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Treatment of metastatic renal carcinoma patients with the combination of gemcitabine, capecitabine, and bevacizumab at a tertiary cancer center

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Abstract

BACKGROUND—We reported the clinical activity of gemcitabine plus capecitabine (GX) in mRCC pts previously treated with cytokines and targeted agents (Tannir et al. JU 2008).

Bevacizumab (A) has activity in mRCC and has been successfully incorporated into several chemotherapy regimens in many tumor types. This provided the rationale to combine GX and A in mRCC.

METHODS—After obtaining IRB approval, we evaluated the combination of GX + A in mRCC pts using institutional databases. Data included demographics, previous therapies, number of metastatic sites, MSKCC risk stratification variables, and prior nephrectomy status. Descriptive statistics and survival analysis were employed for data analysis.

RESULTS—Between January 2005 and October 2008, 28 patients were identified. Mean age was 55.7 years. Fifteen (53.57%) pts had prior tyrosine kinase inhibitor (TKI). Nine (32.14%) pts had clear cell histology, 10 (35.71%) pts had sarcomatoid features on histopathology, and 19 (67.86%) had prior nephrectomy. Initial treatment consisted of G (mean dose: 786.07 mg/m^2) every 2 weeks, X (mean dose: 2.73 grams/day), and A (mean dose: 10mg/kg) every 2 weeks. Median progression free survival (PFS) was 5.9 months and the median overall survival (OS) was 10.4 months. In pts with previous TKI therapy, median PFS was 6.2 months and median OS was 11.7 months. In pts with sarcomatoid features, median PFS was 3.9 months and OS was 9.0 months. Three patients discontinued >=1of the drugs due to adverse reactions.

CONCLUSIONS—The combination of GX + A demonstrates potential efficacy and acceptable tolerability in patients with intermediate and poor prognosis mRCC. Based on these observations, a phase II trial is now underway assessing this combination in pts with sarcomatoid RCC.

Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of all malignant diseases in adults. Worldwide, it accounts for 209,000 new cases per year, with 102,000 deaths. The incidence of all stages of renal cell cancer has been on the increase over several years, and subsequently, contributes to a steadily increasing mortality rate per unit of population.[1] It is a disease characterized by lack of early warning signs, diverse clinical manifestations, and resistance to many forms of standard therapies. Most patients do not have an identifiable risk factor and the pathogenic mechanisms underlying the known risk factors are not well understood.[2] RCC has several histological subtypes including clear cell (75%), papillary (15%), chromophobe (5%), and collecting duct (2%). The sarcomatoid variant, which can occur with any histological cell types, is associated with significantly poorer prognosis.[3]

Approximately 30% of patients with RCC present with metastatic disease. Initial systemic therapies for metastatic RCC were focused on cytokine based therapies, which have low anti-tumor activity. During the past four years, the US Food and Drug Administration (FDA) has approved six new targeted agents for metastatic RCC. They are sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab and pazopanib.[4] These agents likely target specific molecular pathways directly or indirectly involved in angiogenesis, and have expanded our systemic therapy options. However, they do not produce complete responses in the majority of the patients, and most patients eventually develop progressive disease. Treatment of non-clear cell histologies and RCC with sarcomatoid features remains a challenge. Therefore, there is a continued need to develop new approaches to the treatment of metastatic RCC.

Phase II trials have lead to the observation that the combination of gemcitabine with fluoropyrimidines may benefit treatment-resistant patients. [5–8] The combination of chemotherapy with antiangiogenic therapy has proven to be of benefit in other tumor types, including renal cell cancer.[9] We hypothesized that the combination of gemcitabine, capecitabine, and bevacizumab may be a viable option in high-risk or treatment refractory patients. We report here the retrospective evaluation of this triple therapy combination, which has formed the basis for a formal prospective phase II trial currently underway.

Patients and Methods

This retrospective study was conducted at the University of Texas M. D. Anderson Cancer Center in Houston, Texas, and was approved by the institution's review board. All use of gemcitabine, capecitabine, and bevacizumab in RCC patients was identified from January, 2005 to October, 2008, in both inpatient and ambulatory care setting through the pharmacy dispensing database. All data was verified through the actual medical records, nursing medication administration records and physician records, and individual patients were identified. Inclusion criteria included patients who had received at least one course of gemcitabine, capecitabine and bevacizumab during the study period. For the purpose of this study, the following data was collected: demographics, tumor histology, previous therapies, number of metastatic sites, MSKCC risk stratification variables, prior nephrectomy status, drug therapy duration, subsequent drug therapies, cost of the triple drug therapy, and PFS and OS till end of August, 2009.

The data was analyzed by descriptive statistics with the number of patients used as the denominator. Survival analysis using Kaplan-Meier estimates and Wilcoxon was utilized to determine if there was any difference in PFS and overall survival between the group with higher number of poor risk factors (3 or more) or previous TKI therapy. Cox proportional hazards ratio was utilized to determine if there were any important covariables with impact on the outcome of importance, mortality, specifically in terms of PFS and overall survival, again between the group with higher number of poor risk factors (3 or more) or previous TKI therapy. Hazard ratio values with confidence intervals that do not cross 1.0 and P-value <0.05 were considered to be statistically significant. Average costs of therapy for the total study population, as well as, the different subgroups were calculated and a cost per progression-free life years saved (PFLYS) was imputed. All costs were calculated using January 2008 average wholesale price for the three respective agents.

Results

Demographics and Baseline Disease Characteristics

Twenty-eight patients met the inclusion and exclusion criteria. The mean age of the population was 55.7 years, 82% were male and Caucasian. Eighty-nine percent of the patients were less than one year from diagnosis of their disease, 32% had clear cell histology. Ten patients (36%) demonstrated sarcomatoid or rhabdoid features in their tumors. Sixty-eight percent underwent prior nephrectomy, and 11% received previous radiation treatment. All of the study population had metastases, documented by a CT, MRI, or Bone scan, and 39% of patients had at least 3 or more MSKCC risk factors. The

demographics and baseline characteristics are given in Table 1. Table 2 lists details on MSKCC risk stratification, metastatic sites, and pathology for each of the 28 patients.

Other Therapies and Dosing Information

Table 3 lists the prior, concurrent, and post therapies, patients received over the course of the study period. Fifty-four percent of the patients were on a targeted kinase inhibitor (TKI) prior to starting the combination therapy of gemcitabine, capecitabine, and bevacizumab, while only four patients (14%) of the patients were treated with an interferon and/or interleukin. Post progression on the triple therapy, fourteen patients were switched to another agent, the majority 11 (79%) of them to a TKI.

Table 4 lists the dosing information of the three drugs of interest. The initial dose of therapy was 786.07 mg/m2 every two weeks for gemcitabine, 2.73 grams/day daily for capecitabine, and 852.59 mg every two weeks for bevacizumab. The average length of therapy was 202.25 days for gemcitabine, with dose modifications occurring in 6 patients. For capecitabine the average duration of therapy was 222.61 days with 14 patients requiring a dose change, and for bevacizumab, the average length of therapy was 174.94 days with four patients requiring a dose change. Three patients discontinued one or all of the study medications due to an adverse drug reaction (ADR), which included thrombocytopenia, nausea, vomiting, increase in liver enzymes, and fatigue.

Survival Analysis

The median PFS and OS for the study population were 5.9 months and 10.4 months, respectively. The median PFS and OS in patients with previous TKI therapy were 6.2 months and 11.7 months, and in patients with no previous TKI therapy, the PFS was 4.7 months and OS was 7.6 months, as indicated in Table 5. For the ten patients with sarcomatoid features, the PFS and OS were 3.9 months and 9.0 months respectively, versus 5.64 months and 10.03 months respectively for patient without sarcomatoid features. When adjusted for age, sex, race, previous TKI therapy, sarcomatoid features, and number of risk factors, no covariate was noted to be significant, in the Cox Proportional Hazard’s ratio univariate analysis.

COST OF THERAPY

Table 6 lists the average cost of therapy for the total study population, as well as, for the three subgroups of interest. Overall, for the total 28 patients, the cost per progression-free live years saved (PFLYS) is $212,766. The range of cost per PFLYS was from $218,431for patients with no previous TKI therapy to $236,817 for patients with previous TKI therapy. Also, the range of cost per PFLYS was from $264,132 for patients with less than three risk factors to $316,007 for patients with three or more risk factors. And the range of cost per PFLYS was from $131,360 for patients with no sarcomatoid features to $392,941 for patients with sarcomatoid features.

Discussion

An improved understanding of the molecular biology of RCC and of angiogenesis has resulted in the rapid evolution of the therapeutic landscape for this group of diverse tumor subtypes. Because of the near ubiquity of the VHL mutation in patients with clear cell RCC, and the knowledge that this mutation results in unbridled HIF1a and HIF2a levels and consequent overproduction of proangiogenic factors including vascular endothelial growth factor (VEGF), RCC has become a proof of concept for the utility of antiangiogenic therapies. Nevertheless, some sobering facts are emerging from clinical studies using these agents. Virtually no patient has a complete response, and a large majority of patients develop resistance to antiangiogenic therapy at some point in time.

The reasons for the development of resistance are unclear. It is possible that remodeling of the endothelium occurs over time, with resistant subsets of endothelial cells replacing those who are dependent on VEGF signaling. This remodeling may be a stochastic event, or it may be driven by paracrine factors produced by the adjacent tumor epithelium and stroma. If the latter is true, then administering agents that alter epithelial tumor function and decrease paracrine factor secretion may potentiate antiangiogenic therapy.

A subset of renal cell carcinomas appear to be primarily refractory to most therapies. No model predicts for these patients with perfect accuracy, but in general, patients with poorer performance status, evidence of paraneoplastic effects on various organs, multiple sites of larger volume disease and sarcomatoid histology do not do well. Different prognostic models are now published, incorporating five or six factors, and are capable of classifying patients into clinically relevant subgroups.

We selected individuals to receive the combination of gemcitabine, capecitabine and bevacizumab based on the premise that patients with aggressive tumor characteristics, including multiple negative risk factors, multiple sites of disease and sarcomatoid histology, and refractoriness to antiangiogenic therapies will not fare well using monotherapy. A retrospective review from our institutional data suggests that use of a fluorpyrimidine containing regimen in patients with sarcomatoid features showed a trend towards better outcome.[10] We assumed that a combined blockade at the level of the epithelium and endothelium would be even better at controlling their disease.

Clinical outcomes bear out these assumptions. Despite the very high risk characteristics of these patients, the PFS of patients on this study was 5.9 months, and OS was 10.4 months. Unfortunately, numbers are too small perform meaningful comparative subset analyses, but the patients who received prior antiangiogenic therapy had a PFS of 6.2 months and an OS of 11.7 months. Whether these patients would have done better than on established monotherapy regimens requires prospective validation, but when compared to outcomes of patients with high risk features treated with sunitinib and with sorafenib, these numbers are provocative. In addition, when compared to second line everolimus therapy in patients who progressed on sunitinib or sorafenib, PFS data are similar, despite the fact that our study was populated by a larger percentage of patients with poor risk features.[11] Side effects of this combination were relatively minor. A combination of relatively low-dose gemcitabine, and

an aggressive policy of dose reduction or dose withholding for capecitabine when any side effects were manifest resulted in relative tolerability.

Cost of therapy is consistent with other studies where bevacizumab is used in second and third line setting. Specifically in colorectal cancer, incremental cost effectiveness ratios (ICERs) range from $170,000 to $240,000 when a monoclonal antibody is added to the regimen.[12–14] Here, in our study though there is no comparison group, if no treatment or supportive care is assumed as the comparator, then these values could also represent the ICER, with patients with disease characteristics of having three or more risk factors and sarcomatoid features by histology having the highest ICER, indicating the benefit is only modest for the extra cost.

Several patients started out receiving chemotherapy alone, and then had bevacizumab added on later. Incremental benefit was seen when such a strategy was employed, with tumor growth kinetics changing as a function of adding antiangiogenic therapy.

A major shortcoming of these data is their retrospective nature. However, based on these findings we have initiated a prospective phase II trial evaluating the combination of gemcitabine, capecitabine and bevacizumab in patients with sarcomatoid histology. We anticipate this trial will provide us with further evidence for the utility of combination chemotherapy and antiangiogenic regimens in patients with aggressive metastatic RCC.

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Table 1

Demographics and Baseline Characteristics of Study Population (N=28)

Variable	N (%) unless otherwise noted
Age (median, range)	55.7 (10.10)
Sex	
Males	23 (82.1)
Females	5 (17.8)
Race	
Caucasian	23 (82.1)
Black	1 (3.5)
Hispanic	4 (14.2)
Number of patients less than one year from diagnosis	25 (89.2)
Tumor Histopathology	
Clear cell	9 (32.1)
Clear cell plus sarcomatoid features	8 (28.5)
Chromophobe	1 (3.5)
Papillary	1 (3.5)
Unclassified/Other	7 (28)
Unspecified plus sarcomatoid	2 (7.1)
Prior nephrectomy	19 (67.8)
Prior radiation	3 (10.7)
Metastasis	
Number of patients with metastasis	28 (100)
Mean number of metastasic sites (mean, standard deviation)	3.29 (2.12)
Mean LDH (IU) (mean, standard deviation)	785 (657.79)
Number of patients with LDH >1.5 X ULN	6 (21.43)

Variable	N (%) unless otherwise noted
Mean Hemoglobin (g/dL) (mean, standard deviation)	11.27 (1.80)
Number of patients with Hgb <12g/dL	23 (82.14)
Mean Calcium (g/dL) (mean, standard deviation)	9.01 (0.73)
Number of patients with Calcium >10.2g/dL	3 (10.71)
Total Number of Risk Factors	
One	4 (14.29)
Two	13 (46.43)
Three	8 (28.57)
Four	3 (10.71)
Patients with 3 or more factors	11 (39.28)

LDH: Lactic dehydrogenase

ULN: Upper limit of normal

Hgb: Hemoglobin

IU: International Units

Table 2

Individual Patient Characteristics (N=28)

Patient	Prev Nephrectomy (prior to Gem)	Tumor-histologic type (pathology reports)	Tumor histo grade	Prognostic Score	LDH 1.5 ULN	Hemoglobin <12g/dL	Calcium >10.2g/dL	Time from diagnosis to treatment <1 year	Number of risk factors	Karnofsky score (0–100)	Sites of metastasis
1	Yes	clear cell type	Fuhrman grade 3	2	0	1	1	1	4	N/D	Bone, Lungs, Liver
2	Yes	clear cell type	Fuhrman grade 4	1	0	1	0	0	1	N/D	Lung
3	Yes	clear cell with sarcomatoid differentiation (30–40%)	Fuhrman Grade 4	1	0	1	0	1	2	N/D	Bone, Lung, Abdomen
4	Yes	clear (90%)and eosinophillic (5–10%) type	Fuhrman Grade 4	1	0	0	0	1	1	N/D	Lung, Pleura
5	No	poorly differentiated carcinoma	N/D	1	1	1	0	1	3	N/D	Muscle, Nodes, Adrenal
6	Yes	clear cell type with sarcomatoid differentiation (40–50%)	Fuhrman Grade 4	0	0	1	0	1	2	N/D	Bone, Lung, Pleura
7	Yes	clear cell type	Fuhrman Grade 3	2	1	0	0	0	2	N/D	Pericardium, Mediastinum, Chest Cavity, Pleura
8	Yes	papillary type 1	Fuhrman Grade 2	1	0	1	0	1	2	N/D	Nodes
9	Yes	clear cell type	Fuhrman's Nuclear Grade 2	1	0	1	0	1	2	N/D	Bone Brain, Nodes Adrenal
10	Yes	unclassified type	Fuhrman Grade 4	1	0	0	0	1	1	N/D	Bone Lung, Nodes, Liver
11	No	poorly differentiated carcinoma	N/D	0	0	1	0	1	2	N/D	Nodes, Adrenal
12	No	unclassified type	N/D	1	0	1	0	1	2	N/D	Nodes
13	No	metastatic pleomorphic carcinoma with clear and granular cells	N/D	2	1	1	0	1	4	N/D	Skin, Bone
14	No	chromophobe	N/D	3		1	0	1	3	N/D	Nodes, Liver
15	No	rhabdoid features	Fuhrman Grade 4	3	0	1	1	1	4	N/D	Retroperitoneal Space, Bone, Lung, Peritoneum, Liver
16	Yes	clear cell type	Fuhrman Grade 3	1	0	1	0	1	2	N/D	Retroperitoneal Space, Lung, Pleura, Nodes, Liver, Duodenum, Adrenal, Bone
17	Yes	clear cell type with sarcomatoid diffentiation (20%)	Fuhrman's Nuclear Grade 4	1	1	1	0	1	3	N/D	Nodes, Spine, Bone, Lung,
18	Yes	clear cell type	Fuhrman's Nuclear Grade 3	0	0	1	0	1	2	N/D	Lung
19	No	poorly differentiated renal neoplasm with focal sarcomatoid features	N/D	3	0	0	0	1	2	N/D	Nodes
20	Yes	clear cell type	Fuhrman's Nuclear Grade 4	1	0	1	1	1	3	N/D	Lungs, Nodes Adrenal
21	No	poorly differentiated renal cell carcinoma	N/D	1	0	1	0	1	2	N/D	Peritoneum (Generalized)
22	Yes	clear cell type with sarcomatoid differentiation (30–40%)	Fuhrman's Nuclear Grade 4	3	1		0	1	3	N/D	Lung, Liver, Adrenal, Nodes

Patient	Prev Nephrectomy (prior to Gem)	Tumor-histologic type (pathology reports)	Tumor histo grade	Prognostic Score	LDH 1.5 ULN	Hemoglobin <12g/dL	Calcium >10.2g/dL	Time from diagnosis to treatment <1 year	Number of risk factors	Karnofsky score (0–100)	Sites of metastasis
23	Yes	clear cell type with focal sarcomatoid features (15–20%)	Fuhrman's Nuclear Grade 4	2	0	1	0	1	3	N/D	Lung
24	Yes	sarcomatoid type	N/D	3	0	1	0	1	3	N/D	Bones, Lung, Pleura, Nodes
25	No	clear cell type	N/D	3	1	1	0	1	4	N/D	Bones, Lung, Nodes, Liver, Left Adrenal
26	Yes	clear cell with sarcomatoid differentiation	Fuhrman's Nuclear Grade 4	1	0	1	0	1	2	N/D	Lung, Renal bed
27	Yes	clear cell with sarcomatoid differentiation	N/D	1	0	1	0	0	1	N/D	Lung, lymph nodes
28	Yes	clear cell with sarcomatoid differentiation	N/D	1	0	1	0	1	2	N/D	Lung, brain

Table 3

Therapies (N=28)

Prior Therapies	**N (%)**
Chemotherapy (gemcitabine+adriamycin, followed by carboplatinum plus paclitaxel)	1 (3.57)
Interferon alfa	4 (14.29)
TKI:	15 (53.57)
Sunitinib alone	4
Sorafenib alone	2
Sorafenib plus interferon	2
Sequential sorafenib and sunitinib	4
Bevacizumab plus erlotinib only	2
Bevacizumab plus erlotinib followed by sunitinib	1
None	10 (35.71)
Post Therapies	
TKI	11 (39.29)
Other (interferon, temsirolimus, and thalidomide)	3 (10.71)

Table 4

Details of the Three Drug Combination, N=28

Drug Details	Number (%) or Mean (SD)
Gemcitabine	
Mean Initial Dose (mg/m2/dose)	786.07 (270.44)
Mean Length of Therapy (days)	202.25 (187.01)
Number of Patients with Change in Dose	6 (23.08)
Capecitabine	
Mean Initial Dose (grams/day)	2.73 (0.50)
Mean Time on Therapy (days)	222.61 (210.07)
Number of Patients with Change in Dose	14 (50)
Bevacizumab	
Initial Dose (mg/kg)	10
Mean Length of Therapy (days)	174.96 (170.81)
Number of Patients with Change in Dose	4 (14.29)
Number Discontinued due to ADR	3 (10.71)

Table 5

Patient Outcomes

Outcomes for All Patients, N=28	**Median (Months)**
PFS	5.9
OS	10.4
Outcomes for Patients on Previous TKIs, N=15	
PFS	6.2
OS	11.7
Outcomes for Patients with no Previous TKIs, N=13	
PFS	4.7
OS	7.6
Outcomes for Patients with ≥3 Poor Risk Factors, N=11	
PFS	2.2
OS	5.0
Outcomes for Patients with <3 Poor Risk Factors, N=17	
PFS	6.2
OS	11.7
Outcomes for Patients with Sarcomatoid Features N=10	
PFS	3.9
OS	9.0
Outcomes for Patients without Sarcomatoid Features N=18	
PFS	6.1
OS	10.9

Table 6

Cost of Therapy for the Study Population

Study Population	Median PFS (Months)	Average Costs ($)	Cost ($)/ PFLYS
All Patients, N=28	5.93	105,142	212,766
Patients on Previous TKIs, N= 15	6.18	121,961	236,817
Patients with no Previous TKIs, N= 13	4.71	85,734	218,431
Patients with ≥3 Poor Risk Factors, N=11	2.18	57,408	316,007
Patients with <3 Poor Risk Factors, N=17	6.18	136,028	264,132
Patients with Sarcomatoid Features, N=10	3.86	126,396	392,941
Patients with No Sarcomatoid Features, N=18	6.11	66,884	131,360