A Population-Based Overview of Sequences of Targeted Therapy in Metastatic Renal Cell Carcinoma

Nimira Alimohamed,[1] Jae-Lyn Lee,[2] Sandy Srinivas,[3] Georg A. Bjarnason,[4] Jennifer J. Knox,[1] Mary J. Mackenzie,[5] Lori Wood,[6] Ulka N. Vaishampayan,[7] Min-Han Tan,[8] Sun Young Rha,[9] Frede Donskov,[10] Srinivas Tantravahi,[11] Christian Kollmannsberger,[12] Scott North,[13] Brian I. Rini,[14] Toni K. Choueiri,[15] Daniel Y.C. Heng[16]

Abstract

The optimal sequence of targeted therapies (TTs) to treat metastatic renal cell carcinoma (mRCC) is unknown. This population-based registry evaluation of 2106 patients with mRCC treated with different sequences of TT did not demonstrate superiority of one sequence of therapy. First- and second-line progression-free survival rates were similar regardless of targeted agent used.

Background: Several TTs are available to treat mRCC; however, the optimal sequence of therapy remains unknown. **Patients and Methods:** Consecutive population-based samples of patients with mRCC treated with TT were collected from 12 cancer centers via the International Metastatic Renal Cell Carcinoma Database Consortium. Patient characteristics, first-line and second-line progression-free survival rates and overall survival data were collected based on sequencing of TT. Multivariable analysis was performed when there were significant differences on univariable analysis. **Results:** A total of 2106 patients were included with a median follow-up of 36 months; 907 (43%) and 318 (15%) patients received subsequent second-line and third-line TT, respectively. Baseline characteristics were well matched among different sequences apart from more patients with non–clear-cell histology in the vascular endothelial growth factor (VEGF) to mammalian target of rapamycin (mTOR) group compared with the VEGF to VEGF group sequence. When adjusting for the Heng risk criteria and non–clear-cell histology, the hazard ratio for death for the VEGF to mTOR group versus the VEGF to VEGF group was 0.833 (95% confidence interval [CI], 0.669-1.037; $P = .1016$). More specifically, the adjusted hazard ratio for death for the sunitinib to everolimus versus sunitinib to temsirolimus sequences was 0.774 (95% CI, 0.52-1.153; $P = .2086$). **Conclusion:** In this large multicenter analysis evaluating different sequences of TT in mRCC, no substantial effect on outcome based on sequence of TT was identified.

Clinical Genitourinary Cancer, Vol. 12, No. 4, e127-31

Keywords: Kidney cancer, Mammalian target of rapamycin, Sequencing, Treatment, Vascular endothelial growth factor

Toni K. Choueiri and Daniel Y.C. Heng are cosenior authors.

[1]Princess Margaret Hospital, Toronto, Ontario, Canada
[2]Asan Medical Centre, Seoul, South Korea
[3]Stanford Cancer Centre, Stanford, CA
[4]Sunnybrook Odette Cancer Institute, Toronto, Ontario, Canada
[5]London Health Sciences Center, London, Ontario, Canada
[6]Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, Canada
[7]Wayne State University, Detroit, MI
[8]National Cancer Center, Institute of Bioengineering and Nanotechnology, Singapore
[9]Yonsei University Hospital, Seoul, South Korea
[10]Aarhus University Hospital, Aarhus, Denmark
[11]Huntsman Cancer Institute, Salt Lake City, UT
[12]BC Cancer Agency, Vancouver, British Columbia, Canada
[13]Cross Cancer Institute, Edmonton, Alberta, Canada
[14]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH
[15]Dana-Farber Cancer Institute, Harvard University, Boston, MA
[16]Tom Baker Cancer Centre, Calgary, Alberta, Canada

Submitted: Sep 9, 2013; Revised: Nov 22, 2013; Accepted: Dec 23, 2013; Epub: Dec 27, 2013

Address for correspondence: Nimira Alimohamed, MD, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario M5G 2M9, Canada
Fax: 416-946-2170; e-mail contact: nimira.alimohamed@uhn.ca

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2013.12.003

Introduction

The treatment of metastatic renal cell carcinoma (mRCC) mainly consists of agents targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways. With these targeted therapies (TTs), improvements in survival have been attained. Despite these advances and the increasing number of targeted agents available, important questions remain regarding the optimal sequencing of these agents.

Inhibitors of the VEGF signaling pathway including sunitinib, sorafenib, pazopanib, and bevacizumab have improved progression-free survival (PFS) in the first-line setting.[1-6] Temsirolimus, a competitive inhibitor of mTOR kinase, has also shown improvement in overall survival (OS) in poor-prognosis patients with mRCC as first-line targeted therapy (TT).[7] Prospective studies in the second-line setting with targeted agents have also demonstrated improvements in PFS with the VEGF tyrosine kinase inhibitor (TKI) axitinib[8] and with the mTOR inhibitor everolimus.[9]

The ideal sequence of TT requires further elucidation. The recently reported INTORSECT (Investigating Torisel As Second-Line Therapy) trial randomized patients with mRCC after progression while receiving sunitinib to either the VEGF inhibitor, sorafenib, or the mTOR inhibitor, temsirolimus.[10] Although no statistical difference in PFS was demonstrated, a 4-month difference in OS favored sorafenib. However, questions remain regarding subsequent therapies used, and it is important to note that the second-line mTOR and VEGF inhibitors with level 1 evidence in randomized trials (everolimus and axitinib) were not part of this study.

One strategy has been the use of VEGF inhibitors sequentially, implying a lack of complete cross-resistance among the various VEGF TKIs. Retrospective studies[11,12] and phase II prospective studies have validated this strategy.[13] Another strategy uses mTOR inhibitors in the second-line setting after VEGF inhibitors. Everolimus after cytokines or VEGF TTs (sunitinib and or sorafenib) was beneficial as noted in the RECORD (Efficacy and Safety Comparison of RAD001 versus. Sunitinib in the First-line and Second-line Treatment of Patients With Metastatic Renal Cell Carcinoma)-1 trial.[9] This benefit was observed across different prognostic risk groups. Temsirolimus after VEGF- TT was evaluated retrospectively and demonstrated stable disease in 50 patients (65%), most of whom had either intermediate- or poor-prognosis disease.[14] Rechallenging patients with the same targeted agent after disease progression has been another approach beyond second-line therapy, and has been evaluated retrospectively in a highly selected cohort of patients treated with sunitinib, with 5 patients (22%) demonstrating a partial response to rechallenge, thus suggesting that resetting of sensitivity to a targeted agent is possible.[15]

Despite these strategies, none have proven clear superiority. A previous study from our group showed that second-line comparisons between VEGF inhibitors and mTOR inhibitors found a longer time to treatment failure with second-line VEGF therapy, however, OS from the start of second-line therapy was not significantly different.[16] Similarly, another retrospective analysis of patients who had primary resistance to first-line VEGF inhibitors, found no difference in OS between those treated with second-line VEGF therapy versus mTOR inhibitors.[17]

This multicenter retrospective review of patients from 12 different oncology treatment centers demonstrated outcomes based on different sequences of TTs used. To our knowledge, this is the largest population based analysis of real-world practice patterns and outcomes in the era of TT.

Patients and Methods

Patient Population and Clinical Evaluation

Patients with mRCC treated with TT were included in this study. Consecutive population-based patient samples were collected between 2005 and 2011 at 12 international cancer centers in Canada (Alberta Health Services Cancer Care, Sunnybrook Odette Cancer Center, Princess Margaret Hospital, London Health Sciences Center, Queen Elizabeth II Health Sciences Center, British Columbia Cancer Agency), the United States (Dana-Farber Cancer Institute, Cleveland Clinic, Karmanos Cancer Center, Beth Israel Deaconess Medical Center), Singapore (National Cancer Center), and Denmark (Aarhus University Hospital) as previously described.[18] Patients may have been treated as part of a clinical trial or as per the standard of care at the time. Baseline patient characteristics and outcome data were collected using uniform data collection templates. Inclusion criteria consisted of a diagnosis of mRCC of any pathologic subtype and treatment with first-line approved TT including sunitinib, sorafenib, bevacizumab, pazopanib, temsirolimus, everolimus, and axitinib.

Patient characteristics, first-line, and second-line (if applicable) PFS, and OS data were collected for different groups of patients based on sequencing of TT. Approval from local institutional review boards or research ethics boards was obtained for each center.

Statistical Analyses

Summary statistics are provided for patient demographic data. PFS was assessed for each line of therapy and defined as the time from initiation of that line of therapy to disease progression, drug cessation, death, or censored at the date of last follow-up. OS was also investigated and defined as the time from initiation of TT to time of death or censored at the date of last follow-up. Kaplan-Meier curves were constructed to compare PFS and OS for patients based on the sequence of TT used, and log rank test was used to compare these censored outcomes.

Associations between patient characteristics and sequence of TT were assessed using the log rank test in univariate analysis. If a statistically significant difference in OS ($P < .05$) was detected on univariate testing, proportional hazards regression modeling was used to adjust hazard ratio according to baseline characteristics that were statistically different between the 2 sequences. All statistical calculations were performed using SAS version 9.2 (Cary, NC).

Results

A total of 2106 consecutive patients were identified as having received first-line TT with a median follow-up of 36 months. Most of the patients received sunitinib in the first-line setting (n = 1542), followed by sorafenib (n = 412) or bevacizumab (n = 97). Other targeted agents used in the first-line setting included pazopanib, temsirolimus, everolimus, or axitinib. The patients received subsequent second-line (n = 907; 43%) and third-line (n = 318;