months-6.3 months) versus 2.7 months for patients receiving placebo (95% CI, 2.5 months-7.2 months) (hazards ratio, 1.0 [95% CI, 0.6-1.8]).

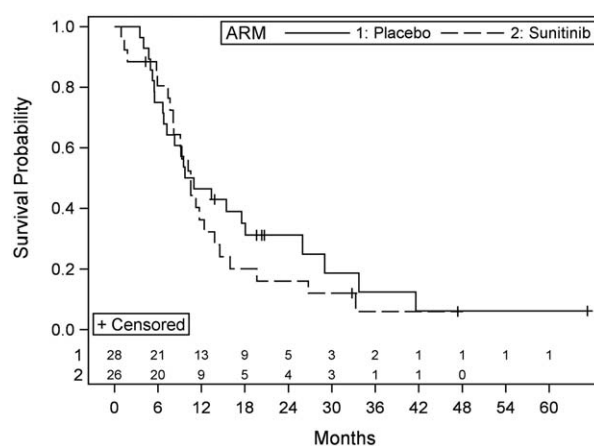


Figure 3. Kaplan-Meier plots of overall survival are shown. The median overall survival for patients treated with sunitinib was 10.5 months (95% confidence interval [95% CI], 8.1 months-13.8 months) versus 10.3 months for patients receiving placebo (95%CI, 6.8 months-18.1 months).

at this time point in the disease setting.^{22,23} Data from two phase 2 trials of sunitinib in patients with metastatic UC (with or without prior chemotherapy) indicated modest response rates (range, 3%-8%), and short PFS and OS (range, 6 months-8 months for median OS).^{22,23} Similarly, in a phase 2 study, patients with recurrent/refractory UC received pazopanib at a dose of 800 mg daily with a 17% confirmed objective PR rate (95% CI, 7.2%-32.1%) and a disease control rate of 51.2%. In that study, 1 patient achieved a PR and was free of disease progression

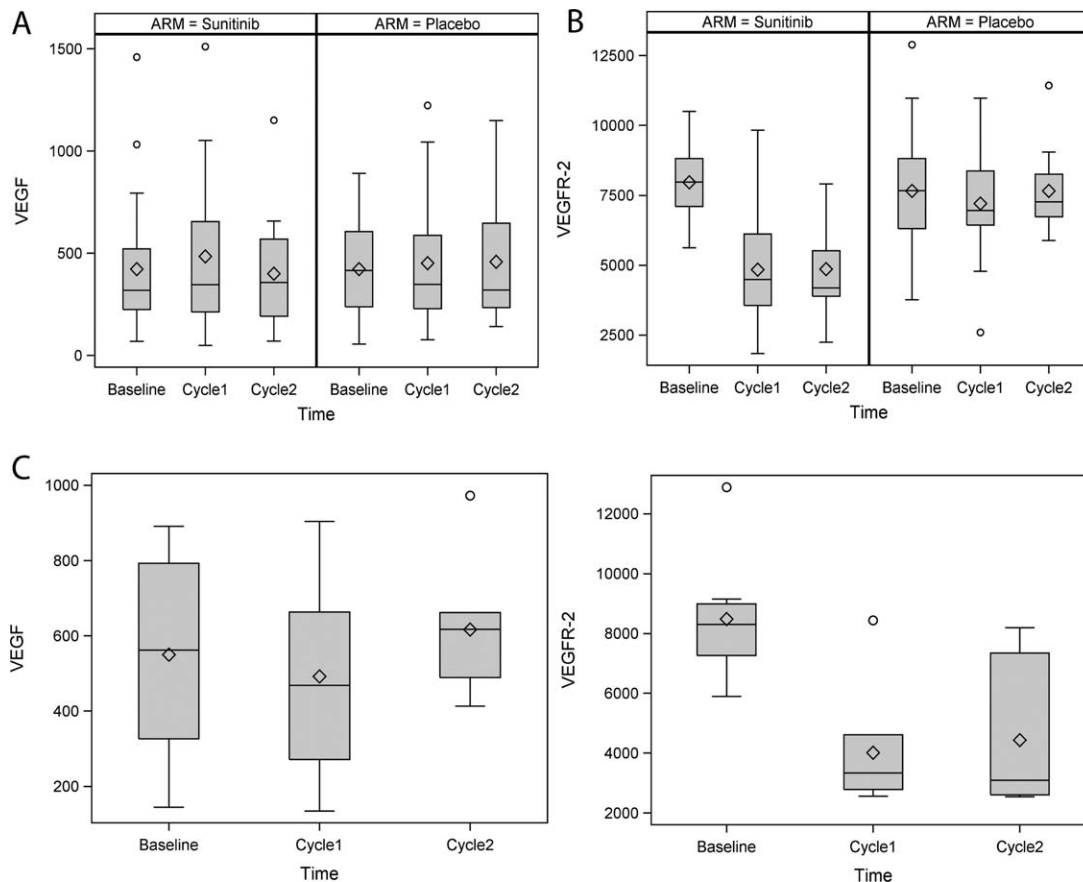


Figure 4. Box plots of serum vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-2 (sVEGFR2) levels (in pg/mL) are shown for the sunitinib and placebo treatment arms. At the end of cycle 1, serum levels were collected on days 27 to 35; at the end of cycle 2, serum levels were collected on days 69 to 84. (A) Serum VEGF levels are shown at baseline (sunitinib/placebo) (N = 20/23), at the end of cycle 1 (N = 17/21), and at the end of cycle 2 (N = 12/15) in the blinded phase. (B) Serum sVEGFR2 levels are shown at baseline (N = 20/23), at the end of cycle 1 (N = 17/21), and at the end of cycle 2 (N = 12/15) in the blinded phase. (C) Serum VEGF and sVEGFR2 levels are shown at baseline, at the end of cycle 1, and at the end of cycle 2 in the open-label phase (N = 7).

after 19.2 months of follow-up; however, the median PFS and OS were very modest (2.6 months and 4.7 months, respectively).¹¹ Although low single-agent activity makes an agent suboptimal as the primary therapy, the current study was designed with the hypothesis that sunitinib would have better effects, particularly in delaying disease progression in the setting of a relatively lower tumor burden as an adjunct therapy and not as the main treatment.

The current study did not achieve the predefined power due to poor accrual and premature closure, which is unfortunately a recurring theme in UC trials. However, outcome trends between the treatment arms strongly suggest that sample size was not likely the main reason for the negative results. Given the importance of prior response and duration of prior therapy, we stratified patients by response to prior therapy to ensure relative balance in the 2 arms and limited accrual to patients who had received

4 to 6 cycles to minimize variability. However, the median PFS was shorter than expected in both treatment arms. This occurred despite the finding that nearly one-half of the patients had responded (at least partially) to prior chemotherapy, which is considered a favorable prognostic factor.²⁴

Although a maintenance strategy is attractive from the perspective of potentially consolidating the chemotherapy response while minimizing toxicity by preselecting the responders, it may not be optimal strategy when targeting angiogenesis, and combination therapy may be better. However, a recent clinical trial of gemcitabine and cisplatin combined with sunitinib for the treatment of metastatic as well as earlier-stage muscle-invasive UC reported that this combination was not feasible due to significant toxicity.²⁵ A phase 2 trial of combination bevacizumab (anti-VEGF monoclonal antibody) and cisplatin/

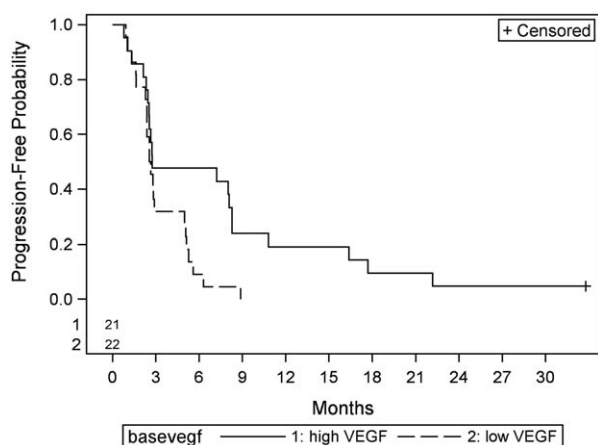


Figure 5. Kaplan-Meier plots of progression-free survival based on baseline serum vascular endothelial growth factor (baseveg) (high vs low) (N = 43). VEGF indicates vascular endothelial growth factor.

gemcitabine as first-line treatment for patients with metastatic UC had CR and PR rates of 19% and 53%, respectively, in addition to a ≥ 12 weeks SD rate of 9%.²⁶ The median PFS was 8.2 months and the median OS was 19.1 months. Because of the higher-than-expected antitumor effect with chemotherapy and bevacizumab, the Alliance cooperative oncology group is conducting a phase 3 trial with this combination (ClinicalTrials.gov identifier NCT00942331). Another phase 2 trial of the combination of gemcitabine and carboplatin with bevacizumab in chemotherapy-naïve patients with advanced/metastatic UC who are not candidates for treatment with cisplatin reported a grade 3/4 AE rate of 39%, a response rate of 49%, a median PFS of 6.5 months, and a median OS of 13.9 months.²⁷ Two other randomized phase 2 trials failed to demonstrate a benefit with the addition of antiangiogenic agents to chemotherapy in patients with advanced/metastatic UC (the combination of docetaxel and vandetanib as second-line therapy; the combination of gemcitabine, cisplatin, and sorafenib as first-line therapy).^{28,29} An ongoing phase 2 study is evaluating 2 other antiangiogenic agents (ramucirumab or icrucumab) with docetaxel as second-line therapy in patients with advanced/metastatic UC (ClinicalTrials.gov identifier NCT01282463).

The report of the patient in the current study who received open-label sunitinib and that of the patient in the previously mentioned pazopanib trial with long-term disease control suggest that antiangiogenic therapy may have efficacy in a small but as-yet undefined subset of patients. This highlights the importance of identifying appropriate

predictive biomarkers. However, to the best of our knowledge, to date there is no established predictive biomarker for antiangiogenic therapy in general and sunitinib in particular. Previous reports have suggested the value of biomarkers that are predictive of response to sunitinib and other antiangiogenic agents.³⁰ A low interleukin-8 baseline serum level was associated with prolonged TTP, whereas baseline tumor contrast enhancement with > 40 Hounsfield units was associated with clinical benefit in patients with UC who were receiving sunitinib.²³ Data have suggested that inhibition of hypoxia-inducible factor- α may be required for a response to sunitinib in patients with RCC.³¹

In the current study, the serum VEGF level did not appear to change significantly with either treatment; variations in the time point of serum collection can affect the VEGF level, which can regress to a normal range when the patient is off therapy. However, the serum sVEGFR2 level significantly decreased during sunitinib therapy and at the time of disease progression, corresponding to previous reports. This could be explained by the disruption of vasculature and endothelial cells that express VEGFR2. Plasma (vs serum) level most likely reflects more accurately circulating VEGF because platelets may contain/ secrete VEGF into the blood, and platelet number can change during treatment.³² Similar reductions in the serum or plasma sVEGFR2 level and increases in the VEGF level with sunitinib were reported in patients with UC, gastrointestinal stromal tumors, and RCC.^{20,23,33} Larger changes in plasma VEGF, sVEGFR2, and sVEGFR3 levels were noted in patients who responded to sunitinib versus nonresponders with RCC; in our trial, changes in the serum VEGF and sVEGFR2 levels from baseline after cycle 1 did not correlate with outcome. In exploratory analysis, we found that a baseline serum VEGF level greater than the median was associated with longer PFS. This finding should be interpreted with caution due to the small sample size, but may merit further exploration.

Because of the limitations of the current trial, the negative results should not preclude future exploration of other antiangiogenic or alternative maintenance strategies. It is interesting to note that both lapatinib (anti-epidermal growth factor receptor/human epidermal growth factor receptor 2 tyrosine kinase inhibitor) and vinflunine are currently being tested as maintenance therapies in patients with metastatic UC (ClinicalTrials.gov identifiers NCT00949455 and NCT01529411).

Despite the limitations of this randomized trial, maintenance sunitinib after standard chemotherapy did not appear to impact disease progression and is unlikely to

confer a benefit in this setting. Sunitinib was found to have modest activity when initiated at the time of disease progression. The role of antiangiogenic therapy and the predictive value of the serum VEGF level in response to such therapy remain unclear in patients with UC. A better understanding of de novo and acquired mechanisms of resistance to antiangiogenic therapies in this disease is critically needed to enhance treatment effects and provide potential predictive biomarkers.

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CONFLICT OF INTEREST DISCLOSURES

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