Original Study

Outcomes and Drug Costs of Sunitinib Regimens for Metastatic Renal Cell Carcinoma: A Provincial Population-Based Study

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Abstract

Conventional sunitinib dosing in metastatic renal cell carcinoma administers 50 mg daily on a 4 weeks on/2 weeks off (4/2) schedule. Many patients undergo modifications to schedule, dose, or both. An adjusted-dose regimen is associated with improved overall survival and progression-free survival over standard intermittent dosing, with lower overall drug costs.

Background: Conventional sunitinib dosing in metastatic renal cell carcinoma (mRCC) administers 50 mg daily on a 4 weeks on/2 weeks off (4/2) schedule. Not all patients tolerate this regimen and many undergo modifications to schedule, dose, or both. **Material and Methods:** All patients with mRCC treated with sunitinib by the Saskatchewan Cancer Agency between January 1, 2006, and January 1, 2013, were included. Regimens were categorized as standard intermittent dosing (SID), modified intermittent schedule (MIS), modified intermittent dosing (MID), combination of modified schedule and dosing (MSD), or continuous dosing (CD). The primary objective was to compare overall survival (OS) between regimens. Secondary outcomes included progression-free survival (PFS), discontinuation due to adverse effects (AE), and medication cost. **Results:** Among 161 patients, 18.0%, 51.6%, and 30.4% had favorable, intermediate, and poor Heng risk prognoses, respectively. A total of 140 (87.0%) received sunitinib as first-line therapy. MID was associated with longer OS compared with SID (estimated median 28.4 vs. 11.2 months). PFS was longer for MID, MSD, and CD compared with SID (estimated median 12.0, 9.0, and 8.0 months vs. 3.0 months, respectively). Adjustment for potential confounders did not negate these associations. SID also had higher average monthly drug costs than MIS, MID, and MSD. Overall discontinuation rate due to AE was high (24%). **Conclusion:** An adjusted-dose sunitinib regimen is associated with improved OS and PFS over SID, with lower costs. The development of toxicities requiring dose reductions serves as a predictive biomarker for better outcomes.

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Introduction

More than 1700 Canadians die every year from renal cancer, and the overall incidence is increasing by 2% per year.[1,2] Five-year survival rates for stage IV disease are unfortunately only 0% to 30%,[2,3] although the advent of targeted therapies has significantly improved median overall survival (OS) of this disease.[4] Prognostic factors have been identified that negatively impact survival in metastatic renal cell carcinoma (mRCC) and are used to risk-stratify patients and predict outcomes.[5]

Sunitinib malate (Sutent) is a tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptors and is approved as first-line systemic therapy for mRCC. Conventional dosing of sunitinib in mRCC is traditionally given at 50 mg orally daily on a 4-week on/2-week off (4/2) schedule to give patients a break from the cumulative toxicities associated with sunitinib. Common adverse effects (AEs) associated with sunitinib are fatigue, mucositis, diarrhea, rash, and hand-foot syndrome.[6] Due to these collective side effects, many patients undergo modifications to their sunitinib dosing regimen as either a change in dose, change in schedule, or a combination strategy between the two.

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Several studies have retrospectively investigated dose-schedule adjustments of sunitinib in mRCC. The goal has been to identify an optimal administration algorithm that reduces toxicity-related AEs and maximizes overall drug exposure with the anticipation that it will translate into improved patient outcomes.[7-10] It is currently unknown what the optimal dose-schedule modification strategy is for patients who do not tolerate the traditional 50 mg 4/2 regimen or what, if any, associated drug cost savings are had with alternate dosing regimens. However, common alternative regimens include a switch to a 2-week on/1-week off (2/1) schedule, a reduced dose to 37.5 or 25.0 mg, continuous dosing schedule without breaks, and the inclusion of individualized 7-day breaks.[7-13]

Here we report real-world outcomes and drug costs associated with alternative dose-schedule modifications in a population-based study for the province of Saskatchewan, Canada.

Methods

Sample and Study Design

The Saskatchewan Cancer Agency is responsible for the cancer care of approximately 1 million people across the province, which mainly occurs at 2 sites: the Saskatoon Cancer Centre and the Allan Blair Cancer Centre (Regina). This is a 7-year retrospective population-based study of all patients treated with sunitinib for mRCC in the province of Saskatchewan from these 2 sites between January 1, 2006, and December 31, 2012. The Biomedical Research Ethics Board at the University of Saskatchewan approved this study. A pharmacy database was used to identify all patients who were dispensed sunitinib therapy for mRCC during the study dates. Patient characteristics, laboratory investigations, and clinical outcomes were recorded from the electronic health record and medical charts. Heng prognostic risk was calculated and categorized as favorable, intermediate, or poor as previously cited.[5] Patients were stratified by the sunitinib dosing and schedule adjustments they received during treatment:

- Standard intermittent dosing (SID), given as 50 mg by mouth (PO) daily, 4 weeks on followed by 2 weeks break (4/2). No other dose or schedule adjustment was received.
- Modified intermittent schedule (MIS), given as 50 mg PO daily, 2 weeks on followed by 1 week break (2/1).
- Modified intermittent dosing (MID), given as 37.5 mg, 25.0 mg, or 12.5 mg PO daily, 4/2 schedules.
- Modified intermittent schedule and dosing (MSD) combination given as 37.5 mg, 25.0 mg, or 12.5 mg PO daily, 2/1 schedules.
- Continuous dosing (CD) regimen, given as 37.5 mg, 25.0 mg, or 12.5 mg PO daily without scheduled breaks.

Physician preference dictated which treatment adjustment schema patients received when intolerant from SID. Patients also may have had unscheduled breaks and best supportive care for the management of AEs not otherwise specified previously. The Saskatchewan Cancer Agency pharmacy department also provided the total drug cost of sunitinib for each patient during the study period.

The primary endpoint of this study, OS, was defined as the time between the date of any systemic treatment and death. There were 3 secondary endpoints, the first of which was progression-free survival (PFS), defined as the interval between sunitinib initiation and the date of progression as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria or the date of sunitinib discontinuation for any reason, including death from any cause. The second was rates of discontinuation due to AEs. The third was total drug cost over time on treatment.

Statistical Analysis

Overall comparisons of subject characteristics across treatment groups, including discontinuation for AEs, were made using Kruskal-Wallis testing for continuous variables and χ^2 testing or Fisher exact testing for categorical variables. Kaplan-Meier survival analysis of OS and PFS was undertaken, using log-rank tests; pairwise evaluations also were made between groups using the Sidak adjustment for multiple comparisons. This was followed up with Cox proportional-hazards regression modeling for multivariable analysis of these outcomes in an effort to ensure that any observed differences between dosing regimens were not actually attributable to underlying differences in subject characteristics, such as age or prognostic score. Average monthly drug costs were compared overall by analysis of variance, followed by pairwise comparison between all groups, using the Tukey correction for multiple comparisons. All analysis used SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient characteristics for each treatment group are summarized in Table 1. There were no statistically significant differences in clear-cell histology, nephrectomy status, or brain metastases. Although data were too sparse for Fisher exact comparison of Heng score and Eastern Cooperative Oncology Group values by group, 41% of SID patients had a poor Heng score compared with 17% and 32% in the MID and MSD groups, respectively. Age at treatment also was found to differ between groups ($P = .008$), as did time from diagnosis to initiation of sunitinib therapy ($P = .0002$). Regarding the latter, mean intervals from metastatic diagnosis to sunitinib therapy were 1.9, 4.7, 15.2, 2.9, and 6.7 months for CD, MIS, MID, MSD, and SID, respectively. There were 39 patients (24%) who discontinued sunitinib therapy due to AEs. The rates of discontinuation were not significantly different between the treatment groups.

Median OS and PFS times for each treatment group are summarized in Table 2, both overall and by Heng category. From the Kaplan-Meier estimates examining the subjects overall, all alternate regimens were found to have longer median OS compared with SID (11.2 months), with the greatest differences noted for patients in the MID (28.4 months) and MIS groups (23.1 months). Pairwise comparisons on log-rank testing found statistically significant differences in OS between the SID and CD ($P = .02$), MIS ($P = .03$), and MID ($P = .001$) groups. OS was also longer for MID subjects compared with those on MIS ($P = .03$) and CD ($P = .03$) schedules. Similarly, although median PFS was longer for all other treatment profiles when compared with SID (3.0 months), MID subjects again had the longest interval (12.0 months). Pairwise comparisons found all groups to have statistically significantly longer median PFS compared with the SID group (all $P < .02$), and the MID group was found to have longer PFS than both the MIS and CD groups as well ($P = .01$ and 0.04, respectively). When these outcomes were examined by prognostic subgroup, modified regimens generally continued to be favored over SID.