Original Study

Real-World Effectiveness of Everolimus Subsequent to Different First Targeted Therapies for the Treatment of Metastatic Renal Cell Carcinoma: Synthesis of Retrospective Chart Reviews

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Abstract

This study examines the effect of first targeted therapy on outcomes with everolimus as second targeted therapy in patients with metastatic renal cell carcinoma. Overall survival, treatment failure, and discontinuation are analyzed in 3 chart reviews, and results are synthesized in a meta-analysis. Results indicate that first targeted therapy does not significantly affect outcomes of patients using everolimus as second targeted therapy.

Background: The effect of first targeted therapy on outcomes with second targeted therapy for metastatic renal cell carcinoma is not well known. The purpose of this study was to compare outcomes for patients receiving a second targeted therapy with everolimus by type of first targeted therapy. **Patients and Methods:** Data were drawn from 3 separate retrospective chart reviews conducted in 2011, 2012, and 2014. Inclusion criteria and study design were similar across the 3 studies. To be included in this analysis, patients had to meet the following criteria: aged $\geq$ 18 years; received first targeted therapy with pazopanib, sunitinib, or sorafenib; and received second targeted therapy with everolimus. Overall survival, time to treatment failure, and time to treatment discontinuation outcomes were measured from second targeted therapy initiation. Outcomes were compared among treatment groups by Cox proportional hazard models adjusting for demographic and clinical characteristics. Hazard ratios for overall survival, time to treatment failure, and time to treatment discontinuation obtained from the 3 chart reviews were synthesized in meta-analyses. **Results:** Of 696 patients treated with everolimus as second targeted therapy, 605 patients received first targeted therapy with sunitinib/sorafenib and 91 with pazopanib. After synthesizing the hazard ratios from all studies in meta-analyses, there were no significant differences in study outcomes between patients receiving sunitinib/sorafenib versus those receiving pazopanib as first targeted therapy. **Conclusion:** There were no significant differences among outcomes while receiving second targeted therapy with everolimus for patients treated with pazopanib versus sunitinib/sorafenib as first targeted therapy.

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Introduction

Over the past decade, the advent of targeted therapies has revolutionized treatment for metastatic renal cell carcinoma (mRCC).[1-3] Seven targeted agents are currently approved in the United States.[4] These include the 4 vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (TKIs) axitinib, sorafenib,

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sunitinib, and pazopanib, the 2 mammalian target of rapamycin inhibitors (mTORis) temsirolimus and everolimus, and the VEGF-directed monoclonal antibody bevacizumab. Most patients with mRCC eventually experience disease progression while receiving their first targeted therapy.[5] Sequential use of targeted therapies has become the mainstay of mRCC treatment.

Everolimus was the first targeted therapy to be approved for sequential use after a prior targeted therapy,[6] and it remains one of the most commonly used treatments in this setting.[7-10] RECORD-1, the pivotal trial for everolimus, demonstrated efficacy among patients who had previously received sunitinib, sorafenib, bevacizumab, or cytokine therapy for the treatment of mRCC.[11,12] After the approval of everolimus, pazopanib was approved for use as initial targeted therapy in mRCC,[13] and use of cytokines has become less common.[3,14,15] Pazopanib and everolimus are now guideline recommended as first and second targeted therapies, respectively.[16] However, few studies have evaluated whether everolimus outcomes after use of pazopanib are comparable to those after use of sorafenib or sunitinib. The consistency of everolimus outcomes after pazopanib, sorafenib, or sunitinib treatment is an important component of a broader question—the identification of optimal treatment sequences in mRCC—which is of high interest to clinical practitioners, given the growing number of treatment options.[17-19]

In order to determine individualized treatment selection, several prognostic nomograms have been evaluated and validated for mRCC patients treated with cytokine therapy, TKIs, mTORis, or a combination of all of the above.[20-25] In addition, several studies have published information on current treatment patterns and their outcomes with various sequences of targeted therapies.[9,15,26-29] However, as a result of the relatively recent approval of pazopanib, the combination of first targeted therapy with pazopanib and second targeted therapy with everolimus therapy has received little attention so far. To date, there are no real-world studies comparing the clinical outcomes of patients treated with everolimus as second targeted therapy after the failure of first targeted therapy with pazopanib versus those after the failure of first targeted therapy with sunitinib or sorafenib. This study addressed the knowledge gap by assessing the impact of different first targeted therapies (pazopanib, sunitinib, sorafenib) on the effectiveness of everolimus as second targeted therapy using real-world data collected in 3 recent chart reviews with similar design. The estimated effects of first targeted therapy on outcomes of everolimus as second targeted therapy are synthesized in a meta-analysis.

Methods

Data Source and Sample Selection

This study included patients from 3 previously conducted retrospective chart review studies (published in 2011, 2012, and 2014), the overall designs and covered periods of which are summarized in Table 1.[30-32] In each prior study, medical oncologists and hematologists/oncologists were recruited from nationwide panels of physicians in community and academic practice. All studies included charts from adults diagnosed with mRCC who initiated second targeted therapy after discontinuation of first targeted therapy for medical reasons (eg, disease progression, nonresponse without disease progression, drug intolerance). All studies used a retrospective cohort design in which inclusion and exclusion criteria were applied up to the initiation of second targeted therapy. After the initiation of second targeted therapy, patients were followed, as a retrospective cohort, for outcomes. In each chart review, data were collected via a standardized electronic case report form that included real-time error checking. All studies were exempted from full ethics review by the New England Institutional Review Board because all data were deidentified and collected retrospectively.

To be included in the current analysis, patients were further required to have received pazopanib, sunitinib, or sorafenib as their first targeted therapy and to have received everolimus as their second targeted therapy. These patients were classified into 2 study groups on the basis of the first targeted therapy: one group consisted of patients treated with pazopanib as first targeted therapy, and the other consisted of patients treated with sunitinib or sorafenib as first targeted therapy.

Study Outcomes

Overall survival (OS), time to treatment failure (TTF), and time to treatment discontinuation (TTD) were studied after the

Table 1 Study Designs of 3 Chart Review Studies

Characteristic	2011 Chart Review[30]	2012 Chart Review[31]	2014 Chart Review[32]
Time period study was conducted	September 2011 to December 2011	May 2012 to June 2012	June 2014 to July 2014
Time window of initiation of second targeted therapy	October 2009 to June 2010	January 2010 to June 2012	February 2012 to January 2013
No. of participating physicians	159	36	318
No. of patient charts physicians were asked to contribute	Up to 5	At least 5, up to 15	Up to 5
Selection of patient charts	Random	Sequential selection of patients most recently initiating second targeted therapy	Random
Total number of mRCC patient charts collected	534	281	1173
Eligible first targeted therapy	Sunitinib, sorafenib, or pazopanib	Sunitinib, sorafenib, axitinib, or pazopanib	Sunitinib, sorafenib, axitinib, or pazopanib
Eligible second targeted therapy	Sunitinib, sorafenib, pazopanib, or everolimus	Sunitinib, sorafenib, axitinib, pazopanib, everolimus, or temsirolimus	Sunitinib, sorafenib, axitinib, pazopanib, everolimus, or temsirolimus

Abbreviation: mRCC = metastatic renal cell carcinoma.