Oral Anticancer Agent (OAA) Adherence and Survival in Elderly Patients With Metastatic Renal Cell Carcinoma (mRCC)

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OBJECTIVE To examine real-world adherence to oral anticancer agents (OAAs) and its association with outcomes among Medicare beneficiaries with metastatic renal cell carcinoma (mRCC).

METHODS SEER-Medicare retrospective cohort study of patients with metastatic renal cell carcinoma (mRCC) who received an OAA between 2007 and 2015. We examined A) adherence and B) overall and disease-specific 2-year survival landmarked at 3 months after OAA initiation. Adherence was assessed by calculating the proportion of days covered (PDC) within 3 months of OAA initiation, with adherent use being defined as PDC > 80%.

RESULTS A total of 905 patients met study criteria, of whom 445 patients (49.2%) were categorized as adherent to initial OAA treatment. Adjusting for clinical and demographic factors revealed decreased odds of adherence associated with living within an impoverished neighborhood (OR 0.49, CI 0.0.33 − 0.74) and out-of-pocket costs > $200 (OR 0.68, CI 0.47-.98). Adherence was associated with improved 2-year survival in univariate analysis (logrank test, $P = .01$) and a non-significant trend toward an association with decreased all-cause (HR 0.87, CI 0.72 − 1.05) and RCC-specific survival (HR 0.84, CI 0.69 − 1.03) in multivariable analysis.

CONCLUSION Local poverty levels and high out-of-pocket costs are associated with poor initial adherence to OAA therapy in Medicare beneficiaries with mRCC, which in turn, suggests a trend toward poor overall and disease-specific survival. Efforts to improve outcomes in the broader mRCC population should incorporate OAA adherence and economic factors. UROLOGY 168: 129−136, 2022.

In 2005 the U.S. Food and Drug Administration (FDA) approved the first new medication to treat renal cell carcinoma (RCC) in more than a decade, followed shortly by several other therapies that improved progression-free and/or overall survival in randomized clinical trials.[1,2] By 2008 there was a measurable reduction in all-cause mortality among the U.S. population of patients with RCC.[3-5] Previously known disparities in outcomes between black and white patients[6] persisted following the introduction of these agents.[4,5] These disparities were not observed in health care settings where access is more equitable, such as the Veterans Health Administration,[7] suggesting that such disparities were non-biologic in nature and instead were likely due to differences in socioeconomic considerations that may limit access to quality care.

The majority of RCC treatments approved since 2005 have been oral anticancer agents (OAAs), including 4 of the 6 agents approved by 2009[3] and 7 out of the 10 agents approved by 2016. One of the fundamental differences

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between IV and oral agents is that oral agents are administered by the patient themselves and outside of a carefully monitored health care setting. Although adherence is typically excellent in clinical trials,[8] observed real world adherence in other disease sites has been considerably lower.[9] Adherence may be particularly poor in RCC given known toxicities associated with tyrosine kinase inhibitors particularly for older patients, those with underlying health conditions, and socioeconomically disadvantaged individuals. This concern is supported by studies of patients with chronic myelogenous leukemia where low-income subsidies for OAA copayments have been associated with decreased rates of adherence.[10] Differences in real-world adherence create the potential to widen population-level disparities if present and ignored.

In this study, we characterize OAA adherence within the SEER-Medicare patient population and investigate clinical, demographic, and socioeconomic factors associated with adherence and outcomes as potential drivers of disparities in Americans with de novo synchronous or metachronous metastatic RCC presenting between 2007 and 2015.

METHODS

Data Source and Study Population

This was a retrospective cohort study of the SEER (Surveillance Epidemiology and End Results) cancer registry patients with linked Medicare claims who were diagnosed with mRCC from 2007 to 2015 and initiated OAA treatment within 12 months of metastatic disease diagnosis. Inclusion criteria included enrollment in Medicare fee-for-service (FFS) parts A, B and D for at least 1 year prior to and following mRCC diagnosis or until death if patients lived less than a year. Exclusion criteria included initial RCC diagnosis at autopsy or death, diagnosis of a second malignancy between the initial SEER RCC diagnosis date and metastatic diagnosis date, and age < 65 years at metastatic diagnosis date. Metastatic diagnosis date was defined as the date of initial diagnosis for incident/synchronous metastatic disease or as the date of the first claim for metastatic disease for patients with metachronous metastatic disease. Initiation of an OAA was determined using Part D prescription drug fill record for one of the following OAAs: sorafenib (approved 2005), sunitinib (2006), pazopanib (2009), everolimus (2009), and axitinib (2012).

Patient Demographics and Clinical Characteristics

Patient and clinical characteristics including race/ethnicity (categorized as non-hispanic white, non-hispanic black, hispanic, and Other race), age at metastatic diagnosis, sex, stage at initial RCC diagnosis, histology at initial RCC diagnosis, marital status, geographic region of residence, metropolitan residence, and zip code-level socioeconomic characteristics were drawn from the SEER Patient Entitlement and Diagnosis Summary File. We used validated coding algorithms to assess comorbidities in the 12 months prior to the mRCC diagnosis date using diagnosis codes (Supplemental Appendix B) from inpatient, outpatient, and carrier Medicare claims files.[11,12] Out-of-pocket costs were calculated as the total patient responsibility for the first 30 days of their OAA (part D). Adherence to an oral antihypertensive drug (listed in Supplemental Appendix C) in the 12 months prior to mRCC diagnosis was calculated for patients with a diagnosis of hypertension to serve as a benchmark of patient drug adherence behavior for non-cancer therapies.

Adherence to OAAs

We examined patient OAA refill patterns with frequencies, percentages, and histograms. The number of days' supply provided on each Part D prescription fill record was used in combination with medication fill claim dates to calculate the percentage of days covered (PDC) in the 3 months following OAA initiation. Sunitinib adherence calculations were modified to account for the standard dosing of 4 weeks on followed by 2 weeks off by substituting 42 days of coverage for a 28 day prescription fill. Adherence was analyzed both as a continuous percentage of days covered by an OAA and as a binary variable: we defined adherent as ≥80% days covered and non-adherent <80% days covered based on previously reported cutoffs for adherence.[10,13-15] Patient adherence was considered based on receipt of any OAA within the first 3 months, (ie a patient who filled prescriptions for a 60 day supply of drug A and then for a 30-day supply of drug B, without a break in between would be considered 100% adherent).

Statistical Analysis

Factors Associated with Adherence to Oral Anticancer Agents. Univariable and multivariable-adjusted log-binomial regression analysis was used to identify associations between patient characteristics and OAA adherence in the 3 months following the OAA initiation; the length of time for assessment of adherence was set at the time when approximately 25% of the patients had been empirically observed to have discontinued the drug. Among patients with hypertension who received both an antihypertensive drug and an OAA, the Pearson correlation coefficient was used to assess correlation between patients' antihypertensive drug PDC prior to mRCC diagnosis and their OAA PDC. Among pazopanib initiators who survived at least 3 months, the effective dose of pazopanib received was calculated using the dose per pill multiplied by the quantity of pills dispensed, divided by 90 days.

OAA Adherence, All Cause-Mortality, and RCC-Specific Mortality. Among patients surviving at least 3 months following their first OAA prescription, the cumulative incidence of all-cause 2-year mortality and RCC-specific 2-year mortality was calculated with 3 months post-OAA initiation serving as the landmarked index date. Patients were censored at the end of 2 years of follow-up, at the end of study follow-up (Jan 1, 2017), or at the time of death from another cause for RCC-specific mortality analyses. Out-of-pocket (OOP) costs were defined using the initial 30 day costs of drug, and patients were arbitrarily categorized as having OOP costs less than or greater than $200.

In post-hoc analyses we noted that patients were most likely to receive multiples of 1, 2, or 3 months' supply of OAAs. Therefore, we conducted a post-hoc analysis of both RCC-specific survival (ie disease-free survival) and overall survival using Kaplan-Meier plots of patients stratified by PDC rates of 0 - 33%, > 33 - 66%, or > 66 - 100% (ie 1, 2, or 3 month OAA equivalent usage).

RESULTS

Cohort Characteristics and Overall OAA Adherence

A total of 905 patients met study criteria and initiated an OAA within 3 months of metastatic RCC diagnosis (Table 1). Of these, 445 patients (49.2%) were categorized as having PDC ≥ 80% within the first 3 months of OAA initiation. Compared with patients with PDC ≥ 80%, a larger proportion of patients with lower adherence lived in impoverished neighborhoods (27.0% vs 19.6%, P = .008), were female (40.4% vs 33.9%, P = .02), and were older (P < .001). No other differences in patient or clinical characteristics were observed. Overall adherence as measured by PDC was highest in patients treated with sunitinib and lowest in patients treated with sorafenib or pazopanib (Supplementary Table 1, Kruskal-Wallis P = .05). Adherence varied substantially between patients, with an overall median PDC of 79% and half of all patients ranging between 46% and 97%. The median PDC did not significantly differ between Non-hispanic black (65%), non-hispanic white (77%), and Hispanic (85%) patients (Kruskal-Wallis P = .3). OOPs > $200 for the first 30 days of OAA fills were associated with worse OAA adherence (Supplemental Fig. 1, P = .02). Race and ethnicity were not significantly associated with total months of OAA adherence (Supplemental Fig. 1, P = .7).

Multivariable Analysis of OAA Adherence

Multivariable analysis of OAA adherence revealed socioeconomic factors associated with lower odds of adherence (PDC > 80%) including living within an impoverished neighborhood (OR 0.49, CI 0.33 − 0.74) and taking drugs with OOP costs > $200 (OR 0.68, CI 0.47 − 0.98). Lower adherence was reported in the Northeast compared with the West (OR 0.63, CI 0.42 − 0.95; Table 2). Patients aged 76-80 had lower odds of being adherent (OR 0.53, CI 0.37 − 0.78) as did patients aged 81+ (OR 0.55, CI 0.35 − 0.85), compared with patients aged 66-70 years. Adherence was decreased in patients taking pazopanib (OR 0.63, CI 0.45 − 0.90) and sorafenib (OR 0.53, CI 0.31 − 0.90) compared with patients taking sunitinib. Males had higher prevalence of adherence than females (OR 1.39, CI 1.03 − 1.88). No significant association was observed between adherence and black race, hispanic ethnicity, marital status, Medicaid dual enrollment, or higher comorbidity score.

Correlation between Chronic Medication and OAA Adherence

To investigate the ability of past chronic medication adherence to predict future OAA adherence, a subgroup analysis was conducted on 722 patients who received an oral antihypertensive medication in the year prior to diagnosis and subsequently received an OAA. Median PDC adherence to oral antihypertensive (HTN) medications within this group over the 12 months prior to OAA initiation was high (93%, IQR 75 − 98). Compared to HTN medications, median adherence to OAAs was far lower and varied substantially between patients (79%, IQR 46 − 97%). There was no discernable correlation between OAA adherence vs HTN medication adherence (Supplemental Fig. 2). Living within an impoverished zip code was associated with decreased adherence both for HTN medications (P = .05) and OAAs (Supplemental Fig. 1, P = .02).

All-Cause and RCC-Specific Mortality

Overall and RCC-specific 2year mortality was investigated limited to patients who survived at least 3 months following initiation of their first OAA therapy, with follow-up starting 3 months after OAA initiation. Higher adherence of OAA treatment was associated with superior RCC-specific survival among all patients who had initiated any OAA prescription (Fig. 1A; P = .01) as well as limited to patients whose first OAA received was sunitinib (Fig. 1B; P = .003). Survival varied by initial agent, with patients receiving sunitib and pazopanib having superior 2year survival compared everolimus, sorafenib, or axitinib (Fig. 1C; P < .0001).

After adjusting for clinical and demographic factors, OAA adherence was not significantly associated with either overall mortality (HR 0.87, CI 0.72 − 1.05, P = .15) or RCC-specific mortality (HR 0.84, CI 0.69 − 1.03, P = .09; Table 3). In sensitivity analyses using alternative cutoffs we observed that PDC < 50% (ie severe non-adherence) was significantly associated with both lower all-cause (HR 0.65, CI 0.58 − 0.87) and RCC-specific mortality (HR 0.63, CI 0.49 − 0.80). No significant association was observed with area-level SES indicators including those for race, poverty, or education. Using sunitinib as the reference group, receipt of sorafenib was associated with a significantly higher overall mortality (HR 1.40, CI 1.02 − 1.92) and RCC-specific mortality (HR 1.45, CI 1.04 − 2.00). Post-hoc analysis of patients receiving pazopanib as their initial OAA (N = 252) demonstrated significantly superior overall survival in patients receiving the recommended dose of 800 mg vs lower dose treatment (Fig. 1D, P = .002). An effective dose of 800 mg per day was also associated with decreased all-cause mortality in minimally adjusted Cox proportional hazards models that included race/ethnicity, age, and effective dose (HR 0.56, CI 0.37 − 0.83). Non-modifiable factors associated with significantly decreased overall mortality included patients who presented with metachronous metastatic disease with HRs ranging from 0.42 to 0.65, male sex (HR 0.73, CI 0.60 − 0.88), and clear cell histology (HR 0.67, CI 0.50 − 0.90). Factors associated with overall mortality above all showed highly similar associations with RCC-specific survival.

DISCUSSION

This study reports the first population-level investigation of factors associated with OAA adherence and survival in a nationally-representative cohort of older patients with mRCC. We found that markers of socioeconomic status including living within an impoverished neighborhood and receiving an OAA with an initial out-of-pocket copayment over $200 were predictors of poor adherence to OAAs. Furthermore, we found that lower adherence was associated with worse overall survival in univariate analysis with a trend toward adverse overall and disease-specific mortality in adjusted analyses. These findings suggest that OAA adherence and related economic considerations may play a central role in real world mRCC outcomes in the era of OAAs and warrant further investigation.

Two previous claims-based analyses investigated empiric adherence to pazopanib and sunitinib. A MarketScan Database study observed rates of adherence with pazopanib that were slightly higher than the present study,[13] reporting that over half (56%) of patients received therapy for at least 3 months with a mean PDC

Table 1. Baseline characteristics of all metastatic renal cell carcinoma (RCC) patients initiating oral anticancer agents (OAAs) stratified by adherence (PDC ≥ 80%) In the 3 months following initiation or until death (N=905)[21]

Variable	Adherent (≥80% PDC)	Non-adherent (<80% PDC)	*P*-value
N (row %)	445 (49.2)	460 (50.8)	
Characteristics			
Age at metastatic diagnosis, in years			<.001
66-70	161 (56.1)	126 (43.9)	
71-75	145 (52.3)	132 (47.6)	
76-80	84 (40.6)	123 (59.4)	
81+	55 (41.0)	79 (58.9)	
Drug at first fill			.030
Other (Everolimus or Axitinib)	29 (53.7)	25 (46.3)	
Pazopanib	111 (44.0)	141 (55.9)	
Sorafenib	30 (39.0)	47 (61.0)	
Sunitinib	275 (52.7)	247 (47.3)	
Race			.181
black Non-hispanic	20 (41.7)	28 (58.3)	
Hispanic	63 (55.3)	51 (44.7)	
white Non-hispanic	317 (47.8)	346 (52.2)	
Other	45 (56.3)	35 (43.7)	
Charlson Score, Median (Q1, Q3)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	.120
Sex			.043
Female	151 (44.8)	186 (55.2)	
Male	294 (51.8)	274 (48.2)	
Stage at initial SEER diagnosis			.281
I/II	60 (56.6)	46 (43.4)	
III	75 (51.0)	72 (49.0)	
IV	292 (47.0)	329 (53.0)	
Unknown	18 (58.1)	13 (41.9)	
Histology			.414
Other	52 (53.1)	46 (46.9)	
Clear cell	393 (48.7)	414 (51.3)	
Married	258 (48.3)	276 (51.7)	.536
Lives in metropolitan area	356 (48.8)	374 (51.2)	.619
Geographic region of the United States			.405
Midwest	51 (11.5)	55 (11.9)	
Other	32 (7.2)	36 (7.8)	
Northeast	66 (14.8)	89 (19.3)	
South	73 (16.4)	68 (14.8)	
West	223 (50.1)	212 (46.1)	
Dual enrollment in Medicaid	140 (50.7)	136 (49.3)	.535
Census Tract Highest quartile: black race	95 (48.7)	100 (51.3)	.886
Highest quartile: adults 25+ with less than high school education	115 (47.5)	127 (52.5)	.548
Highest quartile: households living below poverty level	87 (41.2)	124 (58.8)	*.008*
Partial/ Radical Nephrectomy in the 12 mo prior to metastatic diagnosis	65 (56.5)	50 (43.5)	.210
Myocardial infarction	37 (43.0)	49 (57.0)	.230
Hypertension	397 (49.5)	405 (50.5)	.579
Peripheral vascular disease	114 (52.0)	105 (47.9)	.327
Congestive heart failure	82 (44.1)	104 (55.9)	.119
Dementia	<11 (<2.5%)*	<11 (2.4%)*	.826
Cardiovascular disease	84 (47.7)	92 (52.3)	.669
Chronic obstructive pulmonary disease	141 (49.6)	143 (50.3)	.846
Rheumatologic disease	17 (41.5)	24 (58.5)	.312
Peptic ulcer disease	11 (39.3)	17 (60.7)	.287
Mild liver disease	74 (50.3)	73 (49.6)	.757
Renal disease	137 (53.1)	121 (46.9)	.135
Diabetes with complications	83 (52.2)	76 (47.8)	.400
Hemiplegia or paraplegia	<11 (<2.5%)*	<11 (2.4%)*	.397
Out-of-pocket payment for initial prescription			.072
0-$200	236 (53.0)	217 (47.2)	
>$200	209 (47.0)	243 (52.8)	
Year of metastatic diagnosis			.162
2007	34 (44.2)	43 (55.8)	
2008	39 (53.4)	34 (46.6)	

Continued

Table 1. Continued

Variable	Adherent (≥80% PDC)	Non-adherent (<80% PDC)	*P*-value
2009	24 (40.7)	35 (59.3)	
2010	37 (51.4)	35 (48.6)	
2011	50 (46.3)	58 (53.7)	
2012	72 (60.0)	48 (40.0)	
2013	80 (52.3)	73 (47.7)	
2014	57 (46.3)	66 (53.6)	
2015	52 (43.3)	68 (56.7)	

* Values <11 suppressed in accordance with SEER-Medicare cell size suppression policy.

of 88%. Although differences in methodology preclude a direct comparison, approximately 40% of our cohort received therapy for at least 3 months with a mean PDC of 67%. Unlike the present study, they observed increased time on therapy and adherence (PDC) in patients with more medical comorbidities. A second retrospective claims analysis used the Optum Research Database and the Impact National Benchmark Database[15] observed comparable rates of adherence as the MarketScan study for both medications with 52%-56% of patients having PDC > 80%. The somewhat higher rates of adherence in previous studies likely reflects a combination of differences in data composition and analyses, but also real differences in adherence associated with a younger, mostly working patient population that includes commercial insurance.[13,15]

Our observation, that patient socioeconomic status and out-of-pocket costs influence OAA adherence, although

Table 2. Log-binomial regression for associations between patient characteristics and having at least 80 percent days covered (PDC) by an OAA in the 3 months post-OAA initiation (N = 905)[31]

Effect	*Unadjusted OR (95% CI)*	*Adjusted OR (95% CI)*
Race (ref Non-hispanic white)		
Non-Hispanic black	0.78 (0.43-1.41)	0.66 (0.34-1.29)
Hispanic	1.35 (0.90-2.01)	1.46 (0.89-2.37)
Other	1.40 (0.88-2.24)	1.28 (0.75-2.19)
Age at metastatic diagnosis, in years (ref 66-70)		
71-75	0.86 (0.62-1.20)	0.87 (0.62-1.23)
76-80	*0.53 (0.37-0.77)*	*0.53 (0.37-0.78)*
81+	*0.54 (0.36-0.83)*	*0.55 (0.35-0.85)*
First OAA (ref Sunitinib)		
Axitinib	0.80 (0.30-2.10)	0.80 (0.28-2.24)
Everolimus	1.18 (0.60-2.31)	1.12 (0.55-2.28)
Pazopanib	*0.71 (0.52-0.96)*	*0.63 (0.45-0.90)*
Sorafenib	*0.57 (0.35-0.94)*	*0.53 (0.31-0.90)*
Male	*1.32 (1.01-1.73)*	*1.39 (1.03-1.88)*
Stage at initial SEER diagnosis (ref IV)		
I	1.58 (0.98-2.56)	1.50 (0.89-2.55)
II	1.21 (0.57-2.54)	1.15 (0.52-2.55)
III	1.17 (0.82-1.68)	0.9 8(0.63-1.52)
Unknown	1.56 (0.75-3.24)	1.58 (0.72-3.46)
Clear cell histology	0.84 (0.55-1.28)	0.71 (0.46-1.11)
Geographic region of the United States (ref West)		
Midwest	0.88 (0.58-1.35)	0.87 (0.54-1.42)
Other	0.85 (0.51-1.41)	1.01 (0.54-1.88)
Northeast	0.70 (0.49-1.02)	*0.63 (0.42-0.95)*
South	1.02 (0.70-1.49)	1.21 (0.75-1.97)
Married	0.92 (0.71-1.20)	0.78 (0.57-1.06)
Lives in metropolitan area	0.92 (0.66-1.28)	0.95 (0.64-1.40)
Dual enrollment in Medicaid	1.09 (0.82-1.45)	0.72 (0.47-1.12)
Highest quartile: black race	0.91 (0.68-1.23)	1.13 (0.75-1.69)
Highest quartile: adults 25+ with less than high school education	0.98 (0.71-1.34)	1.21 (0.80-1.81)
Highest quartile: households living below poverty level	*0.66 (0.48-0.90)*	*0.49 (0.33-0.74)*
Nephrectomy in the 12 mo prior to metastatic diagnosis (ref None)		
Partial	1.80 (0.65-5.00)	1.20 (0.40-3.59)
Radical	1.35 (0.89-2.05)	1.28 (0.78-2.13)
Comorbidity score	1.02 (0.97-1.08)	1.01 (0.95-1.07)
Year of metastatic diagnosis	1.00 (0.95-1.05)	0.99 (0.93-1.06)
Out of Pocket payment for initial OAA (ref 0-$200)		
>$200	0.79 (0.61-1.03)	*0.68 (0.47-0.98)*

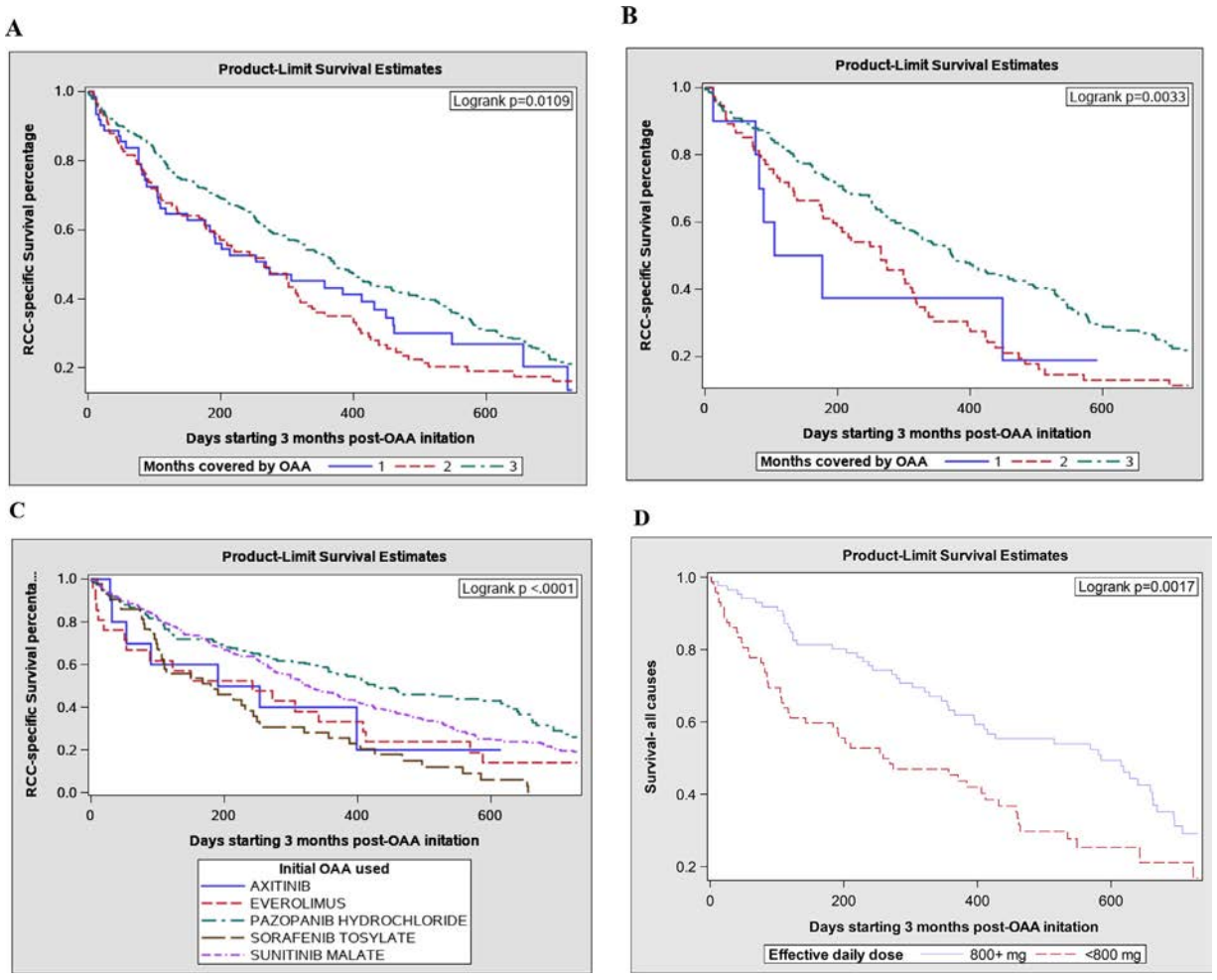

Figure 1. Renal cell carcinoma (RCC)-specific and overall 2year survival limited to oral anticancer agents (OAA) users who survived at least 3 months post-initiation stratified by OAA adherence, initial OAA choice, and dose level. (**A**) RCC-specific 2year survival by number of months OAA use. (**B**) RCC-specific 2year survival by number of months OAA use limited to initial treatment with sunitinib. (**C**) RCC-specific 2year mortality by initial agent (N=905). (**D**) All-cause 2year mortality following initiation of pazopanib by dose level. (Color version available online.)

not previously investigated in RCC, has been well documented in breast[9] and other cancers[10,16-18] and is unsurprising in the setting of out-of-pocket costs that often exceed a thousand dollars per month.[19-21] Although our study focused on sociodemographic and socioeconomic disparities, it should be noted that many other factors inform and influence OAA adherence including treatment dissatisfaction, patient-provider communication, and caregiver burden.[22-24] A fifth of patients may intentionally skip doses, with close to half not reporting it to their physician.[22] The eventual introduction of generic equivalents will likely lower out-of-pocket costs and improve adherence, as has been observed in patients with breast cancer.[17]

We observed that receipt of sorafenib vs sunitinib was significantly associated with inferior survival and further observed higher point estimates of mortality for axitinib and everolimus that did not reach significance due to wide confidence intervals and the small number of patients taking these OAAs. We suspect that differences in outcomes associated with these drugs are more related to patient selection and approved line of treatment than an indication of efficacy. There are limited randomized trials directly comparing the efficacy of current first-and second-line therapies for mRCC.[2,25-29] Meta-analyses suggest that risk-benefit profiles may vary by patient and disease risk groups[25] and support our finding that sunitinib appears to be associated with favorable outcomes in older or potentially more frail patients with metastatic disease[29] in a cohort that is predominantly of European descent.[26] Much of first-line treatment of mRCC is shifting to include immunotherapy in first-line regimens for all risk profiles of metastatic disease. Nonetheless, OAAs remain a key part of the treatment paradigm, including in new first-line combinations with immunotherapy (eg axitinib and pembrolizumab). Although previous studies have observed favorable outcomes in women, we did not observe this phenomenon in our study. Differential outcomes by sex may be limited to younger patients only, which were not included in our study.[30]

The present study was retrospective and may be biased by the presence of unmeasured patient and disease factors.

Table 3. Landmarked multivariable-adjusted cox proportional hazards regression for risk of all-cause mortality and RCC-specific 2year mortality starting 3 months post-OAA initiation[41]

Parameter	*All-Cause HR (95% CI)*	*RCC-specific HR (95% CI)*
Race (ref Non-hispanic white)		
Non-hispanic black	0.91 (0.58-1.41)	0.98 (0.63-1.55)
Hispanic	0.85 (0.61-1.17)	0.86 (0.61-1.21)
Other	0.90 (0.62-1.30)	0.86 (0.58-1.27)
Age at metastatic diagnosis, in years (ref 66-70)		
71-75	0.92 (0.73-1.16)	0.92 (0.72-1.16)
76-80	0.99 (0.77-1.26)	0.96 (0.74-1.25)
81+	1.01 (0.75-1.36)	0.99 (0.73-1.36)
Adherent to OAA (≥80% d covered)	0.87 (0.72-1.05)	0.84 (0.69-1.03)
First OAA (ref sunitinib)		
Axitinib	1.47 (0.70-3.09)	1.59 (0.76-3.34)
Everolimus	1.48 (0.97-2.25)	1.46 (0.94-2.26)
Pazopanib	1.07 (0.84-1.37)	1.06 (0.82-1.37)
Sorafenib	*1.40 (1.02-1.92)*	*1.45 (1.04-2.00)*
Male	*0.73 (0.60-0.88)*	*0.71 (0.58-0.87)*
Stage at initial SEER diagnosis (ref IV)		
I	*0.62 (0.44-0.89)*	*0.66 (0.46-0.95)*
II	*0.42 (0.23-0.78)*	*0.39 (0.20-0.74)*
III	*0.65 (0.48-0.88)*	*0.65 (0.48-0.90)*
Unknown	0.88 (0.52-1.51)	0.86 (0.49-1.52)
Clear cell histology	*0.67 (0.50-0.90)*	*0.67 (0.50-0.91)*
Geographic region of the United States (ref West)		
Midwest	1.14 (0.83-1.57)	1.08 (0.77-1.51)
Other	0.89 (0.60-1.32)	0.88 (0.58-1.33)
Northeast	0.99 (0.75-1.30)	1.00 (0.75-1.33)
South	1.18 (0.86-1.61)	1.23 (0.89-1.71)
Married	1.14 (0.94-1.39)	1.17 (0.95-1.44)
Lives in metropolitan area	0.90 (0.70-1.17)	0.88 (0.68-1.15)
Dual enrollment in Medicaid	0.84 (0.63-1.13)	0.88 (0.65-1.19)
Highest quartile: black race	1.29 (0.99-1.69)	1.23 (0.93-1.62)
Highest quartile: adults 25+ with less than high school education	1.03 (0.79-1.34)	0.96 (0.73-1.27)
Highest quartile: households living below poverty level	0.83 (0.63-1.08)	0.86 (0.65-1.14)
Nephrectomy in the 12 mo prior to metastatic diagnosis (ref None)		
Partial	0.51 (0.18-1.40)	0.57 (0.20-1.57)
Radical	1.30 (0.93-1.82)	1.36 (0.97-1.92)
Myocardial infarction	0.96(0.69-1.33)	0.83 (0.58-1.19)
Hypertension	1.06 (0.79-1.43)	1.13 (0.84-1.54)
Peripheral vascular disease	1.00 (0.80-1.25)	1.01 (0.80-1.28)
Congestive heart failure	1.17 (0.91-1.50)	1.10 (0.84-1.43)
Dementia	*2.38 (1.22-4.64)*	*2.84 (1.46-5.55)*
Cardiovascular disease	0.99 (0.78-1.26)	0.90 (0.70-1.16)
Rheumatologic disease	0.93 (0.59-1.47)	0.88 (0.54-1.44)
Peptic ulcer disease	1.79 (1.00-3.23)	*2.13 (1.18-3.86)*
Mild liver disease	0.91 (0.71-1.18)	0.90 (0.69-1.17)
End stage renal disease	0.96 (0.76-1.22)	1.00 (0.78-1.28)
Diabetes with complications	1.08 (0.83-1.40)	1.03 (0.78-1.35)
Hemiplegia or paraplegia	*0.37 (0.14-0.97)*	*0.24 (0.07-0.80)*
Year of metastatic diagnosis	1.01 (0.96-1.06)	1.02 (0.97-1.07)
OOP initial prescription cost >$200	0.87 (0.68-1.11)	0.96 (0.74-1.25)

SEER registries do not conduct follow-up on metastases occurring after diagnosis and all metastases identified after initial SEER diagnosis are identified using Medicare claims only. It is likely that cases of metastatic RCC were missed, and there may be misclassification of metastatic RCC as well. The present study used drug fills as a proxy for administration, but could have overestimated compliance for patients who obtained but did not take all filled OAAs. Although we used a cutoff of 80% PDC based on previous literature, our exploratory analyses observed significant associations between PDC > 50% and survival and further research is warranted to identify more biologically and/or clinically motivated thresholds that should be used to best inform practice guidelines.

CONCLUSION

Socioeconomic factors including neighborhood levels of poverty and high out-of-pocket costs are associated with poor adherence to OAA therapy in Medicare beneficiaries with metastatic RCC, which is in turn suggests an association with poor overall and disease-specific mortality. Efforts to improve outcomes and mitigate disparities in the general mRCC population should incorporate financial and economic considerations as they relate to OAA adherence.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2022.07.012.

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