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Phase II Study of Aflibercept (VEGF-Trap) in Patients with Recurrent or Metastatic Urothelial Cancer, a California Cancer Consortium Trial

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Abstract

Background—The efficacy of systemic therapies for advanced urothelial cancer following failure of frontline platinum-based chemotherapy is limited. There is evidence that vascular endothelial growth factor (VEGF) is important in the pathophysiology of urothelial cancer. Aflibercept is a recombinant fusion protein that binds and neutralizes multiple VEGF isoforms.

Methods—Patients with measurable, metastatic or locally advanced urothelial cancer previously treated with one platinum-containing regimen were enrolled. Aflibercept was administered at 4 mg/kg IV q 2 weeks. Response rate (RR) and progression free survival (PFS) were assessed in a 2-stage accrual design (22+18). A maximum of 40 patients were to be accrued to rule out a null hypothesized RR of 4% and PFS of 3 months versus alternative of 15% RR and 5.4 months PFS with α=0.12 and β=0.19.

Results—22 patients were accrued. One partial response (PR) (4.5% RR, 95% CI: 0.1%-22.8%) was seen. Median PFS was 2.79 months (95% CI: 1.74-3.88). Attributable grade 3 toxicities included: fatigue, hypertension, proteinuria, pulmonary hemorrhage, pain, hyponatremia, anorexia and lymphopenia. There was no treatment attributable to grade 4+ toxicities.

Conclusions—Aflibercept was well tolerated with toxicities similar to those seen with other VEGF pathway inhibitors; however, it has limited single agent activity in platinum-pretreated urothelial carcinoma patients.

INTRODUCTION

Bladder cancer is diagnosed in approximately 70,000 Americans each year and is the eighth leading cause of cancer death (1). Although non-invasive papillary urothelial cancer is the most common subtype, virtually all deaths from bladder cancer derive from muscle invasive disease that recurs and/or metastasizes after local therapy (2). Metastatic urothelial cancer arises not only from the bladder, but also from the upper genitourinary tract and is a chemotherapy sensitive tumor. Platinum-based regimens have been and still are the cornerstone of therapy for recurrent or metastatic bladder cancer. The regimen of methotrexate, vinblastine,

doxorubicin, and cisplatin (MVAC) has produced overall response rates of 40% to 72% with 13% to 28% of patients having complete response in Phase II trials (3). A randomized trial comparing MVAC with gemcitabine and cisplatin (GC) showed that GC treated patients had similar survival as those treated with MVAC, with somewhat less toxicity (4). The median overall survival in patients treated with either of these platinum based regimens remains between 12 and 14 months (5).Unfortunately, less than 10% of patients become long-term disease-free survivors and no regimen has been shown to be more effective than MVAC (5). For patients with recurrent disease following platinum based therapy, multiple studies with various compounds have been conducted with most demonstrating only modest response rates. The only agent to have demonstrated a survival benefit in a phase III trial is vinflunine, for which reports suggest a very modest improvement over best supportive care alone (6) Given the almost universal failure of first line therapy and ineffectiveness of salvage regimens, there is strong rationale and need for exploration of new treatment options in patients with recurrent bladder cancer.

It is generally accepted that solid tumor growth and metastases are dependent upon the acquisition of an adequate blood supply (angiogenesis) (7-9). VEGF plays a critical role in angiogenesis by stimulating endothelial cell proliferation and capillary permeability (10). There is ample evidence that angiogenesis and VEGF are important in the pathophysiology of urothelial malignancies (11).

Targeting VEGF with bevacizumab (a recombinant humanized anti-human VEGF monoclonal antibody), in combination with DNA targeting chemotherapy, results in improved clinical outcomes in patients with metastatic colorectal, lung, and breast carcinomas (12-16). The mechanism of anti-tumor activity of VEGF inhibition in these situations is complex. Treatment with bevacizumab may have a direct anti-angiogenic effect, but other data suggest that bevacizumab leads to “normalization” of disorganized tumor blood vessels, leading to better chemotherapy delivery (17). Aflibercept is a unique fusion protein combining the Fc portion of human IgG_1 with the principal extracellular ligand-binding domains of human vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR receptor 2 (VEGFR2). It acts as a high-affinity soluble VEGF receptor and potent angiogenesis inhibitor. Aflibercept has several potential advantages over other VEGF inhibitors. It has a much higher VEGF-A binding affinity (~1.5 pM dissociation constant for $VEGF_{165}$ and $VEGF_{121}$) than humanized monoclonal antibody (~800 pM) and binds VEGF-B and placental growth factors (PlGF1 and PlGF2) which have independent pro-angiogenic effects. Aflibercept has a longer circulating half-life compared to other soluble receptor constructs that have been studied in animals and unlike the humanized monoclonal antibody to VEGF, aflibercept is entirely comprised of human protein sequences. Given these considerations, a phase II trial of aflibercept in patients with refractory metastatic urothelial cancer was conducted.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients were adults (>18 years) with a pathologic diagnosis of urothelial carcinoma of the bladder, renal pelvis, ureter or urethra. Tumors must have had predominance of transitional histology, but foci of squamous and/or adenocarcinoma histology was allowed. Patients were required to have measurable, metastatic or locoregionally advanced disease that was not amenable to curative surgery and/or radiation. Patients must have received at least one prior chemotherapy regimen containing platinum compound and no more than one regimen for metastatic disease. Systemic therapy and radiation must have been completed at least 4 weeks prior to entering the study. Patients must have recovered from toxicities related to prior treatments. Eligible patients had to have an Eastern Cooperative Oncology Group performance score of 0, 1, or 2, a creatinine of $\leq$ 2.5 X institutional upper limit of normal or creatinine

clearance of ≥40 mL/min. and urine protein/creatinine ratio (UPCR) of < 1. In patients with UPCR ≥ 1, a 24-hour urine collection must have been obtained to document protein <500 mg. Patients must have had absolute neutrophil count ≥1000/mcL and platelet count ≥75,000/mcL. Patients were excluded if they had CNS metastases, active bleeding or high risk of bleeding, uncontrolled hypertension, New York Heart Association grade III or greater congestive heart failure, unstable angina, DVT or other thromboembolic event within last 6 months. Patients could not have undergone major surgical procedures or experienced gastrointestinal perforation within 28 days of therapy. Female patients were to have negative pregnancy test and all patients were required to use appropriate birth control. HIV positive patients on antiviral therapy were not eligible. The protocol was approved by the institutional review boards of the participating institutions, and all patients provided written informed consent.

Treatment with Aflibercept

Patients received Aflibercept at 4 mg/kg administered IV over 1 hour on day 1 of each 14-day cycle. No routine premedications were administered. Delays of up to 2 weeks in case of unresolved toxicity were allowed. Study treatment was continued until disease progression or unacceptable toxicity occurred. Patients had their blood pressure monitored weekly during the first cycle of therapy and subsequently prior to each infusion of aflibercept. Urine protein to creatinine ratio (UPCR) was measured prior to the beginning of each cycle and a ratio of ≥1 necessitated measurement of 24 hour urinary protein excretion. Presence of grade 2 hypertension required initiation of antihypertensive therapy. The occurrence of grade 3 hypertension or grade 3 proteinuria required resolution of toxicity to ≤ grade 2 and subsequent dose reduction. Once the patient had dose reduction the dose was not increased.

Efficacy and Safety Evaluation

Tumor response was evaluated by computed tomography (CT) or magnetic resonance imaging (MRI) every 4 cycles (8 weeks) using the RECIST (Response Evaluation Criteria in Solid Tumors). Progression-free survival was defined as the interval between the date of start of treatment and the date of either documentation of disease progression (either radiologic or symptomatic progression) or death owing to any cause. Patients not known to have progressive disease or who died were censored at the date the patient was last known to be progression-free. A physical examination was conducted, and vital signs, hematology, clinical chemistry, urine protein to creatinine ratio were assessed every cycle before treatment. Toxicity was graded on an ongoing basis throughout the study using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0

Statistical Analysis

Response rate (RR) and progression free survival (PFS) were assessed in a 2-stage accrual design (22+18). A maximum of 40 patients were to be accrued to rule out a null hypothesized RR of 4% and PFS of 3 months versus alternative of 15% RR and 5.4 months PFS (corresponding to 4 month PFS of 40% vs 60%) with α=0.12 and β=0.19. If no more than 1 objective response (no more than 4.5%), and no more than 10 instances of 4-month PFS (no more than 45%), were observed among the initial 22 patients, the study would be terminated early and declared negative. Accrual was not permitted to continue past the interim analysis while response evaluation and the four month progression evaluation were pending for the previously accrued patients.

RESULTS

Patient Characteristics

Patient demographics and clinical characteristics at diagnosis are summarized in Table 1. Median age was 67. The majority of patients were male Caucasians with ECOG PS 0, with the primary site in the bladder. Twenty-three percent of the patients had received prior therapy in both the peri-operative as well as metastatic setting. All patients had metastatic disease (Table 1)

Toxicity

Table 2 summarizes the grades 2 and 3 toxicities; possibly, probably or definitively attributable to therapy. There were no Grade 4 or 5 toxicities. There were no thromboembolic events. Seven courses of therapy were delayed and three patients required dose reductions of afilbercept to 3 mg/kg. Dose reductions were related to grade 2 hypertension (2 patients) and grade 3 anorexia and fatigue (1 patient) Four patients were taken off the protocol because of toxicities that included grade 3 hemoptysis (1 patient), grade 2 and 3 proteinuria (3 patients) and grade 3 hypertension (1 patient).

Efficacy

Median number of completed cycles of therapy was 3 with the longest duration of 18 cycles One confirmed partial response (4.5% RR, 95% CI: 0.1%-22.8%) was seen in a patient with peritoneal carcinomatosis and foci of adenocarcinoma differentiation. Median PFS was 2.79 months (95% CI: 1.74-3.88). Five patients had a PFS of at least 4 months. Fourteen patients had documented progression, three patients were taken off the protocol by the treating physician and 1 patient decided to discontinue protocol treatment. Since neither the requirement for response rate or PFS were met at the interim analysis of 22 patients, the trial was terminated.

DISCUSSION

Aflibercept was well tolerated with side effects that were expected for this class of agents. No thromboembolic events were noted. No grade 4 toxicities were seen, although grade 3 toxicities led to the discontinuation of therapy in 18%. The degree of fatigue was in the range observed with single agent bevacizumab (18) and in at least one patient was associated with neuro-psychiatric depression. Unlike the fatigue seen with VEGFR tyrosine kinase inhibitors, this was not associated with thyroid abnormalities and the mechanism of this toxicity remains unclear. The hypothesis of this trial was based on preclinical evidence indicating a role for VEGF family members in urothelial cancer progression and the more potent inhibition of VEGF and VEGF family by aflibercept as compared to other VEGF inhibitors. Unfortunately, only one patient experienced an objective response by standard criteria and the median time to progression also did not meet trial defined criteria to justify further development of this compound as a monotherapy in the salvage setting of urothelial carcinoma. The results of the present study are consistent with other clinical experience indicating that single agent VEGF inhibition has limited antitumor activity unless VEGF is clearly the dominant driving pathway of the cancer growth as exemplified by clear cell renal cell carcinoma. (18) The one patient with prolonged apparent benefit had unique clinical features and thus this tumor may have had a different biology than the typical urothelial cancer. In other tumor types VEGF inhibition demonstrated clinical benefit when applied in combination with chemotherapy (12-14) or as a component of inhibition of other angiogenic and tumorigenic pathways (19). There is considerable uncertainty regarding the mechanism of action of VEGF inhibitors in the majority of solid tumor types. Some evidence points towards the occurrence of “vascular normalization” which is responsible for a temporary increase in tumor blood flow, allowing for more effective

delivery of chemotherapeutic agents. Under this hypothesis single agent VEGF inhibition would be of limited benefit. Lack of efficacy of VEGF inhibition may also be related to the presence of important alternative angiogenic pathways driven by fibroblast growth factor (FGF) or platelet derived growth factor (PDGF), which are not inhibited by aflibercept. Other mechanisms of resistance to angiogenesis inhibition involve recently described phenomena of vascular mimicry and vascular cooption that allow tumor growth without a need for VEGF and endothelial cell proliferation. (20)

The inhibition of angiogenesis remains a valid concept in the therapy of urothelial malignancies but single agent VEGF ligand inhibition with aflibercept does not demonstrate sufficient activity to warrant further development. The potential for further development of angiogenesis inhibition in urothelial cancer likely lies in combination with chemotherapy or in utilizing compounds with broader effect on multiple angiogenic pathways as demonstrated successfully in other tumor types.

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Table 1

Patient demographics and clinical characteristics

Demographic/Characteristic	No.of Patients N=22	%
Age, years		
Median	67	
Range	45-79	
Sex		
Male	15	68
Female	7	32
Race		
Caucasian	20	90
American Indian	1	5
Pacific Islander	1	5
Site of primary tumor		
Bladder	18	82
Renal pelvis/ureter	4	18
Sites of metastases		
Lymph nodes	16	73
Lungs	8	36
Liver	7	32
Prior cystectomy	14	64
Prior chemotherapy		
Adjuvant/neoadjuvant only	7	32
Metastatic only	10	45
Metastatic and Adjuvant/Neoadjuvant	5	23
ECOG PS		
0	14	64
1	8	36

Table 2

Toxicities

Toxicity	Grade 2 N (%)	Grade 3 N (%)
Fatigue/asthenia	2 (9)	2 (9)
Hypertension	8 (36)	2 (9)
Pulmonary hemorrhage		1 (5)
Anorexia	3 (14)	1 (5)
Lymphopenia	3 (14)	1 (5)
Pain	6 (27)	1 (5)
Proteinuria	6 (27)	1 (5)
Hyponatremia		1 (5)
Infection	3 (14)	
Creatinine elevation	2 (9)	
Rash	2 (9)	
Thrombocytopenia	1 (5)	
GU Hemorrhage	1 (5)	
AST, SGOT elevation	1 (5)	
Heartburn\dyspepsia	1 (5)	
Taste Alteration\dysqeusia	1 (5)	
Hyperglycemia	1 (5)	
Hypoglycemia	1 (5)	
Weight Loss	1 (5)	
Diarrhea	1 (5)	
Nausea	1 (5)	
Hypoalbuminemia	1 (5)	
Edema-limb	1 (5)	