First-Line Mammalian Target of Rapamycin Inhibition in Metastatic Renal Cell Carcinoma: An Analysis of Practice Patterns From the International Metastatic Renal Cell Carcinoma Database Consortium

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Abstract

Using an established international renal cell carcinoma (RCC) database, we retrospectively characterized the use and efficacy of mammalian target of rapamycin (mTOR) inhibitors in treatment-naive metastatic RCC (mRCC) patients. Front-line mTOR inhibitors are used in clinical practice mostly in select patients, who have non-clear cell histology, poor prognostic features, or as part of clinical trials.

Introduction/Background: Approval of the mTOR inhibitors for the treatment of mRCC was based on efficacy in poor-risk patients in the first-line setting for temsirolimus and in vascular endothelial growth factor inhibitor-refractory patients for everolimus. We strove to characterize temsirolimus and everolimus use and effectiveness in the first-line setting. **Patients and Methods:** We performed a retrospective database analysis of mRCC patients who received mTOR inhibitors as first-line targeted therapy. The Kaplan-Meier product-limit method was used to estimate the distribution of progression-free survival (PFS) and overall survival (OS). **Results:** We identified 127 mRCC patients who had received a first-line mTOR inhibitor. Temsirolimus was administered in 93 patients (73%) and everolimus in 34 patients (27%). The main reasons for choice of temsirolimus were poor-risk disease (38%), non-clear cell histology (27%), and clinical trial availability (15%), whereas clinical trial (82%) and non-clear cell histology (6%) drove everolimus selection. Of the temsirolimus and everolimus patients, 58% and 32% were poor-risk according to the International mRCC Database Consortium criteria, respectively. The median PFS and OS were 3.4 and 12.5 months and 4.8 and 15.9 months with temsirolimus and everolimus, respectively. Although limited by small numbers, this study characterizes a real-world, international experience with the use of mTOR inhibition in treatment-naive mRCC patients. **Conclusion:** Poor-risk RCC, non-clear cell histology, and clinical trials were the predominant reasons for mTOR inhibitor selection in the front-line setting. Because of the different patient populations in which they were administered, direct comparisons of the front-line efficacy of temsirolimus and everolimus cannot be made.

Clinical Genitourinary Cancer, Vol. 12, No. 5, 335-40
Keywords: Everolimus, mTOR inhibitor, Targeted therapy, Temsirolimus, Treatment-naive

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Submitted: Dec 31, 2013; Revised: Mar 3, 2014; Accepted: Mar 11, 2014; Epub: Mar 15, 2014

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2014.03.003

Introduction

Two major classes of targeted therapies, the vascular endothelial growth factor (VEGF) inhibitors and the mammalian target of rapamycin (mTOR) inhibitors, have been developed for the treatment of metastatic renal cell carcinoma (mRCC). By inhibiting angiogenesis and growth factor pathways critical to the growth of mRCC, these agents elicit significant improvements in progression-free survival (PFS), in objective responses, and in some cases, overall survival.[1-12]

Mammalian target of rapamycin is integral to the regulation of cell growth, proliferation, metabolism, and autophagy.[13] Two mTOR inhibitors are approved to treat advanced renal cell carcinoma (RCC): temsirolimus and everolimus. Through an allosteric interaction, these rapalogs complex with an intracellular protein, FK 506 binding protein-12, bind to mTOR, and competitively inhibit its signaling.[14] Because of its role in the regulation of hypoxia-inducible factor (HIF), mTOR blockade also inhibits angiogenesis and other key HIF genes critical to tumorigenesis and survival.[15]

With their similar mechanisms of action, temsirolimus and everolimus are often assumed to have equivalent efficacy. However, they were prospectively studied in very different patient populations.[3,4] Temsirolimus is approved for use in treatment-naive patients based on level 1 evidence that it increases overall survival in poor-risk disease. However, it is important to remember that it has not been directly compared with a VEGF-targeted therapy in that setting. Everolimus is a standard therapy in the second-line setting based on its ability to stabilize disease and prolong PFS in VEGF inhibitor-refractory patients. To enhance our knowledge of their efficacy and to understand the reasons they are chosen over VEGF inhibitors, we interrogated the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) databank and the longitudinal medical records of our institutions for the outcomes of patients who received mTOR inhibitors as first-line targeted therapy in a real-world, unselected setting.

Patients and Methods

Patient Population

The IMDC is a group of academic institutions from Canada, the United States, Singapore, Denmark, and South Korea. Patient inclusion into the database requires advanced or metastatic RCC of any histology and treatment with a targeted therapy. For the current study, 14 centers had data on RCC patients who had received first-line mTOR inhibitors. Patients were excluded if they received a concurrent VEGF-targeted therapy.

We queried the database for baseline demographic, clinical, laboratory, and outcomes information. Investigators retrospectively reviewed clinic notes to assess the reason behind the choice of an mTOR inhibitor. Reasons included IMDC[16] or Memorial Sloan-Kettering Cancer Center (MSKCC)[17] poor-risk status, non-clear cell histology or sarcomatoid features, clinical trial, comorbidity or toxicity concerns with administration of a VEGF inhibitor, physician choice, insurance issues, history of renal transplant (with the rationale that rapamycin would be effective at preventing rejection too), and unknown. Survival data were retrieved from the patient's medical record or publically available records. Institutional review board approval was secured from each center.

Statistical Analysis

Summary descriptive statistics were created for baseline characteristics. The Kaplan-Meier product limit method was used to estimate the distributions of PFS and overall survival for all patients, and stratified by prognostic groups defined at therapy initiation or by other covariates of interest. Comparisons between groups were conducted using the log rank test. PFS was defined as time from drug initiation to progression, cessation of therapy, death, or censored at last follow-up. Overall survival was defined as time from drug initiation to death or censored at last follow-up. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). The cutoff date for data analysis was February 4, 2013.

Results

From July 2004 to January 2013, 127 patients received a first-line mTOR inhibitor for metastatic RCC. Median follow-up was 22.1 months. Temsirolimus was administered in most cases and 34 patients received everolimus. Baseline demographic characteristics are shown in Table 1. Median age in both cohorts was 61 to 62 years. Median Karnofsky performance status was slightly lower in the temsirolimus group at 80% compared with 90% in the everolimus group. Approximately half of the patients in each group had clear cell disease with 40% to 41% of the patients having non-clear cell disease. Sarcomatoid features were present in 14% of the temsirolimus patients and in 26% of the everolimus patients. Temsirolimus patients had a lower incidence of previous nephrectomy (62% vs. 82%) and a greater number of metastatic sites (> 1 site: 84% vs. 76%) compared with the everolimus cohort. Of the temsirolimus and everolimus patients, 58% and 32% were poor risk according to IMDC criteria, 27% and 29% were intermediate risk, and 6% and 15% were favorable risk, respectively.

Retrospective review of clinic notes revealed the reasons behind the choice of an mTOR inhibitor. Reasons identified included IMDC or MSKCC poor-risk status, non-clear cell histology or sarcomatoid features, clinical trial, comorbidity or toxicity concerns prohibiting administration of a VEGF inhibitor, physician choice, insurance issues, history of renal transplant (with the justification that rapamycin would also be effective at preventing rejection too), and unknown. Poor risk status (38%), non-clear cell histology (27%), and clinical trial (15%) motivated physicians to select temsirolimus and clinical trial (82%) and non-clear cell histology (6%) drove choice of everolimus (Table 2).

The median PFS in all patients was 3.4 months (n = 90) for temsirolimus and 4.8 (n = 32) months for everolimus (Table 3). There were no significant differences in efficacy between the clear cell and non-clear cell subsets (Kaplan-Meier curves not shown). In clear cell disease, temsirolimus induced a median PFS of 3.3 months (n = 47) and 4.8 months (n = 36) in non-clear cell disease ($P = .61$). Median PFS was 5.5 months (n = 17) for clear cell disease and 3.3 months (n = 14) for non-clear cell disease when treated with everolimus ($P = .6$). Temsirolimus elicited a median PFS of 8.3 (n = 6), 5.3 (n = 25), and 3.1 (n = 40) months in good-, intermediate-, and poor-risk patients, respectively. Everolimus administration resulted in a median PFS of 11.3 (n = 5), 2.3 (n = 10), and 5.3 (n = 7) months in good-, intermediate-, and poor-risk patients.