Metastatic Renal Cell Carcinoma: Patient Characteristics, Treatment Patterns, and Schedule Compliance in Clinical Practice


Gregory P. Hess, MD, MBA


Chi-Chang Chen, PhD


Jerrold W. Hill, PhD

Gregory P. Hess, MD, MBA; Chi-Chang Chen, PhD; and Jerrold W. Hill, PhD
Outcomes Research, SDI Health, Plymouth Meeting, PA, United States


Zhimei Liu, PhD

Zhimei Liu, PhD
Novartis Pharmaceuticals
East Hanover, NJ
United States


Dean H. Gesme, MD

Dean H. Gesme, MD
Minnesota Hematology-Oncology
Minneapolis, MN
United States


Sanjiv S. Agarwala, MD

Sanjiv S. Agarwala, MD
St. Luke's Cancer Center
Bethlehem, PA
United States

Renal cell carcinoma (RCC) represents approximately 3% of adult cancers and approximately 90% of neoplasms that originate in the kidney.[1] The majority of patients with RCC develop metastases; approximately one-third of patients present with metastatic disease.[2] It is well established that metastatic renal cell carcinoma (mRCC) is resistant to conventional chemotherapy and to radiation therapy. Until recently, treatment was limited to cytokine therapy with interleukin-2 or interferon-α.[3,4] Advances in the understanding of the biology of mRCC have contributed to the development of several new classes of molecular-targeted therapies including tyrosine kinase inhibitors (TKIs; sunitinib, sorafenib, pazopanib); an antivascular endothelial growth factor (anti-VEGF) agent (bevacizumab); and mammalian target of rapamycin signaling inhibitors (mTORs; temsirolimus, everolimus).[2]

Molecular-targeted therapies, many of which can be taken orally, have generally been associated with better efficacy and tolerability than cytokine therapy.[4-7] With the introduction of these new therapies in the past 5 years, the treatment of mRCC is undergoing a paradigm shift from predominant use of cytokine therapy to the use of molecular-targeted agents.[6] For mRCC, sequential therapy with targeted agents is the current standard of care.[8]

Keywords: Renal cell carcinoma; metastases; targeted therapy.

Address for reprints and correspondence: Gregory Hess, MD, MBA, Vice President & Chief Medical Officer, SDI, 1 SDI Drive, Plymouth Meeting, PA 19462; email: Greg.Hess@Wharton.Upenn.edu.

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While benefits of molecular-targeted agents over cytokine therapy have been established in clinical trials, little information from real-world use of the molecular-targeted agents is available to inform their best use in clinical practice.[6,7,9] Such information is needed to elucidate the therapeutic profiles of these agents in clinical populations not subject to the restrictive inclusion and exclusion criteria of clinical trials; to define the optimal sequencing and combinations of therapy; to identify prognostic factors; and to assess adherence, which is key to optimizing outcomes with molecular-targeted therapies.[5,6,10] In addition, information from real-world clinical use of molecular-targeted agents is necessary to inform policy decisions and the development and modification of treatment guidelines, which have been rapidly evolving with the introduction of the new therapies.[5,9]

This article reviews a study that was undertaken to characterize real-world clinical use of molecular-targeted agents for mRCC. Patient characteristics, treatment patterns, and medication schedule compliance were assessed in a large cohort of newly diagnosed patients with mRCC in the United States.

Materials and Methods

Data source

Data for this retrospective, observational, cohort study were extracted from SDI's private-practice databases of longitudinal, patient-level medical and pharmacy claims collected from physicians and other health care providers across the United States. The pharmacy claims database, established in 2001, includes claims (National Council for Prescription Drug Programs [NCPDP] version 5.2) for more than 1.8 billion prescriptions dispensed annually. The medical claims database, established in 1999, includes more than 600,000 annual

claims (CMS 1500 forms). It contains diagnosis and visit information and represents activity of more than 450,000 physicians per month. Data in the databases are de-identified, and the databases are certified as being compliant with the Health Insurance Portability and Accountability Act (HIPAA). This study was exempt from institutional review board approval as it was retrospective, did not involve an intervention, and used anonymized data.

Sample

The study included male or female patients aged 18 years or older who had been newly diagnosed with mRCC (ie, having an RCC diagnosis with a concomitant or subsequent International Classification of Diseases, 9th edition [ICD-9] code for secondary neoplasm) from April 1, 2008 through February 28, 2010 (the study period) or patients previously diagnosed with RCC and newly treated with cytokine therapy, sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, or bevacizumab (excluding intravitreal injection) during the study period.

Additional eligibility criteria included presence of a 90-day or longer look-back period without an mRCC diagnosis or receipt of a treatment of interest; 1 or more visits to a treating physician (defined as someone who administered chemotherapy or monoclonal antibody therapy during the study period), and presence in the dataset for 3 months or longer from first treatment, unless mortality occurred earlier. Patients with unknown age or gender; with a primary diagnosis of breast, uterine, or colon cancer or of melanoma; or with a dosing/procedure code indicative of intravitreal injection of bevacizumab for wet age-related macular degeneration; or those who received care from physicians or pharmacies without stable claims in the databases during the look-back and follow-up periods were excluded.

Data analysis

Eligible patients were indexed, using the 90-day or longer look-back period, to the first therapy postmetastasis. The index mRCC date was considered to be the first confirmed mRCC treatment date with one of the drugs of interest (cytokine therapy, sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, or bevacizumab excluding intravitreal injection). The first-line regimen was considered to have ended when a 90-day gap was observed or when a drug addition/switch occurred after the first 28 days of treatment and the original regimen had been administered for at least 2 cycles. Descriptive statistics were used to summarize demographics and clinical characteristics, first-line and second-line regimens, and treatment sequences.

Schedule compliance was measured as the medication possession ratio (MPR), which was calculated as (distinct days with drug on hand)/(observed period for a line of therapy) × 100%.[11,12] For oral drugs, distinct days of drug on hand were calculated as days supply dispensed (+ 14-day grace period to the end of each sunitinib prescription). The 14-day grace period was added for sunitinib because of its usual 4-weeks-on, 2-weeks-off dosing schedule. For infused therapies, distinct days of drug on hand were calculated as administration days + duration of clinical benefit for each administration (interferon 6 days; proleukin 4 days; temsirolimus 6 days; bevacizumab 13 days). Observed period for a line of therapy was the number of days between start of a line of therapy and either end of the line or last follow-up, whichever occurred earlier. The MPR was compared between regimens using t-tests.

Table 1. Demographics and Other Characteristics

	N = 1080
Men, n (%)	737 (68.2)
Age, years	
Mean	65.9 (11.0)
Median	65.0
Region, n (%)	
Midwest	246 (22.8)
Northeast	177 (16.4)
South	383 (35.5)
West	274 (25.4)
Payer, n (%)	
Commercial	637 (59.0)
Medicare	373 (34.5)
Medicaid	35 (3.2)
Other	35 (3.2)
Physician specialty, n (%)	
Hematolgy/oncology	882 (81.7)
Internal medicine	76 (7.0)
Nephrology	2 (0.2)
Other	120 (11.1)
Physician affiliation	
Community	482 (44.6)
Affiliated with academic institution	472 (43.7)
Other	126 (11.7)
Year of mRCC initial diagnosis/treatment, n (%)	
2008	399 (36.9)
2009	642 (59.4)
2010	39 (3.6)
Patients with known sites of metastasis, n (%)	336 (31.1)
Bone	148 (13.7)
Lung	105 (9.7)
Liver	31 (2.9)
Colon/rectum	9 (0.8)
Head and neck	5 (0.5)
Brain	2 (0.2)
Skin	2 (0.2)
Bladder	2 (0.2)
Breast	1 (0.1)
Other	31 (2.9)
Charlson Comorbidity Index, mean (SD)	3.9 (2.1)

Results

Sample

The sample comprised 1080 newly treated, predominantly male patients with mRCC with a median age of 65 years (**Table 1**). Approximately 31% of patients were coded as metastatic (n = 336); bone, lung, and liver were

Table 2. Common mRCC Treatment Regimens

	Sunitinib	Temsirolimus	Bevacizumab	Interferon	Sorafenib	All others
2008-2010						
First line (N = 1080)						
n (%)	525 (48.6)	319 (29.5)	90 (8.3)	58 (5.4)	42 (3.9)	46 (4.4)
Observed days[a]						
Mean	136	121	94	48	102	146
Median	77	85	81	36	49	126
	Sunitinib	**Everolimus**	**Temsirolimus**	**Bevacizumab**	**Sorafenib**	**All others**
Second line (N = 246)						
n (%)	55 (22.4)	45 (18.3)	44 (17.9)	39 (15.9)	26 (10.6)	37 (15.1)
Observed days[a]						
Mean	94	72	106	65	78	NA
Median	48	60	56	39	37	NA
	Temsirolimus	**Sunitinib**	**Bevacizumab**	**Interferon**	**Everolimus**	**All others**
Treatment initiated in 2009						
First line (N = 711)						
n (%)	291 (40.9)	283 (39.8)	50 (7.0)	31 (4.4)	23 (3.2)	33 (4.6)
	Everolimus	**Bevacizumab**	**Sunitinib**	**Temsirolimus**	**Sorafenib**	**All others**
Second line (N = 155)						
n (%)	35 (22.6)	30 (19.4)	29 (18.7)	22 (14.2)	12 (7.7)	27 (17.4)

[a]Actual treatment durations for each agent could be longer than the observed days, which were right censored at the last follow-up date

the most common sites of metastases (**Table 1**). The remainder of patients were also considered to have metastatic disease because of the use of cytokines and/or targeted therapies. More than half of the patients (59%) had commercial insurance, and the majority (59.4%) of the patients entered the study in 2009 (first mRCC diagnosis or mRCC treatment). The average baseline Charlson Comorbidity Index (CCI) was 3.9 (standard deviation [SD] = 2.1, maximum possible CCI = 32). The majority of patients were treated by either an oncologist or a hematologist (81.7%). Approximately 43.7% of treating physicians had an affiliation with an academic institution.

Treatment patterns

The most common first-line treatments were sunitinib, temsirolimus, bevacizumab, and interferon; the most common second-line treatments were sunitinib, everolimus, temsirolimus, and bevacizumab (**Table 2**). Common first-line/second-line regimens were similar between men and women and between those who were younger than 65 years and those who were 65 years or older. For patients initiating mRCC first-line therapy in 2009, the most common first-line treatments were temsirolimus, sunitinib, bevacizumab, and interferon. The most common second-line treatments were everolimus, bevacizumab, sunitinib, and temsirolimus (**Table 2**).

Among the 246 second-line patients with mRCC, a first-line TKI (sunitinib/sorafenib) followed by second-line everolimus or sunitinib were the most common treatment sequences (**Figure 1**). Among the 155 second-line patients who initiated their first-line treatment in 2009, a first-line TKI (sunitinib/sorafenib) followed by second-line everolimus, and a first-line mTOR (temsirolimus/everolimus) followed by second-line bevacizumab were the most common treatment sequences (**Figure 1**).

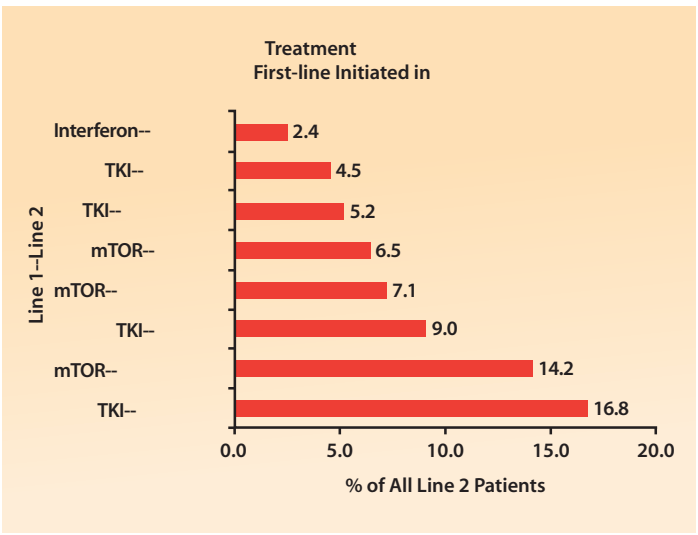

Figure 1. Common mRCC treatment sequences.

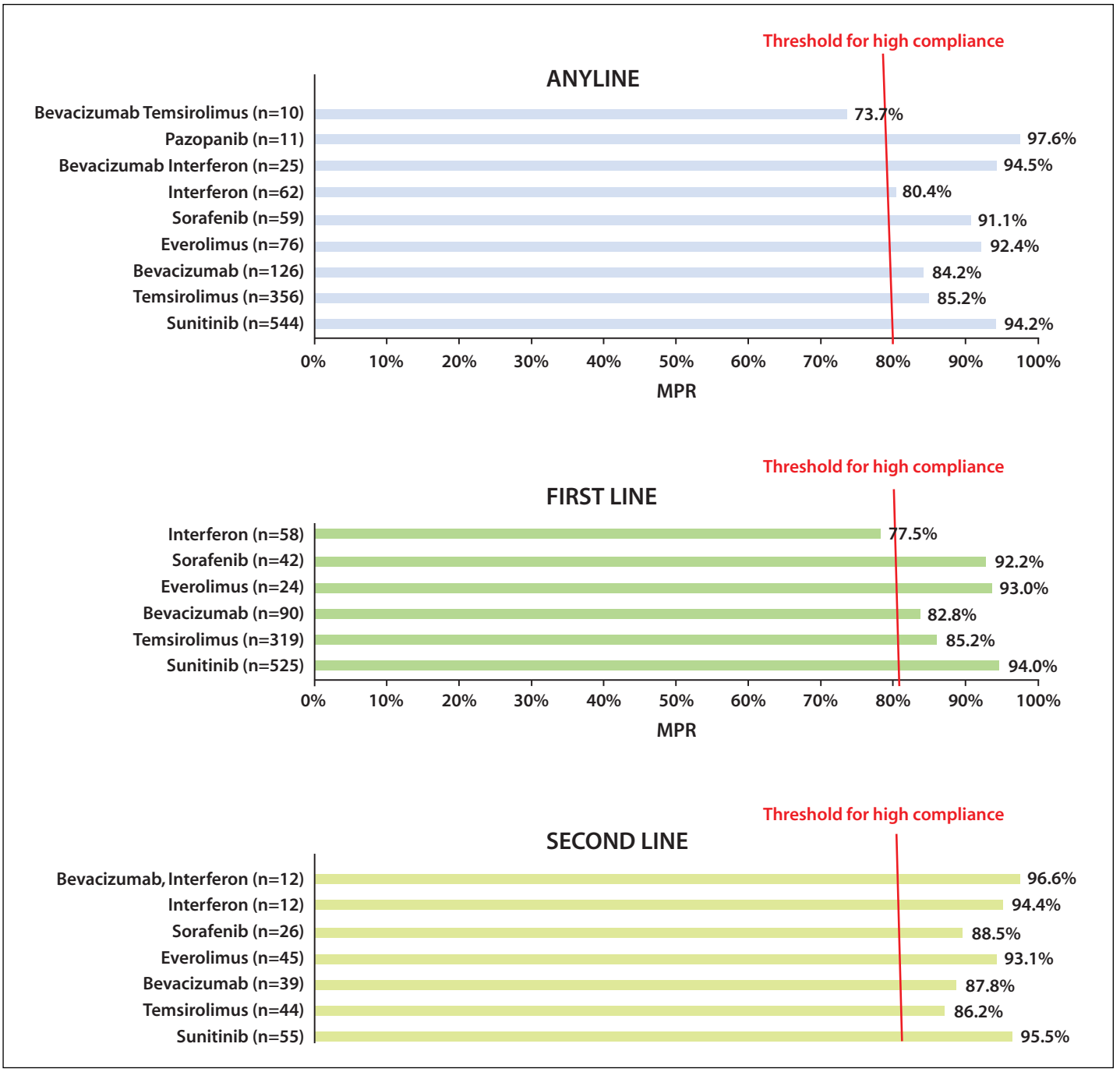

Figure 2. MPR by line of therapy.

Schedule compliance

Patients were followed on first-line therapy for a mean of 121 days and a median of 75 days and on second-line therapy for a mean of 80 days and a median of 44 days (**Figure 2**). The majority of patients (81.1%) had an MPR of 0.80 or higher, a value that reflects good compliance. Within first-line therapy, the oral therapies sunitinib and sorafenib (MPR 0.92-0.94) had significantly ($P <$ .001) higher schedule compliance than the infused therapies temsirolimus, bevacizumab, or interferon (MPR 0.78-0.85). Within second-line therapy, sunitinib (MPR 0.96), everolimus (MPR 0.93), and interferon (MPR 0.94) were statistically equivalent and were associated with significantly ($P <$ .001) higher schedule compliance than bevacizumab (MPR 0.88), sorafenib (MPR 0.89), or temsirolimus (MPR 0.86).

Sensitivity analyses

Treatment patterns remained similar when minimum follow-up period was extended from 3 months to 6 months. The results of the schedule compliance analysis with 6-month minimum follow-up period concurred with that of the primary analysis where the minimum follow-up period was 3 months—the majority of

patients still had high MPR, and within the first line of therapy, oral regimens were associated with better schedule compliance than infused regimens.

Discussion

The rapidly evolving therapeutic landscape for mRCC, with the addition of 6 new molecular-targeted treatments since 2005 in the United States, has led to calls for studies to characterize the use of and outcomes with the new therapies in real-world clinical practice.[5,9] Such information is a necessary complement to information from clinical trials in informing clinical use and policy decisions involving the new agents. The current study characterized patient characteristics, treatment patterns, and schedule compliance with molecular-targeted agents in a large, nationally representative cohort of patients with mRCC (N = 1080).

The characteristics of the identified patients with mRCC were similar to the known demography of mRCC.[1] The most common first-line treatments were sunitinib and temsirolimus, and the most common second-line treatments were sunitinib and everolimus. The most common treatment sequence was sunitinib or everolimus after a first-line TKI (sunitinib/sorafenib). These treatment patterns should be interpreted with the knowledge that the line of therapy reported in this study was based on analysis of claim activities, which might not completely reflect patients' actual drug-taking behavior. However, these treatment choices and sequences appear to reflect application of findings from clinical trials and are consistent with current treatment guidelines.[8,13]

Sunitinib and temsirolimus have been demonstrated to be superior to the cytokine interferon-α in prolonging progression-free survival and/or overall survival time[14-18]; and temsirolimus has been demonstrated to be active in patients with poor prognosis.[3] Everolimus was demonstrated to be superior to placebo plus best supportive care in a phase 3 trial of patients with mRCC refractory to VEGF receptor TKIs.[19,20]

Schedule compliance with mRCC treatments was generally high among the majority of patients: 81.1% of patients had an MPR of 0.80 or higher, a value that reflects good compliance. Within first-line therapy, schedule compliance was higher with oral treatments than with infused treatments. Within second-line therapy, sunitinib, everolimus, and interferon were associated with higher schedule compliance than other commonly used second-line agents. While better schedule compliance with oral treatments compared with infused treatments was not unexpected, the reasons for the differences in schedule compliance among individual oral molecular-targeted therapies are unknown and warrant further study.

It is important to note that schedule compliance measured how well patients refilled their prescriptions or received the infusions according to the recommended dosing schedule; whether patients actually took the drug and whether physicians instructed the patient to use a lower dose or delayed the infusion because of toxicity are unknown. Schedule compliance with molecular-targeted agents is crucial for optimizing therapy, and adequate exposure to targeted agents is associated with greater probability of improved survival.[10] Differences in schedule compliance among targeted agents may have an effect on therapeutic outcome. However, the MPRs reported here only reflect patient schedule compliance during the therapy period while they were observed.

The results of this study should be interpreted in the context of limitations of the study. Claims data can be inherently limiting because they are collected for billing and reimbursement purposes rather than for research purposes. Therefore, claims data often lack information that could be important to the research question at hand. For example, information on histology and prior nephrectomy was not available for this study. In addition, data entry errors at the site of care could not be corrected for in data analysis.

The retrospective, observational nature of the study also should be borne in mind in interpreting the results. Retrospective analyses demonstrate associations but do not indicate causality. Furthermore, the retrospective, observational nature of the study could make the results subject to selection bias. Finally, in this rapidly evolving era of molecular-targeted therapy of mRCC, results should be interpreted with awareness of the time frame in which the study was conducted. The data from this investigation can be considered complementary to other analyses that may assess populations that differ from the current one on dimensions such as payer influences or geographic region or that differ in methods of data capture or analysis.

Conclusion

This study provides new information about contemporary, real-world use of molecular-targeted therapies and cytokine therapy in a large, nationally representative sample of patients with mRCC in the United States.

- The most common first-line treatments were sunitinib and temsirolimus; the most common second-line treatments were sunitinib and everolimus.
- The most common treatment sequence was a TKI (sunitinib/sorafenib) followed by sunitinib or everolimus.
- Schedule compliance with the new molecular-targeted therapies was generally high with better schedule compliance rates with oral therapy than infused therapy during first-line therapy and better schedule compliance rates with sunitinib, everolimus, and interferon than other commonly used agents during second-line therapy. The schedule compliance results in particular warrant confirmation and further study in other treatment settings and mRCC patient populations.

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