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Outcomes of Patients With Metastatic Renal Cell Carcinoma and End-Stage Renal Disease Receiving Dialysis and Targeted Therapies: A Single Institution Experience

Aditya V. Shetty¹, Marc R. Matrana², Bradley J. Atkinson³, Amber L. Flaherty⁴, Eric Jonasch⁵, and Nizar M. Tannir⁵

¹Internal Medicine Residency Program, University of Texas Medical School at Houston, Houston, TX

²Department of Hematology and Oncology, Ochsner Medical Center, New Orleans, LA

³Department of Pharmacy Clinical Programs, The University of Texas M.D. Anderson Cancer Center, Houston, TX

⁴Hematology and Medical Oncology Fellowship Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

⁵Department of Genitourinary Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

Abstract

Data are limited regarding outcomes in patients with end-stage renal disease (ESRD) and metastatic renal cell carcinoma (mRCC) receiving targeted therapy. We retrospectively identified patients with mRCC and ESRD treated at the University of Texas M.D. Anderson Cancer Center from 2002 to 2012. Fourteen patients were identified with a median number of targeted therapies (TTs) per patient of 3 (range, 1–4). Outcomes in patients with mRCC and ESRD were similar to those reported in patients with normal kidney function.

Introduction—Limited data are available regarding patients with renal cell carcinoma and ESRD treated with TTs. The objective of this study was to explore the tolerability and safety of TT in patients with mRCC and ESRD.

Patients and Methods—We retrospectively identified patients with mRCC and ESRD treated at the University of Texas M.D. Anderson Cancer Center from 2002 to 2012. Patient characteristics including demographic, histology, treatment, and adverse events are reported. Duration of treatment (TOT) was determined from date of drug initiation to discontinuation. Overall survival (OS) was determined from initiation of TT to death. Statistics are descriptive.

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Address for correspondence: Marc R. Matrana, MD, MS, Department of Oncology, Gayle and Tom Benson Cancer Center, Ochsner Medical Center, 1514 Jefferson Highway, New Orleans, LA 70121, Fax: 504-842-4533; mamatrana@ochsner.org.

Disclosure

All other authors state that they have no conflicts of interest.

Results—Fourteen patients were identified. Ten patients had clear-cell histology and 4 had papillary histology. The median number of TTs per patient was 3 (range, 1–4) with median TOT of 28 months for all TTs. Eighty-eight percent of all toxicities were Grade 1 to 2; no Grade 4 toxicities were noted. Treatment discontinuations included 3 patients treated with sorafenib due to hand-foot syndrome, intolerable fatigue, and squamous cell skin cancer development; 2 patients treated with pazopanib due to intolerable fatigue and increased transaminase levels; and 1 patient treated with everolimus due to pneumonitis. Eight patients died from progressive disease. Median OS from initiation of TT was 28.5 months and 35 months from time of diagnosis.

Conclusion—Toxicities were mild to moderate and consistent with those reported in previous studies. TTs appear to be safe, well tolerated and produce antitumor response in patients with mRCC and ESRD receiving dialysis.

Keywords

Hemodialysis; Kidney cancer; Kidney disease; mTOR inhibitors; VEGF tyrosine kinase inhibitors

Introduction

In 2013, an estimated 65,000 people in the United States will be diagnosed with renal cell carcinoma (RCC) and 14,000 will die from the disease.¹ Approximately 30% of patients present with metastatic disease at the time of diagnosis and 20% to 30% develop recurrent metastatic disease after nephrectomy. Overall, the prognosis for patients with metastatic disease is poor, with an estimated 5-year survival of 10%.²

Improved understanding of the biology and underlying pathogenesis of RCC has led to the development of molecularly targeted therapies (TTs). Currently, 7 TTs are approved by the US Food and Drug Administration for the treatment of metastatic RCC (mRCC): sorafenib, sunitinib, pazopanib, axitinib, bevacizumab, temsirolimus, and everolimus. TTs have largely supplanted cytokine-based therapies in the treatment of patients with mRCC because of their greater tolerability, ease of administration, and improved outcomes.

End-stage renal disease (ESRD) is prevalent in the United States with an estimated dialysis population of 430,000 patients.³ Compared with the general population, the incidence of RCC might be higher in the ESRD population, the underlying biology might be different, and the clinical and pathological features might be more favorable.⁴ Patients with ESRD are often excluded from prospective clinical trials because of their altered pharmacokinetics.

Limited data are available regarding patients with RCC and ESRD treated with TTs. The objectives of our retrospective study were to investigate the safety and efficacy of TTs in patients with mRCC and ESRD.

Patients and Methods

After institutional review board approval, we retrospectively reviewed the institutional electronic health records of patients with mRCC who were seen at the University of Texas M.D. Anderson Cancer Center (MDACC) from 2002 to 2012. Patients 18 years of age or older who were treated with TTs (sorafenib, sunitinib, pazopanib, bevacizumab,

temsirolimus, or everolimus) and underwent renal replacement therapy with hemodialysis (HD) or peritoneal dialysis because of ESRD were included.

Data collected at baseline included demographic characteristics (age, race, sex); medical history; Memorial Sloan Kettering Cancer Center (MSKCC) prognostic variables⁵; and data regarding nephrectomy status, previous therapies, duration of ESRD, mode and duration of dialysis, renal transplantation status, tumor stage and grade, histological subtype of tumor, last available MDACC follow-up, information about adverse drug events (AEs), and date of death.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Duration of treatment (TOT) was defined as the time elapsed between the initiation of TT and the discontinuation of that TT for any reason. Overall survival (OS) was defined as the time from initiation of TT or time of diagnosis to time of death from any cause. Response was objectively assessed by the treating providers. Patient characteristics were summarized using median and range for continuous variables and frequency and percentage for categorical variables.

Results

Patient Characteristics

Fourteen patients with mRCC met our inclusion criteria. The baseline patient characteristics are summarized in Table 1. The population's median age was 57 years, and 50% were male. Eighty-six percent of patients had a nephrectomy, all before the initiation of any TT. Two patients (14%) had Karnofsky Performance Status scores < 80, and 21% had favorable risk, 50% had intermediate risk, and 29% had poor risk disease per MSKCC criteria.⁵ The median number of metastatic sites was 4 (range, 1–9). Three patients (21%) had a Charlson Comorbidity Index score of 8, 6 patients (38%) had a score of 9, and 5 patients (36%) had a score of 10. No patients had received transplants or immunosuppression before or at the time of TT initiation.

Patient Outcomes and Safety

The median number of TTs received was 3 (range, 1–4) with median overall TOT of 27 months for sequential TT and 28 months for sequential therapies including TT, chemotherapy, and cytokines. The percentage of patients who received each TT and their median TOT are summarized in Table 2. Median TOT of 8 months was noted in 4 patients treated with chemotherapy, and 3 months median TOT in 3 patients treated with cytokine therapy (interleukin-2, interferon- α). The objective response rate to all TTs according to treating physician evaluation was 31%. The RCC histology, sequence of TT, and total TOT for each patient are presented in Table 3. At last follow-up, 8 patients (57%) had died with a median OS of 28.5 months (range, 3–65 months).

Targeted therapies were discontinued 6 times (16%) because of AEs. Hand-foot syndrome, intolerable fatigue, and squamous cell skin cancer caused 3 patients to discontinue sorafenib; intolerable fatigue and increased transaminases in 2 patients led to discontinuation of pazopanib; and 1 patient discontinued everolimus because of pneumonitis. Most AEs were

Grade 1 or 2. Although serious AEs were uncommon, those reported during TT treatment included myocardial infarction, congestive heart failure, and pancreatitis. Common AEs reported by patients are shown in Table 4.

Three patients received an intravenous (I.V.) dosage of 10 mg/kg of bevacizumab every 2 weeks. All 3 patients were treated on Fridays after receiving dialysis earlier that day to maximize drug bioavailability. No dose reductions were noted in our study.

Seven patients were treated with sorafenib. Two patients received 400 mg orally twice per day (b.i.d.), with 1 patient requiring dose reduction to 600 mg once per day because of toxicity. Three patients received 600 mg daily dosing, with no dose reductions reported. One patient received 200 mg b.i.d. dosing, but the dosage was reduced to 200 mg b.i.d. administered Monday through Friday because of AEs. One patient was treated with 100 mg daily of sorafenib, with no dosage reduction reported.

Eight patients were treated with sunitinib. All 8 patients were treated on a 4-week on, 2-week off regimen. No dosage reductions were reported. Three patients were treated with 50 mg daily, 4 with 37.5 mg daily, and 1 with 12.5 mg daily.

Three patients were treated with temsirolimus. No dosage reductions were reported. All 3 patients were treated with 25 mg I.V. weekly on Fridays after receiving dialysis earlier that day to maximize drug bioavailability.

Seven patients were treated with everolimus. All 7 were treated with 10 mg daily, with one dosage reduction to 5 mg daily because of AEs.

Nine patients received pazopanib. Five patients were treated with 800 mg daily, with 2 dosage reductions—1 to 400 mg/d and 1 to 600 mg/d—because of AEs. Four patients were treated with 600 mg daily, with all 4 patients requiring dosage reductions to 400 mg daily because of AEs.

No significant interruptions to treatment with TT were reported in the 14 patients examined in this study.

Discussion

Metabolism of tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors occurs in the liver, and it is hypothesized that these drugs are safe in patients with ESRD.^{6–8} To date, only 1 study has been published that examined the efficacy and safety of TT in patients with mRCC requiring HD. Masini and colleagues conducted a retrospective study of 24 patients with mRCC who were treated with sunitinib (16 patients) or sorafenib (8 patients).⁹ Both TKIs appeared to be safe with no unexpected adverse outcomes noted. Outcomes compared with patients with normal kidney function were similar with a reported median progression-free survival (PFS) of 10.3 months and a median OS of 22.6 months.⁹ We similarly found sunitinib and sorafenib to be well tolerated, with no Grade 4 toxicities reported. In our study, patients had a median PFS of 5.6 months with sunitinib treatment and 4.2 months with sorafenib treatment. Although the discrepancy

between our results and those of Masini et al can be explained by the small sample size that limited our conclusions, both studies suggest efficacy of TT in patients with mRCC and ESRD. Although Masini and colleagues studied the efficacy and tolerability of 2 TKIs, we evaluated not only TKIs (sunitinib, sorafenib, and pazopanib), but also a vascular endothelial growth factor monoclonal antibody (bevacizumab), and mTOR inhibitors (temsirolimus and everolimus).

Ten of our patients had conventional clear-cell RCC, and 4 were confirmed to have papillary type RCC. Papillary histology has been observed to occur in patients with ESRD frequently and it tends to confer a worse prognosis than clear-cell RCC.¹⁰ Our results are not consistent with these observations because patients with the papillary subtype were found to have a median total TOT with TT of 27.7 months compared with 23.4 months in patients with clear-cell RCC. In our study, papillary RCC patients received a median of 4 TTs and patients with clear-cell RCC received a median of 3 TTs. Fourteen percent of our patients had bilateral RCC. This incidence rate is consistent with previous reports of increased incidence of bilateral RCC in patients with ESRD.¹¹

Although assessment of efficacy was not the main purpose of this study, the OS results are clinically meaningful in this select patient population and are similar to the results of large, randomized control trials.^{12,13} The median TOT of the 6 evaluated target therapies was comparable with known results in patients with normal kidney function.^{12,13}

In our study, pazopanib was the most commonly prescribed TT (n = 9) with a median TOT of 11.6 months. Although the reasons are not entirely clear, one reason patients treated with pazopanib had a prolonged median TOT might be better tolerability. In PISCES (Patient Preference Study of Pazopanib vs. Sunitinib in Advanced or Metastatic Kidney Cancer), a randomized double-blind crossover study of 169 patients with advanced RCC, patients preferred treatment with pazopanib compared with sunitinib because they were less fatigued and had improved quality of life.¹⁴ The phase III COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma) trial randomized 1110 patients with advanced RCC to either pazopanib or sunitinib as first-line therapy.¹⁵ The results demonstrated comparable OS, PFS, and overall response rate. Additionally, pazopanib was associated with fewer AEs and was favored by patients over sunitinib because of improved tolerability and quality of life. In our review, pazopanib demonstrated sufficient clinical activity in patients with ESRD (n = 7, excluding 2 patients from the total because they discontinued because of AEs) with median TOT of 12.7 months (range, 5.2–39.1). Based on our observations in this study, further studies are warranted to assess the efficacy of pazopanib in patients with ESRD and mRCC.

Overall, TTs appear to be safe and well tolerated in patients with mRCC and ESRD. Our results are comparable with known AEs reported in the general population. Hypertension is associated with improved outcomes in patients with mRCC treated with an antiangiogenic TT (TKIs and bevacizumab). Notably, all patients in our study (n = 14) had preexisting hypertension at baseline; only 2 patients (14%) had exacerbation of hypertension. This small number of patients with exacerbation of hypertension might be partly because of incomplete data or differences in pathogenesis. Of the 6 TTs in our review, sorafenib appeared to be the

least tolerated with 3 of 6 patients discontinuing sorafenib because of AEs. Based on this limited observation, sorafenib might not be well tolerated in patients with mRCC and ESRD. Although TTs appeared to be safe overall, several serious AEs were reported, including myocardial infarction, congestive heart failure, and pancreatitis. Therefore, patients with mRCC and ESRD receiving dialysis and TTs need close monitoring. TTs also appeared to be safe and well tolerated in patients with other comorbidities including diabetes, hypertension, coronary artery disease, or congestive heart failure, of which most patients in this study had at least one.

Limitations of our study include the retrospective study design and small sample size. However, we believe the results are meaningful in this rare and underserved patient population.

Conclusions

Our findings support the use of TTs in patients with mRCC and ESRD with tolerability and safety comparable with a normal mRCC population. Further studies are warranted in this population to assess safety and efficacy, but considering the limited number of patients, prospective trials would be challenging. Future outcome-based studies using large multi-institutional databases might provide additional information about the use of TTs in patients with mRCC and ESRD.

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Clinical Practice Points

- There is very little data on the effects of targeted therapies in patients with metastatic renal cell carcinoma and end-stage renal disease receiving dialysis.
- In our study, the median total time on treatment for sequentially targeted therapies was 27 months with a median overall survival of 28.5 months.
- Although there were a few serious adverse events, targeted therapies were overall well tolerated.
- Our findings support the use of targeted therapies in patients with end-stage renal disease receiving dialysis with tolerability and safety comparable to the general population.

Table 1

Baseline Patient Characteristics (n = 14)

Characteristic	Number (%)
Median Age at Diagnosis (Range), Years	57 (47–74)
Sex	
Male	7 (50)
Female	7 (50)
Ethnic Origin	
White	10 (72)
Black	3 (21)
Hispanic	1 (7)
KPS Score	
90–100	4 (29)
80–89	8 (57)
60–79	2 (14)
Eastern Cooperative Oncology Group Performance Status	
0	4 (29)
1	8 (57)
2	2 (14)
Histology	
Clear-cell	10 (71)
Papillary ^a	4 (29)
Previous Nephrectomy	12 (86)
Bilateral Kidney Tumors	2 (14)
Prognostic Feature	
KPS score <80	2 (14)
Time from diagnosis to treatment <1 year	7 (50)
Hemoglobin <LLN	11 (79)
Corrected calcium >10 mg/dL	2 (14)
LDH >1.5 times the ULN	0 (0)
MSKCC Risk Subgroup	
Favorable	3 (21)
Intermediate	9 (50)
Poor	2 (29)
Heng Risk Subgroup	
Good risk	2 (14)
Intermediate risk	11 (79)
Poor risk	1 (7)
Median Number of Metastases (Range)	4 (1–9)

Characteristic	Number (%)
Sites of Metastases	
Lung	11 (79)
Lymph node	10 (71)
Bone	6 (43)
Adrenal gland	5 (36)
Liver	5 (36)
Contralateral kidney	5 (36)
Brain	1 (7)
Other ^b	6 (43)
Comorbidities	
Hypertension	14 (100)
Dyslipidemia	6 (43)
Diabetes mellitus	5 (36)
CAD/CHF	4 (29)
Hypothyroidism	2 (14)

Data are presented as n (%) except where otherwise noted.

Abbreviations: CAD = coronary artery disease; CHF = congestive heart failure; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; LLN = lower limit of normal; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma; ULN = upper limit of normal.

^aUnknown if type I or II papillary RCC.

^bOther sites included chest wall, abdominal wall, psoas, diaphragm, and sinuses.

Table 2

Targeted Therapies

Therapy	Patients, n (%)	Median Duration of Treatment, Months (Range)
Pazopanib	9 (64)	11.6 (2.4–26)
Sunitinib	8 (57)	6.2 (0.3–12)
Sorafenib	7 (50)	5.3 (1–37)
Everolimus	6 (43)	1.9 (0.4–17)
Bevacizumab	3 (21)	18.3 (0.4–22.7)
Temsirolimus	3 (21)	4.7 (1.4–8)

This table includes targeted therapies as various lines of therapy and is therefore not meant to provide a comparison of efficacy between targeted therapies.

Table 3

Targeted Therapies in Each Patient

Patient	Histology	MSKCC Risk Subgroup	Line of Therapy (Duration of Treatment in Months)					Total Duration of Treatment With Targeted Therapy, Months
			First-Line	Second-Line	Third-Line	Fourth-Line	Fifth-Line	
1	Clear-cell	Poor	Sunitinib 50 mg q.d. (3.8)	Sorafenib 400 mg b.i.d. (5.9)	Everolimus 10 mg q.d. (0.4)	Sunitinib 50 mg q.d. (8.2)	Pazopanib 800 mg q.d. ^a (25.6)	43.9
2	Clear-cell	Intermediate	Sorafenib 400 mg b.i.d. ^b (37.4)	Sunitinib 37.5 mg q.d. (7.1)	Everolimus 10 mg q.d. (1.5)	–	–	46.0
3	Clear-cell	Intermediate	Pazopanib 600 mg q.d. ^c (12.8)	–	–	–	–	12.8
4	Papillary	Intermediate	Sunitinib 37.5 mg q.d. (0.6)	Temsirolimus 25 mg every week ^d (8.0)	Everolimus 10 mg q.d. (1.2)	Bevacizumab 10 mg/kg every 2 weeks ^d (18.3)	–	28.1
5	Papillary	Intermediate	Temsirolimus 25 mg every week ^d (presently receiving therapy)	–	–	–	–	–
6	Papillary	Intermediate	Sunitinib 50 mg q.d. (12.0)	Everolimus 10 mg q.d. ^e (8.6)	Pazopanib 600 mg q.d. ^f (2.4)	Sorafenib 600 mg q.d. (4.2)	–	27.2
7	Clear-cell	Intermediate	Pazopanib 600 mg q.d. ^g (presently receiving therapy)	–	–	–	–	–
8	Clear-cell	Favorable	Pazopanib 800 mg q.d. (presently receiving therapy)	–	–	–	–	–
9	Clear-cell	Poor	Temsirolimus 25 mg every week ^d (1.4)	Sorafenib 600 mg q.d. (1.0)	–	–	–	2.4
10	Clear-cell	Poor	Pazopanib 600 mg q.d. ^h (4.2)	–	–	–	–	4.2
11	Clear-cell	Intermediate	Bevacizumab 10 mg/kg ever 2 weeks ^d (22.7)	Sorafenib 200 mg b.i.d. ⁱ (3.7)	Sunitinib 12.5 mg q.d. (0.3)	–	–	26.7
12	Papillary	Favorable	Sorafenib 600 mg q.d. (14.3)	Everolimus 10 mg q.d. (2.8)	Pazopanib 800 mg q.d. (11.6)	Sunitinib 37.5 mg q.d. (2.7)	–	31.4
13	Clear-cell	Favorable	Sorafenib 100 mg q.d. (5.3)	Sunitinib 37.5 mg q.d. (7.0)	Pazopanib 800 mg q.d. ^j (21.2)	Everolimus 10 mg q.d. (16.6)	–	50.1
14	Clear-cell	Poor	Sunitinib 50 mg q.d. (5.4)	Sunitinib 50 mg q.d. (7.2)	Everolimus 10 mg q.d. (2.2)	Pazopanib 800 mg q.d. (5.2)	Bevacizumab 10 mg/kg every 2 weeks ^d (0.4)	20.4

Patient	Histology	MSKCC Risk Subgroup	Line of Therapy (Duration of Treatment in Months)					Total Duration of Treatment With Targeted Therapy, Months
			First-Line	Second-Line	Third-Line	Fourth-Line	Fifth-Line	
			5.4	7.0	1.9	6.7	13.0	–

Abbreviations: b.i.d. = twice per day; MSKCC = Memorial Sloan Kettering Cancer Center; q.d. = once per day.

- ^aDose reduced to 400 mg q.d. because of diarrhea.
- ^bDose reduced to 600 mg q.d. because of hypertension, fatigue, and arthralgias.
- ^cDose reduced to 400 mg q.d. because of fatigue and decreased appetite.
- ^dTreated on Fridays after receiving dialysis earlier that day to maximize drug bioavailability.
- ^eDose reduced to 5 mg q.d. because of congestive heart failure and myocardial infarction.
- ^fDose reduced to 400 mg q.d. because of myalgias and decreased appetite.
- ^gDose reduced to 400 mg q.d. because of fatigue.
- ^hDose reduced to 400 mg q.d. because of liver toxicity.
- ⁱDose reduced to 200 mg b.i.d. Monday through Friday because of hepatic encephalopathy.
- ^jDose reduced to 600 mg q.d. because of diarrhea and fatigue.

Table 4

Adverse Events Occurring With Each Targeted Therapy

Adverse Event	Drug, Adverse Events Reported, n						
	Sunitinib	Sorafenib	Pazopanib	Temsirolimus	Everolimus	Bevacizumab	
Fatigue							
Grade 1	3	2	6	1	1	1	
Grade 2	3	1	4	1	1	1	
Grade 3	0	1	2	0	0	0	
Increased LFTs	–	–		–	–	–	
Grade 1			2				
Grade 2			1				
Grade 3			1				
Diarrhea				–	–	–	
Grade 1	1	1	3				
Grade 2	1	1	3				
Grade 3	0	0	0				
Hypothyroidism		–		–	–	–	
Grade 1	1		1				
Grade 2	1		1				
Grade 3	0		0				
Nausea/Vomiting	–				–		
Grade 1			2	1		1	
Grade 2			2	1		1	
Grade 3			0	0		0	
Hypertension Exacerbation				–	–		
Grade 1	1	1	1			1	
Grade 2	1	1	1			1	
Grade 3	–	–	–			–	
Cardiovascular (eg, Myocardial Infarction)	–	–	–	–			
Grade 1							

Adverse Event	Drug, Adverse Events Reported, n					
	Sunitinib	Sorafenib	Pazopanib	Temsirolimus	Everolimus	Bevacizumab
Grade 2						
Grade 3						
Hand-Foot Reaction			-	-	-	-
Grade 1	2	2				
Grade 2	2	1				
Grade 3	0	1				
Hair and Skin Changes	-	-		-	-	-
Grade 1			1			
Grade 2			1			
Grade 3			0			

Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4.0. No Grade 4 toxicities were reported. Other adverse events reported once in this study included anemia, poor wound healing, hematuria, and metallic taste sensation during sunitinib therapy; neuropathy, anorexia, and constipation during pazopanib therapy; pancreatitis and squamous cell carcinoma of the skin during sorafenib treatment; lower extremity edema during bevacizumab therapy; and anemia, lymphopenia, thrombocytopenia, pneumonitis, and rash during temsirolimus therapy.

Abbreviation: LFT = liver function test.