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A Phase II Trial of Gemcitabine, Capecitabine, and Bevacizumab in Metastatic Renal Carcinoma

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Abstract

Objectives—Renal cancer is resistant to most DNA and DNA repair targeted chemotherapy; although moderate response rates to nucleotide analog based therapy have been reported. Bevacizumab also has activity. We thus performed a phase II trial of gemcitabine, capecitabine, and bevacizumab in patients with metastatic renal cancer.

Methods—Following significant hematotoxicity, dosing was modified to gemcitabine 1000 mg/m^2 (Days 1, 8), capecitabine 1000 mg twice daily (Days 1–14), and bevacizumab 15 mg/kg (Day 1) on a 21-day cycle with evaluation every 3 cycles. Primary end point was objective response rate.

Results—Twenty-nine patients were enrolled between March 2005 and May 2008. Most patients had been previously treated with a vascular endothelial growth factor receptor tyrosine kinase inhibitor. Seven patients (24%) had a partial response. Median overall and progression-free survival were 9.8 months (95% confidence interval: 6.2, 14.9) and 5.3 months (95% confidence interval: 3.9, 9.9), respectively. The regimen was well tolerated with hematologic toxicity, fatigue, and rash being most common.

Conclusion—The trial was terminated early despite not meeting criteria for success or futility because of slow accrual and because the historical response rate became irrelevant with emerging data using sequential vascular endothelial growth factor therapies. Nevertheless, the observed progression-free and overall survival compare favorably to other phase II trials in this heavily pretreated population.

Keywords

bevacizumab; capecitabine; gemcitabine; metastatic renal carcinoma; phase II

Renal cancer accounts for approximately 58,000 (4%) of new noncutaneous cancer cases and is estimated to result in approximately 13,000 deaths in the United States in 2009.[1] The introduction of mTOR and vascular endothelial growth factor (VEGF) pathway-directed therapy has revolutionized the therapy for renal cancer. To date, the VEGF receptor kinase

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inhibitors sunitinib and sorafenib have been explored most extensively, but phase III data demonstrate that the VEGF binding agent bevacizumab, in combination with interferon-α, improves progression-free survival (PFS) and overall response rate over interferon-α alone in previously untreated renal cancer patients.[2–5] Nevertheless, complete responses to VEGF pathway inhibitors are rare and most patients will eventually progress.[6,7] In addition, while immunotherapy with high-dose interleukin-2 can lead to effective and durable responses, the benefit is enjoyed by only a minority of patients.[8]

Although most metastatic renal cancers are conventionally thought to be resistant to DNA and DNA-repair targeted chemotherapy, moderate response rates to nucleotide analog-based therapy have been reported[9–11]; and the combination of gemcitabine and 5-fluorouracil (5-FU) has been suggested to lead to longer PFS in comparison to historical controls.[12] Capecitabine has been substituted for 5-FU in a number of trials, and the safety of gemcitabine combined with capecitabine has been demonstrated in multiple phase I and II trials.[13–19] In renal cancer, a multi-institutional phase II trial of gemcitabine and capecitabine demonstrated an 11% objective response rate (ORR) and an overall median survival of 14.5 months,[17] but the results were not considered sufficiently robust to warrant advancing this to a phase III trial. Given the aforementioned benefit of VEGF pathway inhibitors in renal cancer, addition of such an agent to the combination of gemcitabine or capecitabine is logical. Thus, a phase II study of gemcitabine, capecitabine, and bevacizumab in metastatic renal cancer was undertaken.

MATERIALS AND METHODS

Patients

Eligibility criteria included histologically confirmed meta-static clear cell or poorly differentiated/unclassified renal cancer; measurable disease by standard Response Evaluation Criteria In Solid Tumors (RECIST) criteria; Eastern Cooperative Oncology Group performance status 0–1; blood pressure less than 140/90 mm Hg; no prior exposure to pyrimidine analogs or VEGF binding agents; no ongoing intercurrent illness including active infections, symptomatic cerebrovascular accident within 6 months, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia requiring medication, more than grade 2 peripheral vascular disease as defined by the National Cancer Institute Common Toxicity Criteria (version 3.0), or psychiatric illness/social situations that would limit compliance with study requirements. The patients were also required to have normal organ function defined as granulocytes >1500/μL, hemoglobin >9.0 mg/dL, platelets >100,000/μL, urine protein/creatinine ratio ≤1.0, total bilirubin less than 2.0 mg/dL, AST/ALT <2.5 times the upper limit of normal, and an estimated creatinine clearance of >30 mL/min. Pregnant or nursing women were excluded from the study. In addition, patients were excluded if exposed to chemotherapy or radiotherapy within 4 weeks before entering the study; treatment with therapeutic anticoagulation; any recent major surgical procedure within 28 days prior to start of treatment; serious nonhealing wound; evidence of bleeding diathesis or coagulopathy; known untreated brain metastasis; evidence of immune deficiency. All patients provided written informed consent, and the protocol was approved by the institutional review board.

Treatment

This was a phase II open-label single arm trial of combination gemcitabine, capecitabine, and bevacizumab in patients with meta-static renal cancer. The initial dosing consisted of gemcitabine 1000 mg/m^2 on Days 1 and 8, and 15, capecitabine 1000 mg (flat dose) oral twice daily on Days 1 through 21, and bevacizumab 10 mg/kg on Days 1 and 15 on a 21-day cycle. After significant hematotoxicity in the first 7 of 8 patients, the treatment regimen was modified to gemcitabine 1000 mg/m^2 on Days 1 and 8, capecitabine 1000 mg (flat dose) twice daily on Days 1 through 14, and bevacizumab 15 mg/kg on Day 1 on a 21-day cycle with disease reevaluation every 3 cycles. Specified dose reductions included the reduction of gemcitabine to 800 mg/m^2 and 600 mg/m^2 for myelosuppression, hepatotoxicity, and skin toxicity; and reduction of capecitabine to 800 mg (flat dose) twice daily and 500 mg (flat dose) twice daily for myelosuppression, skin toxicity, and mucositis/diarrhea. Patients who experienced grade 3 toxicity despite a 2-level dose reduction were removed from protocol treatment. Patients were also removed from the protocol treatment for pulmonary toxicity, microangiopathic hemolytic anemia, or any arterial thrombotic event. Although there were no dose reductions for bevacizumab, bevacizumab was held for grade 3 hypertension, proteinuria, grade 2 bleeding, and discontinued for grade 3 venous thrombosis. Treatment could continue up to a 40% increase in RECIST-based tumor measurements, inability to administer therapy for more than 8 weeks, intercurrent illness that prevented further administration of treatment, unacceptable adverse events, or patient withdrawal. In all cases, however, standard RECIST definitions for progression (20% increase in unidimensional measurements) were used for data reporting and statistical analysis.

Data Collection and Safety Monitoring

Patients underwent computed tomography scans of the chest, abdomen, pelvis at baseline, and every 3 cycles. Response and progression were evaluated using RECIST criteria.[20] Toxicities were monitored every 3 weeks at the start of each cycle except for blood pressure and complete blood count, which was also monitored on Day 8 of each cycle. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

End Point and Statistical Analysis

The original study was designed prior to data on response rates from sunitinib, sorafenib, and the combination of interferon-α and bevacizumab becoming available. The primary end point of the study was the ORR as determined by standard RECIST-based measurements using a Bayesian continuous monitoring method[21] designed to detect an improvement in the ORR from a 12% historical rate of the gemcitabine/capecitabine regimen to 27%, which was considered clinically meaningful.[17] The initial plan specified that a maximum of 55 patients were to be enrolled, and the treatment combination declared promising if the posterior probability that the response rate for the new treatment exceeded that of standard therapy was ≥0.95. Conversely, if there was a very low posterior probability (≤0.025) that the experimental regimen would increase the response rate by 15% or more, the trial would be halted for futility. Operationally, this criteria meant that the trial would be halted for meeting the primary end point if objective responses were observed in 4 of the first 10 or 11 patients,

5 of the first 16 patients, 6 of 20, 7 of 25, 8 of 30, 9 of 35, 10 of 40, 11 of 44, 12 of 49, 13 of 54, or 14 of 55 patients. The trial would be stopped for futility if no responses were observed in the first 10 patients, or only 1 response in 15, 2 in 22, 3 in 28, 4 in 34, 5 in 40, 6 in 45, or 7 in 51 patients. Time to progression was a coprimary end point, using the historical control median time to progression of 5.4 months based on an earlier phase II trial evaluating gemcitabine/capecitabine.[17] Secondary endpoints included survival and toxicity. Because emerging data with VEGF receptor tyrosine kinase inhibitors in both untreated and previously treated patients challenged the clinical relevance of the alternative hypothesis and because the availability of multiple therapies challenged accrual, the study was halted early. Consequently, mainly descriptive statistics are presented here together with Kaplan-Meier curves for OS and PFS.

RESULTS

Thirty patients were enrolled between March 2005 and May 2008 at the University of Chicago Medical Center. One patient died before starting treatment, thus 29 patients were evaluable. Patient characteristics are detailed in Table 1. There was a male and white predominance and the median age was 58 years (range, 36–82 years). All but 1 patient had a performance status of 0 or 1, and 72% of patients had 3 or more metastatic disease sites. Almost two-thirds of the patients were at intermediate risk according to the 2004 Memorial Sloan-Kettering risk stratification criteria followed by 24% who were categorized as favorable risk, and 10% as poor risk. Almost 80% of patients had clear cell histology, with 21% considered to be poorly differentiated or unable to be subtyped more accurately. Eighty-three percent of patients had undergone a prior nephrectomy; more than 50% had undergone prior radiotherapy; 28% patients had received prior cytokine therapy; and almost 70% of patients had been treated with an oral VEGF receptor tyrosine kinase inhibitor such as sunitinib or sorafenib. Although, exclusion criteria included prior treatment with a pyrimidine analog, 1 patient had received prior 5-FU and was thus technically ineligible. Because of the small study size it was elected to not exclude this patient from analysis.

Toxicities are described in Table 2. The majority of toxicity was hematologic and constitutional. Dose reductions were made after hematologic toxicities were observed in the first 8 patients. Two of the first 8 patients developed leukopenia, neutropenia, thrombocytopenia, and anemia (Table 2). One of the first 8 patients was also admitted to the hospital for pancytopenia. Among the next 21 patients on the reduced treatment regimen, all hematologic toxicities with the exception of neutropenia decreased in incidence although these differences did not reach statistical significance. Although no neutropenic fevers were observed, grade 3 or 4 neutropenia developed in 31% of all patients and 33% of the dose-reduced patients. In the dose-reduced patients, 10% of patients were noted to have grade 3 or 4 anemia; 14% had grade 3 leukopenia; and none developed grade 3 or 4 thrombocytopenia. There was minimal difference seen between the first 8 patients and the dose-reduced patients in regards to constitutional symptoms (data not shown). Grade 3 fatigue was noted in 21% of patients; there was no grade 4 fatigue reported (Table 3). Grade 3 dermatologic toxicities (rash or hand-foot syndrome) were observed in 10% of patients. Seven percent of patients had grade 3 dyspnea. Only 1 patient (3%) developed grade 4 proteinuria. Serious adverse events included 1 bowel perforation that led to sepsis and eventual death, 2 patients

developed pulmonary emboli, and 1 patient developed a deep vein thrombosis. One patient developed seizures despite the absence of brain metastasis or bleeding on imaging (Table 3). Common Toxicity Criteria for Adverse Events defined hypertension was not observed, but the average change in mean arterial pressure after 2 cycles was 5.6 mm Hg.

Objective responses according to standard RECIST criteria were observed in 7 patients for an ORR of 24% (95% confidence interval (CI), 10%–44%). There were no complete responses. All of the partial responders were classified as favorable or intermediate prognostic risk groups; and 5 of 20 patients with prior exposure to VEGF receptor tyrosine kinase inhibitors responded. Duration of responses was 6 to 22 months (Table 4). The median PFS for the entire study population was 5.3 months (95% CI: 3.9–9.9 months). By risk group, the median PFS was 3.4 months for the poor risk group, 5.3 months for the intermediate risk group, and 6.2 months for the favorable group (Fig. 1). The median overall survival (OS) for the entire study population was 9.8 months (95% CI: 6.2–14.9 months). The median OS by risk group was 7.0 months for the poor risk group, 9.6 months for the intermediate risk group, and 14.9 months for the favorable group (Fig. 2).

DISCUSSION

Renal cancer is known to be relatively resistant to conventional chemotherapies, which may be in part due to overexpression of the multidrug resistance gene product, *p*-glycoprotein.[22] However, both gemcitabine and 5-FU and its congeners are known to have moderate activity in metastatic renal cancer but response rates are only on the order of 10%, and phase III evaluation has not been pursued.[11,12,17] The addition of bevacizumab, a VEGF binding agent, which has known activity in renal cancer,[23] was investigated to determine whether an improvement in response rate was feasible. In addition, bevacizumab in combination with interferon-α has demonstrated superior response to interferon-α alone in 2 recent phase III trials.[2–5]

Although the ORR of 24% for gemcitabine, capecitabine, and bevacizumab was higher than the historical response rate of either bevacizumab alone or the combination of gemcitabine/capecitabine,[17,23] this study needed to be concluded early and is limited by its small size and single-armed nature. Nevertheless, it is interesting to note that 5 of 7 responses occurred in patients with prior VEGF pathway-directed therapy, and 5 of 7 had durations of response that lasted 11 months or longer. In addition, the median OS of 9.8 months and the median OS of 9.6 and 7.0 months in the intermediate and poor risk groups, respectively, is encouraging. The response rate also compares favorably to the 25.5% to 31% response rate observed in the phase III trials of bevacizumab plus interferon-α in previously untreated patients and the 1% response rate of everolimus in patients refractory to VEGF receptor pathway inhibitors.[4,5,24]

This regimen was fairly well tolerated with few unexpected toxicities. Substantial hematologic and constitutional toxicities seen in a prior trial using gemcitabine and capecitabine[17] may have been improved upon because dose reductions from the prior trial as well as further dose reductions that occurred after the first 8 patients on this current trial were enrolled. The observed serious adverse events including DVT/PE and bowel

perforation are again, not dissimilar to the more recent phase III trials using bevacizumab.[2–5]

Overall, the combination of gemcitabine, capecitabine, and bevacizumab is fairly well tolerated and has moderate activity in patients with metastatic renal cancer with a special highlight in patients in the poor risk group and patients who have been exposed to oral tyrosine kinase inhibitors. Nevertheless, the trial did not meet predefined criteria for success or futility, and the exact value of this combination in the face of multiple new VEGF as well as mTOR pathway inhibitors in renal cancer remains unknown. Further study of the regimen is recommended only after data from ongoing phase III trials of sequential VEGF pathway inhibitor therapy and combination therapy become available. In the meantime, given the apparent eventual progression of all patients treated with VEGF or mTOR pathway-directed therapy, further research identifying the subset of metastatic renal cancer patients in whom nucleoside analog therapy is of benefit will continue to be important.

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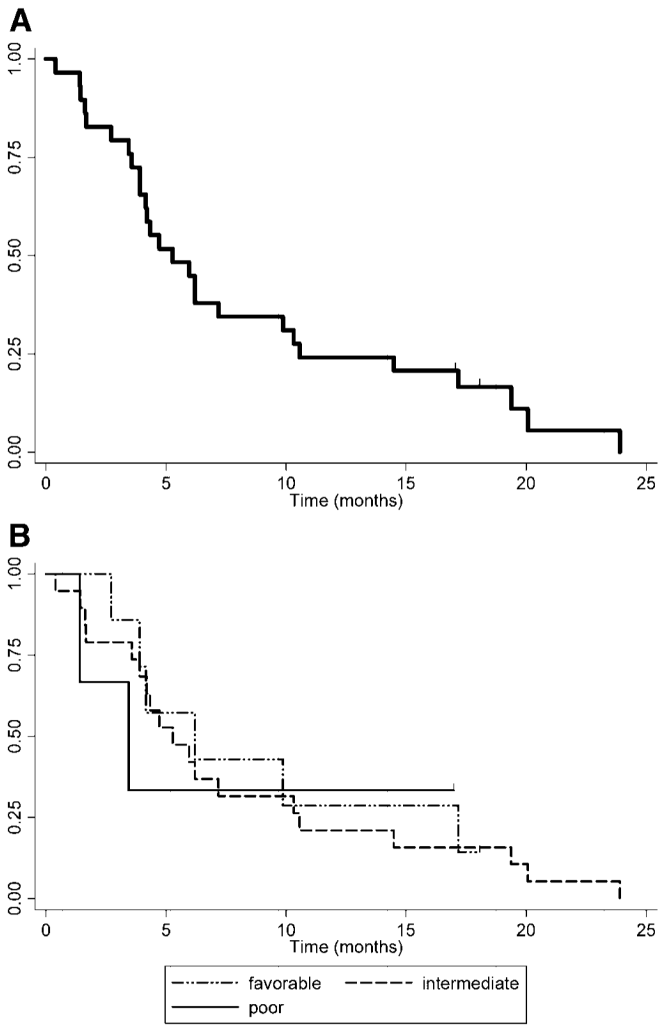

FIGURE 1.

PFS and PFS by MSKCC group. A, PFS: Median PFS 5.3 months, 95% CI (3.9, 9.9). B, PFS across MSKCC prognostic groups. Trend test across risk groups, $P = 0.79$.

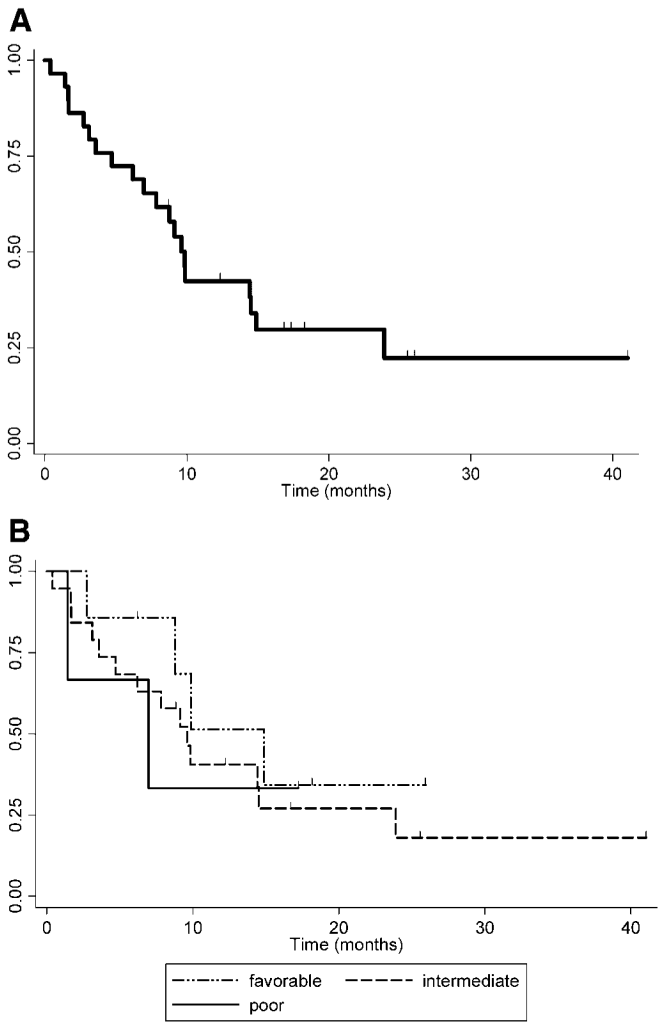

FIGURE 2.

OS and OS by MSKCC prognostic groups. A, OS: Median OS: 9.8 months, 95% CI (6.2, 14.9). B, OS by MSKCC prognostic groups. Trend test across risk groups, $P = 0.43$.

TABLE 1

Patient Characteristics (n = 29)

Characteristic	No. Patients	Percent
Median age (range), yr	58 (36–82)	—
Male: female ratio	24/5	83/17
Race/ethnicity		
White	28	97
African-American	1	3
Performance status		
0	5	17
1	23	79
2	1	3
No. metastatic disease sites		
1	2	7
2	6	21
≥3	21	72
Tumor histology		
Clear cell	23	79
Poorly differentiated/unclassified	6	21
Fuhrman grade		
1	0	0
2	2	7
3–4	21	72
Unknown	6	21
Prognostic risk group		
Favorable	7	24
Intermediate	19	66
Poor	3	10
Prior therapy		
Nephrectomy	24	83
Radiotherapy	15	52
Cytokine therapy	8	28
Oral VEGF receptor Kinase inhibitor	20	69

TABLE 2

Grade 3 or 4 Hematologic Toxicities in the First Eight Patients and in the Dose-Reduced Patients

	1st 8 Patients (n=8)		Dose-Reduced Patients (n = 21)	
Hematologic Toxicity	**Number**	**%**	**Number**	**%**
Leukopenia	2	25	3	14
Neutropenia	2	25	7	33
Anemia	2	25	2	10
Thrombocytopenia	2	25	0	0

Serious adverse events: seizure 3%, sepsis 3%, bowel perforation 3%, PE/DVT 10%.

TABLE 3

Grade 3 or 4 Toxicities and Serious Adverse Events in All 29 Patients

	Grade 3		Grade 4	
Treatment-Related Toxicity	**Number**	**%**	**Number**	**%**
Renal				
Proteinuria	0	0	1	3
Dermatologic				
Hand foot syndrome	2	7	0	0
Rash	1	3	0	0
Respiratory				
Dyspnea	2	7	0	0
Constitutional				
Fatigue	6	21	0	0
Gastrointestinal				
Nausea	2	7	0	0
Emesis	2	7	0	0
Hyperbilirubinemia	1	3	0	0

Serious adverse events: seizure 3%, sepsis 3%, bowel perforation 3%, PE/DVT 10%.

TABLE 4

Characteristics of Patients with Partial Response

Age/Sex	Histology	MSKCC Prognostic Group	N/RT	Prior Treatment	Duration of Response (mo)
43/F	Clear cell	Intermediate	Y/Y	Sorafenib interleukin-2	11
51/M	Poorly diff.	Favorable	N/N	None	15
70/M	Clear cell	Intermediate	Y/Y	None	11
62/M	Clear cell	Intermediate	Y/Y	Interferon imatinib sorafenib, sunitinib	16
44/M	Clear cell	Favorable	Y/N	Sorafenib	22
65/M	Clear cell w/sarcomatoid features	Intermediate	Y/N	Sorafenib	8
56/M	Clear cell	Intermediate	Y/Y	Interferon, interleukin-2 5-FU, cisplatin gemcitabine sorafenib, anti-hepatocyte growth factor	6

N indicates nephrectomy; RT, radiation therapy.