Assessment of Treatment Patterns for Metastatic Renal Cell Carcinoma in Brazil

INTRODUCTION

Cancers of the kidney (including primarily renal cell carcinoma [RCC] and upper tract urothelial cancers) represent the fourth most common malignancy worldwide, with approximately 337,800 patients diagnosed in 2012.1 The incidence varies across individual countries. In developed countries such as the United States, an estimated 63,990 patients will be diagnosed with cancers of the kidney in 2017, and 14,400 patients will die of the disease.2 In developing countries, formal estimates are often challenging to obtain. However, using Brazil as an example, GLOBOCAN estimates suggest that 6,255 patients were diagnosed in 2012, and 3,291 patients died of the disease.3 RCC represents the most common cancer derived from the kidney, constituting approximately 90% of patients. Patients with metastatic RCC (mRCC) are generally considered incurable, although the prognosis in this disease state has improved markedly in recent years. In the cytokine era, when treatment typically constituted agents such as interleukin-2 and interferon alpha, median overall survival (OS) was estimated at slightly longer than 1 year.3 However, with the advent of targeted therapies abrogating signaling via vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR), median OS estimates now are typically in the range of 25 to 30 months.4 The recent advent of novel targeted therapies such as cabozantinib and selective immunotherapeutic agents such as nivolumab have pushed estimates for OS even further.5,6 A foreseeable challenge is that developing and developed countries may have differential access to novel therapies for mRCC. Furthermore, developing countries often have a heterogeneous array of practice settings, with a large dichotomy between public and private practices. In Brazil, the health care system includes public and private settings. Public settings are open to all Brazilian citizens...
Table 1. Patient Characteristics

| Characteristic | Overall Cohort | Private | Public |
|----------------|----------------|---------|--------|
| No.            | 4,379          | 2,473   | 1,906  |
| Median age, years (range) | 59.5 (13-98) | 60.5 (14-98) | 58 (13-89) |
| Female, No. (%) | 1,418 (32) | 7,79 | 639 |
| Male, No. (%) | 2,961 (68) | 1,694 | 1,267 |
| Histology, No. (%) | | | |
| Clear cell     | 3,496 (80) | 1,942 | 1,490 |
| Nonclear cell  | 248 (5.5) | 128 | 120 |
| Unknown        | 635 (14.5) | 372 | 263 |
| Heng risk, No. (%) | | | |
| Good           | 928 (26) | 514 | 414 |
| Intermediate   | 1,670 (48) | 959 | 711 |
| Poor           | 908 (26) | 485 | 423 |
| Metastatic disease, No. (%) | 3,990 (91) | 2,289 | 1,701 |
| Lines of therapy, No. (%) | | | |
| First          | 3,149 (79) | 1,723 | 1,426 |
| Second         | 641 (20) | 424 | 217 |
| Third          | 152 (5) | 103 | 49 |
| Fourth         | 47 (1) | 40 | 7 |

and foreigners, and private settings are open to those who possess supplemental health insurance or, rarely, those who can afford it. Using data acquired across a diverse array of practices in Brazil, we sought to determine patterns in use of systemic therapy for mRCC. Within this database, information from both private and public institutions was housed. The trends we observed were juxtaposed against published data reflecting mRCC practice patterns in developed countries.

MATERIAL AND METHODS

Participants and Setting

We used the Close-Up International database, a commercial data set housing clinical information from both private and public institutions in 55 cities across 18 states in Brazil. The database is more heavily representative of southeast Brazil, with 50% of institutions coming from this territory. Practitioners at participating institutions were queried twice per year regarding patients they had treated for RCC. In a retrospective fashion, data were submitted pertaining to basic demographic characteristics (such as age and gender) and disease stage. When available, histologic data were submitted (eg, clear cell versus nonclear cell). Furthermore, sufficient clinical characteristics were provided for computation of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category. Practitioners submitted treatment-related information, including the type and sequence of systemic agents rendered. For the current study, consecutive patients assessed from March 2013 to October 2016 were assessed.

Statistical Analysis

Descriptive statistics were used to assess the frequency of administration of first-, second-, and third-line therapy in the overall cohort and to characterize trends in specific systemic therapies rendered (eg, sunitinib, pazopanib, etc). The $X^2$ test was used to compare the frequency of use of systemic therapy across first-, second- and third-line settings in private versus public hospitals.

RESULTS

Patient Characteristics

Characteristics of the overall study population ($N = 4,379$) are listed in Table 1. The majority of patients were male (68%), and the median age of the cohort was 59.5 years. The most common histology encountered was clear cell RCC, constituting 80% of the cohort. Most patients were intermediate risk by IMDC criteria. Demographics and clinicopathologic characteristics of patients in private versus public institutions are listed in Table 1. A significantly higher incidence in the proportion of poor-risk patients was identified in patients treated at public versus private hospitals ($P = .01$), as shown in Figure A1.

Treatment-Related Data

In total, 3,990 patients were identified with metastatic disease. Of them, 3,149 patients (79%) were noted to receive first-line therapy, as highlighted in Figure 1. The most common first-line treatment was sunitinib (57%), followed by pazopanib (28%). mTOR inhibitors were infrequently used in this setting (6%). Among patients receiving first-line therapy, only 641 patients (20%) received second-line treatment. In this setting, VEGF and mTOR inhibitors were used with a relatively similar frequency. The most common mTOR inhibitor used for second-line therapy was everolimus, whereas a relatively even proportion of patients received sorafenib, pazopanib, and
sunitinib in the second-line setting. More limited data were available for third-line therapy. Among patients who received first-line treatment, only 5% received third-line treatment. In this setting, a slight preponderance of patients received VEGF tyrosine kinase inhibitors.

Use of Treatments by Time Period (March 2013 to October 2016)

Figure 2 highlights the use of individual systemic therapies over the study period. As noted in Fig 2A, sunitinib and pazopanib were the most frequently used first-line therapies throughout the study period, and a significant trend toward increasing use of pazopanib and decreasing use of sunitinib was observed. In the second-line setting (Fig 2B), everolimus represented the most frequently used agent throughout the study period, and no significant variations in the use of other VEGF tyrosine kinase inhibitors were observed. Figure 3C highlights a lack of consistent treatment patterns across third-line therapy.

Use of Treatments by Setting

Patients with mRCC treated in a private setting more frequently received systemic therapy in a private versus public setting (55% v 45%; \(P = .001\)). A similar trend was observed in the second-line setting (14% v 7%; \(P = .001\)). Although there was a higher proportion of patients in private hospitals versus public hospitals receiving third-line therapy, this difference did not reach statistical significance (3% v 2%; \(P = .16\)).

DISCUSSION

The current data set reflects the largest experience related to treatment patterns for patients with mRCC in Brazil. This study identified that, in general, treatment patterns for patients with mRCC in Brazil have some overlap with treatment patterns in developed countries. Consistent with reports from US-based commercial databases assessing the same period, the vast majority of patients with mRCC received VEGF-directed treatments in the front-line setting, and a relatively even distribution received mTOR- and VEGF-directed agents as second-line therapy.7

One concerning element of our data set, however, pertains to the attrition observed from first- to second-line therapy and from second- to third-line therapy. Our data also highlight marked disparities in treatment between private and public hospitals. Previous reports from the IMDC suggest that approximately 48% of patients who receive first-line therapy proceed to second-line therapy.
In addition, among patients who received first-line therapy in this experience, approximately 21% received third-line therapy. Figure A2 highlights the disparities between the IMDC experience and the Brazilian experience reported herein. The lower frequency of receipt of second- and third-line therapy could hinge on a number of different factors. In particular, we suspect limited availability and cost of second-line treatments to be a barrier, although our data set did not have the capability of confirming this. Another barrier to receipt of second-line therapy might be educational gaps among practitioners. Emerging data from phase III studies supporting the use of agents in the refractory setting may not be widely broadcast. The discordance in receipt of therapies in private and public settings is perhaps the greatest indication that financial and social barriers likely affect treatment paradigms in Brazil. Across each setting (first-line, second-line, and so on), there was a trend toward decreased use in public practice settings. Again, it is impossible to ascertain whether educational gaps could also contribute to this discordance. Evidence of this is shown in Figure A3, which shows the diversity of nontraditional therapies that are applied toward mRCC in Brazil. Although some rationale could be construed
for regimens such as doxorubicin/gemcitabine (which has potential applications in sarcomatoid RCC), the vast majority of cytotoxic regimens listed have little evidence base in mRCC. Furthermore, it seems that expensive novel therapies such as nivolumab are occasionally used in the first-line setting. This expensive application of immunotherapy outside of standard indications is particularly disconcerting in a cost-constrained setting. Limitations of our study include the inability to ascertain treatment-related outcome. It is possible that patients receiving care in resource-limited practices receive first-line therapy for longer periods by more effectively employing dose modification and adverse effect management strategies. These methods may substantially delay the need for second-line therapy. A second limitation is that our data were collected in a retrospective fashion, making it particularly prone to missing data. Finally, although we intend to represent the cumulative experience in Brazil, the majority of centers included in the study were from the southwest region of the country. These areas tend to be less economically deprived, which could artificially inflate our estimates of receipt of therapy. In summary, the current study highlights overarching similarities in the nature of treatments rendered for mRCC between Brazil and other developed countries, and could be representative of other developing countries. Specifically, VEGF-directed therapies represent the mainstay of treatment in the first-line setting, whereas second-line therapy is evenly divided between VEGF- and mTOR inhibitors. With the caveat that our data were collected before the widespread availability of nivolumab and newer targeted therapies, we would anticipate that these trends will persist. However, our data highlight a concerning attrition of systemic therapy use in the second- and third-line setting, extending far beyond what is observed in developed countries. Resources must be allocated to balance these discordances. Furthermore, and perhaps more readily achievable, efforts must be made to educate practitioners regarding the availability and efficacy of novel agents.

DOI: https://doi.org/10.1200/JGO.17.00113
Published online on jgo.org on December 27, 2017.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Research Funding: Pfizer (Inst), Novartis (Inst), Merck (Inst), Exelixis (Inst), TRACON Pharma (Inst), GlaxoSmithKline (Inst), Bristol-Myers Squibb (Inst), AstraZeneca (Inst), Peloton Therapeutics (Inst), Roche/Genentech (Inst), Cellex (Inst), Agensys (Inst)
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Research Funding: Eli Lilly/ImClone, Pfizer, AstraZeneca, Merck Sharp & Dohme, Eisai, Bristol-Myers Squibb
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Appendix

**Fig A1.** Comparison of International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk status of patients treated at private versus public institutions.

**Fig A2.** Comparison of first-, second- and third-line therapy use in Brazil versus the International mRCC International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) data set.
**Fig A3.** Use of nontraditional therapies (eg, therapies lacking regulatory approval for metastatic renal cell cancer) in the first-line setting (n = 240).