Comparison of First-line Pazopanib and Sunitinib in Metastatic Renal Cell Carcinoma: Experiences of the Urologic Cancer Centre for Research and Innovation

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Abstract

**Background:** Sunitinib and pazopanib are orally-administered tyrosine kinase receptor inhibitors (TKIs) approved as first-line therapy for the treatment of metastatic renal cell carcinoma (mRCC). The IMDC criteria are a predictive prognostic model for patients with mRCC when stratified into three prognosis groups: favourable, intermediate and poor. We retrospectively compared the efficacy and safety of sunitinib and pazopanib as first-line therapy for patients with mRCC in our single institution database.

**Methods:** Retrospective analysis was done to compare progression-free survival (PFS) and side effects of sunitinib and pazopanib as first-line therapy in patients with mRCC. Patients were stratified into prognosis groups according to IMDC criteria. Disease assessment was performed on measurable aspects of disease based on computed tomography or magnetic resonance imaging reports. Survival analysis was performed using the Kaplan-Meier method and Cox regression, with disease progression as the endpoint.

**Results:** Data was obtained from 228 patients with mRCC who were treated with either pazopanib (n=57) or sunitinib (n=171). No significant difference in PFS was found between sunitinib and pazopanib (HR for disease progression or all-cause death, 1.10; 95%CI: 0.76-1.57, p=0.62). Median PFS time for patients receiving sunitinib was 9.4 months and for pazopanib, 8.5 months. Median PFS for patients with intermediate-risk disease was similar between groups (9.4 months vs. 9.2 months, respectively, p=0.93). However, patients treated with sunitinib experienced a greater number of side effects compared to pazopanib.

**Conclusions:** Sunitinib and pazopanib are similarly efficacious as first-line therapy for mRCC. However, adverse events are lower with pazopanib.

**Background**

Renal cell carcinoma is the most common type of renal malignancy. In 2017, an estimated 6,600 Canadians will be diagnosed with kidney cancer with 1,900 dying from the disease. 30% of patients with RCC present with synchronous metastatic disease. Metastatic renal cell carcinoma (mRCC) has largely been treated with targeted therapies, with a recent emphasis on the inhibition of vascular...
endothelial growth factor (VEGF) via oral tyrosine kinase inhibitors (TKIs).

Sunitinib and pazopanib are two TKIs approved for first-line treatment of mRCC. Both drugs have conferred superior progression-free survival (PFS) when compared to its therapeutic predecessors. Several landmark studies compared sunitinib and pazopanib to interferon-alpha and placebo, respectively, and demonstrated improved PFS and a favourable trend in overall survival (OS). More recently, the phase III COMPARZ trial compared sunitinib and pazopanib for non-inferiority in the first-line treatment of mRCC. In this study, pazopanib was shown to be non-inferior to sunitinib with respect to PFS (8.4 vs. 9.5 months, hazard ratio [HR] for disease progression or all-cause death 1.05, 95% confidence interval [CI] 0.90–1.22). Several algorithms have been developed to predict the prognosis of mRCC patients. The International Metastatic Renal Cell Carcinoma Database (IMDC) criteria are a set of six clinical parameters used to classify patient prognosis in mRCC as poor, intermediate and favourable. This prognostic model has been extensively used in many mRCC validation studies.

Despite strong clinical evidence in support of sunitinib and pazopanib in treating mRCC in the first-line setting, the efficacy and safety of sunitinib and pazopanib in population-based settings remains underreported. In this prospective population-based study, we compared the efficacy and safety of sunitinib and pazopanib in the first-line treatment of mRCC using a single institution’s experience.

Methods

Data was obtained from patients of the Urologic Cancer Centre for Research and Innovation, captured in the prospective Canadian Kidney Cancer Information System (CKCis) database, and from patients’ health records, from January 2011 to July 2018. Patients included in this database provided consent to collection and entry of their data. Institutional research ethics board approval was obtained for this study. Patients who were clinically diagnosed with mRCC and received first-line sunitinib or pazopanib were included.

Demographic, clinical and laboratory data were collected. Initiation of treatment was at the discretion of the attending physician and patient agreement. All toxicities related to treatment were evaluated
according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3., as CKCIs captures dose-modifying toxicities of Grades 1-4.

The primary outcome, PFS, was defined as the time from treatment initiation to progression or death, whichever came first. We assessed PFS in mRCC patients treated with first-line sunitinib or pazopanib. PFS was modelled using the Kaplan-Meier method. Median PFS and corresponding 95% CIs were reported and PFS was compared between groups using a log-rank test. Multivariable analyses were performed with Cox regression to assess potential prognosticators of PFS. Toxicities pertaining to first-line sunitinib or pazopanib that required dose-modifications or dose schedule changes were compared between treatment groups using Fischer’s exact tests. Toxicities with low occurrences were categorized according to CTCAE version 4.0.3 criteria. All statistics were computed with IBM SPSS Statistics version 18.0.

Results

Patient and disease characteristics

A total of 228 patients were included in this study as described in Table 1. 38 of 57 (67%) pazopanib patients and 153 of 171 (89%) sunitinib patients had progression-related events. Overall, our population had good performance status, most received a prior nephrectomy, and most were male. The median age at mRCC diagnosis was 63 years. 72% of patients had clear cell histology and there was no significant difference between patients with clear cell and non-clear cell histology (p=0.987). Most patients (62% in the pazopanib cohort and 66% in the sunitinib cohort) had IMDC classified intermediate-risk disease. All other characteristics were balanced among patients.

Treatment exposure

Patients received pazopanib (n=57) or sunitinib (n=171) or in the first-line setting, with 81% of pazopanib and 85% of sunitinib patients starting on full dose. With regards to subsequent treatment, 18% of pazopanib patients and 34% of sunitinib patients received second-line therapy. 8% of pazopanib patients and 14% of sunitinib patients received third-line therapy.

Metastatic events

In total, 281 primary metastatic events occurred. The most common site of metastasis was the lung
(38%), followed by lymph node (18%), bone (14%) and liver (10%). Furthermore, 102 secondary metastatic events occurred, with similar frequency, and 36 tertiary sites of metastasis occurred most frequently in the bone (25%), lymph node (22%), lung (11%) and liver (11%).

**Efficacy: Progression-free survival**

When the pazopanib and sunitinib cohorts were compared, median PFS were 8.5 months (95% CI: 6.8-10.2) and 9.4 months (95% CI: 6.2-12.6), respectively [HR: 1.10 (95%CI: 0.76-1.57), p=0.62] (Figure 1). When adjusted for IMDC criteria, the HR for all-cause death for pazopanib vs. sunitinib was 1.04 (95% CI: 0.68-1.59), p=0.57.

When stratified by IMDC risk groups, patients with intermediate-risk disease treated with pazopanib and sunitinib had comparable median PFS (9.4 vs. 9.2 months, p=0.931). Further subgroup analyses for individual IMDC criteria and other clinical and pathological variables demonstrated no significant differences between treatment groups.

**Safety: Adverse events**

Common dose-modifying toxicities including diarrhea, fatigue, and nausea were similar between both treatment groups (Table 2). Prevalence of grade 3 or 4 AEs were similar in sunitinib and pazopanib (8% vs. 6%). Prevalence of treatment discontinuation due to toxicity was also similar (18% vs. 19%, p=0.438). Patients who received sunitinib had significantly elevated incidence of dizziness (3% vs. 1%), limb edema (4% vs. 0%), febrile neutropenia (3% vs. 30%), thrombocytopenia (11% vs. 3%), nervous system disorders (4% vs. 0%), and infections and infestations (3% vs. 0%). Patients who received pazopanib had significantly elevated liver toxicity (29% vs. 3%).

**Discussion**

This study provides a real-world single institution validation of the safety and efficacy findings of previous investigations comparing first-line sunitinib and pazopanib treatment in mRCC patients. Using information collected from our institution, we were able to analyze key endpoints such as PFS and the prevalence of dose-altering toxicities though the experiences of a single institution. Our analysis of 228 mRCC patients treated with first-line sunitinib or pazopanib at a single-institution provides real-world evidence for pazopanib and sunitinib’s similarity in PFS as well as pazopanib’s
favourable tolerability. Initially, the COMPARZ trial demonstrated pazopanib’s non-inferiority to sunitinib, and a trend towards better tolerability with pazopanib. However, the lack of current evidence for its use in population-based settings limits the translation of these findings to real-world patient care. In addressing this disparity, the present study uses the experiences of a single institution to validate previous findings.

As these two TKIs have widely been used in first-line mRCC treatment in the past few years, progress has conceivably been made towards applying the findings of the fundamental COMPARZ trial to real world patient data, including the recent study by Ruiz-Morales et al. using the IMDC. This large retrospective analysis demonstrated similar PFS between pazopanib and sunitinib (8.3 vs. 8.4 months, respectively, p = 0.17). Our analysis showed similar PFS of 8.5 vs. 9.4 months, respectively. This illustrates that the PFS in clinical trial comparisons of pazopanib and sunitinib can also be seen in the practice of real-world institutions.

In addition, the study by Lalani et al. used the CKCis database to investigate overall survival (OS) and dose-individualization for pazopanib and sunitinib, a common practice with sunitinib in Canada. The authors found that patients receiving sunitinib had a significantly longer OS compared to those receiving pazopanib (31.7 vs. 20.6 months, p = 0.028). When patients were stratified by IMDC risk groups, a significant improvement in OS was identified in the intermediate-risk group. Dose-modifying toxicities for sunitinib were elevated, which were similar in this study. While OS was analyzed across all institutions in the CKCis database, our study analyzed PFS in a single institution. PFS has widely been used as a surrogate to OS when comparing therapeutic efficacy in mRCC. As such, our results can be interpreted in the context of similar studies utilizing OS and/or PFS in comparing first-line pazopanib and sunitinib.

While our study provides real-world efficacy and safety validation of PFS in pazopanib and sunitinib through a single institution, several limitations exist. Selection bias may inherently exist as patients with a poorer performance status may have been selected to undergo pazopanib treatment rather than sunitinib, which is a cited issue. In addition, sunitinib has been used for a longer period of time
in the first-line setting than pazopanib. The recent use of first-line pazopanib limited our cohort to 57 patients, compared to 171 patients treated with first-line sunitinib. This limitation can be observed in the difference in median time of follow-up in pazopanib and sunitinib cohorts (10.92 months vs. 19.27 months), median time since the start of treatment (16.04 months vs. 28.24 months), and the large proportion of pazopanib patients still alive (72% vs. 43%). However, all clinical characteristics were well-distributed across both treatment cohorts. Additionally, complete IMDC risk group stratification was not possible due to missing or incomplete data. Overall, the objective of this study was to provide a single-institution validation of pazopanib and sunitinib’s efficacy and safety in a real-world context. As such, our findings must be interpreted in light of these aforementioned limitations and study design.

Conclusions
Based on a single-institution’s experience, pazopanib and sunitinib demonstrate similar efficacy as first-line therapy for mRCC in the context of PFS. However, treatment toxicities are elevated with sunitinib treatment. Our findings support the currently accepted PFS and toxicity profiles of pazopanib and sunitinib in a real-world setting. To strive towards informed treatment decision-making by clinicians, future studies comparing therapeutic efficacy or safety may benefit from real-world data.

Declarations

**Ethics approval and consent to participate:** Approval from the Hamilton Integrated Research Ethics Board was obtained prior to study commencement (approval #: 2018-2162-A).

**Consent for publication:** Not applicable.

**Availability of data and material:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** Not applicable.

**Funding:** Not applicable.

**Authors’ contributions:** ECLW collected, analyzed and interpreted data, and was a major contributor to manuscript writing. CT, GV, AZ, MC, and CL collected and interpreted data. SH and AK provided oversight for the study.
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Abbreviations
mRCC
metastatic renal cell carcinoma
IMDC
International Metastatic Renal Cell Carcinoma Database Consortium
VEGF
vascular endothelial growth factor
TKI
tyrosine kinase inhibitors
PFS
progression-free survival

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Tables

Table 1: Baseline characteristics

| Characteristic, n (%) | Pazopanib (n=57) | Sunitinib (n=171) |
|-----------------------|------------------|--------------------|
| Median age (IQR)      | 64 (58-73)       | 62 (55-68)         |
| Gender                |                  |                    |
| Male                  | 35/57 (61%)      | 113/171 (66%)      |
| Female | 22/57 (39%) | 58/171 (34%) |
|---|---|---|
| Vital status |  |  |
| Alive | 41/57 (72%) | 74/171 (43%) |
| Deceased | 16/57 (28%) | 97/171 (57%) |
| Median time since start of therapy, months (IQR) | 16.04 (5.62-35.24) | 28.24 (12.79-50.00) |
| Median time of follow-up, months (IQR) | 10.92 (3.60-31.56) | 19.27 (6.94-37.58) |
| Histology |  |  |
| Clear cell | 37/57 (65%) | 126/171 (74%) |
| Non-clear cell | 1/57 (2%) | 16/171 (9%) |
| No nephrectomy | 17/57 (30%) | 22/171 (13%) |
| Starting at full dose | 46/57 (81%) | 146/171 (85%) |
| Treatment discontinuation due to toxicity | 10/57 (18%) | 32/171 (19%) |
| Second-line therapy |  |  |
| VEGF-targeted | 7/57 (12%) | 33/171 (19%) |
| mTOR-targeted | 2/57 (4%) | 23/171 (13%) |
| Other | 1/57 (2%) | 2/171 (2%) |
| Third-line therapy |  |  |
| VEGF-targeted | 1/57 (2%) | 16/171 (9%) |
| mTOR-targeted | 2/57 (4%) | 7/171 (4%) |
| Other | 1/57 (2%) | 1/171 (1%) |
| Primary site of metastasis |  |  |
| Lung | 108/281 (38%) |  |
| Lymph node | 51/281 (18%) |  |
| Bones | 38/281 (14%) |  |
| Liver | 28/281 (10%) |  |
| Brain | 9/281 (3%) |  |
| Other | 47/281 (17%) |  |
| Secondary site of metastasis |  |  |
| Lung | 26/102 (25%) |  |
| Lymph node | 24/102 (23%) |  |
| Bones | 15/102 (15%) |  |
| Liver | 15/102 (15%) |  |
| Brain | 5/102 (5%) |  |
| Other | 17/102 (17%) |  |
| Tertiary site of metastasis |  |  |
| Lung | 4/36 (11%) |  |
| Lymph node | 8/36 (22%) |  |
| Bones | 9/36 (25%) |  |
| Liver | 4/36 (11%) |  |
| Brain | 1/36 (3%) |  |
| Other | 10/36 (28%) |  |
| >3 sites of metastasis | 6/57 (11%) | 31/171 (18%) |
| KPS <80% | 9/57 (16%) | 31/149 (21%) |
| Diagnosis to treatment <1 year | 44/57 (77%) | 147/170 (86%) |
| Hemoglobin - low | 35/53 (62%) | 75/143 (52%) |
| Platelets - high | 9/53 (17%) | 13/144 (9%) |
| Neutrophils - high | 6/53 (11%) | 21/133 (16%) |
| Calcium - high | 5/43 (12%) | 6/85 (7%) |
| IMDC risk group |  |  |
| Favourable | 4/50 (8%) | 11/128 (8%) |
| Intermediate | 31/50 (62%) | 84/128 (66%) |
| Poor | 14/50 (28%) | 33/128 (26%) |
| Nephrectomy | 40/57 (70%) | 149/171 (87%) |
| Pathological T |  |  |
| T1 | 6/40 (15%) | 31/149 (21%) |
| T2 | 9/40 (23%) | 24/149 (16%) |
| T3 | 24/40 (60%) | 88/149 (59%) |
| T4 | 1/40 (2%) | 6/149 (4%) |
| Pathological N1 | 7/40 (18%) | 12/149(7%) |
| Grade |  |  |
| G1 | 1/40 (2%) | 4/149 (3%) |
| G2 | 13/40 (33%) | 65/149 (44%) |
| G3 | 17/40 (43%) | 61/149 (41%) |
| G4 | 9/40 (22%) | 19/149 (12%) |
| Adverse event                | Sunitinib (n=451) | Pazopanib (n=135) |
|-----------------------------|------------------|-------------------|
| Abdominal pain              | 4 (11%)          | 3 (2%)            |
| Acute kidney injury         | 0 (0%)           | 4 (2%)            |
| Alanine aminotransferase increased | 2 (1%)               | 10 (18%)          |
| Anemia                      | 16 (9%)          | 2 (4%)            |
| Anorexia                    | 16 (9%)          | 4 (7%)            |
| Aspartate aminotransferase increased | 3 (2%)             | 6 (11%)          |
| Creatinine increased        | 6 (4%)           | 2 (4%)            |
| Diarrhea                    | 39 (23%)         | 16 (28%)          |
| Dizziness                   | 5 (3%)           | 1 (1%)            |
| Dysgeusia                   | 7 (4%)           | 1 (1%)            |
| Dyspepsia                   | 7 (4%)           | 1 (1%)            |
| Dyspnea                     | 5 (3%)           | 2 (4%)            |
| Edema (limbs)               | 6 (4%)           | 0 (0%)            |
| Epistaxis                   | 4 (2%)           | 2 (4%)            |
| Fatigue                     | 51 (30%)         | 32 (56%)          |
| Febrile neutropenia         | 5 (3%)           | 0 (0%)            |
| Fever                       | 4 (2%)           | 0 (0%)            |
| Headache                    | 4 (2%)           | 2 (4%)            |
| Hyperglycemia               | 3 (2%)           | 1 (1%)            |
| Hypertension                | 22 (13%)         | 4 (7%)            |
| Hypothyroidism              | 4 (2%)           | 0 (0%)            |
| Mucositis oral              | 22 (13%)         | 2 (4%)            |
| Myalgia                     | 7 (4%)           | 1 (1%)            |
| Nausea                      | 20 (12%)         | 11 (19%)          |
| Palmar-plantar erythrodysesthesia syndrome | 25 (15%)     | 3 (8%)            |
| Platelet count decrease (thrombocytopenia) | 18 (11%) | 1 (3%) |
| Pneumonitis                 | 4 (2%)           | 0 (0%)            |
| Rash maculo-papular         | 14 (8%)          | 5 (9%)            |
| Vomiting                    | 14 (8%)          | 4 (7%)            |
| Weight loss                 | 2 (1%)           | 4 (7%)            |
| White blood cell decreased (leukopenia) | 11 (6%)       | 3 (8%)            |
| Psychiatric disorders       | 5 (3%)           | 1 (1%)            |
| Investigations (other)      | 12 (7%)          | 1 (1%)            |
| Gastrointestinal disorders (other) | 26 (15%)     | 4 (7%)            |
| Musculoskeletal and connective tissue disorders (other) | 7 (4%) | 4 (7%) |
| Cardiac disorders           | 3 (2%)           | 0 (0%)            |
| Eye disorders               | 2 (1%)           | 0 (0%)            |
| Injury, poisoning and procedural complications | 1 (1%) | 1 (1%) |
| General disorders and administration site conditions | 11 (6%) | 1 (1%) |
| Respiratory, thoracic and mediastinal disorders | 6 (4%) | 1 (1%) |
| Metabolism and nutrition disorders | 5 (3%)       | 1 (1%)            |
| Skin and subcutaneous tissue disorders | 8 (5%) | 1 (1%) |
| Nervous system disorders    | 7 (4%)           | 0 (0%)            |
| Infections and infestations | 5 (3%)           | 0 (0%)            |
| Hepatobiliary disorders     | 1 (1%)           | 0 (0%)            |
| Endocrine disorders         | 1 (1%)           | 1 (1%)            |
| Vascular disorders          | 3 (2%)           | 0 (0%)            |
| Reproductive system and breast disorders | 3 (2%) | 0 (0%) |
| Renal and urinary disorders | 3 (2%)           | 0 (0%)            |

**Figures**
Figure 1

Progression-free survival of first-line sunitinib vs. pazopanib in mRCC