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Third-line Targeted Therapy in Metastatic Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

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Abstract

Background: The use of third-line targeted therapy (TTT) in metastatic renal cell carcinoma (mRCC) is not well characterized and varies due to the lack of robust data to guide treatment decisions. This study examined the use of third-line therapy in a large international population.
Objective: To evaluate the use and efficacy of targeted therapy in a third-line setting.
Design, setting, and participants: Twenty-five international cancer centers provided consecutive data on 4824 mRCC patients who were treated with an approved targeted therapy. One thousand and twelve patients (21%) received TTT and were included in the analysis.
Outcome measurements and statistical analysis: Patients were analyzed for overall survival (OS) and progression-free survival using Kaplan-Meier curves, and were evaluated for overall response. Cox regression analyses were used to determine the statistical association between OS and the six factors included in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model. Subgroup analysis was performed on patients stratified by their IMDC prognostic risk status.
Results and limitations: Everolimus was the most prevalent third-line therapy (27.5%), but sunitinib, sorafenib, pazopanib, temsirolimus, and axitinib were all utilized in over $\geq$9% of patients. Patients receiving any TTT had an OS of 12.4 mo, a progression-free survival of 3.9 mo, and 61.1% of patients experienced an overall response of stable

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disease or better. Patients not receiving TTT had an OS of 2.1 mo. Patients with favorable- (7.2%) or intermediate-risk (65.3%) disease had the highest OS with TTT, 29.9 mo and 15.5 mo, respectively, while poor-risk (27.5%) patients survived 5.5 mo. Results are limited by the retrospective nature of the study.
Conclusions: TTT remains highly heterogeneous. The IMDC prognostic criteria can be used to stratify third-line patients. TTT use in favorable- and intermediate-risk patients was associated with the greatest OS.
Patient summary: Patients with favorable- and intermediate-prognostic criteria disease treated with third-line targeted therapy have an associated longer overall survival compared with those with poor risk disease.

1. Introduction

The past decade has demonstrated an increase in survival for metastatic renal cell carcinoma (mRCC) patients, as we have shifted into the era of targeted therapies that are directed at the angiogenic drivers of mRCC tumors [1]. To date, seven antiangiogenic targeted therapies have been approved in North America and Europe: five targeting the vascular endothelial growth factor (VEGF) pathway and two against the mammalian target of rapamycin (mTOR) pathway. Additionally, nivolumab, an antibody inhibitor of the programmed death 1 immune checkpoint protein, was recently approved by the US Food and Drug Administration after demonstrating a survival benefit over everolimus in a phase 3 clinical trial [2]. Similarly, cabozantinib, a multi-targeting tyrosine kinase inhibitor (TKI), was recently Food and Drug Administration approved following its phase 3 trial demonstrating a better response rate, progression-free survival (PFS), and overall survival (OS) compared with everolimus [3].

As the number of approved therapies continues to expand, controversy over optimal treatment patterns is inevitable [4]. The National Comprehensive Cancer Network and the European Society for Medical Oncology (ESMO) provide some guidance for first- and second-line treatment choices, but the optimal treatment in a third-line setting has not been defined. Despite increasing evidence that third-line targeted therapy (TTT) is beneficial to select patients, physicians have minimal high-quality evidence to guide therapy choice in TTT [5,6]. To date, only four randomized controlled trials, RECORD-1, GOLD, CheckMate 025, and METEOR, have included patients in a third-line setting [2,3,7,8]. Consequently, both the National Comprehensive Cancer Network and ESMO currently recommend clinical trial enrollment for TTT patients where possible; however, these guidelines may be adjusted following the approval of nivolumab and cabozantinib [9,10].

Treatment patterns in TTT continue to vary by center and jurisdiction, and many patients still do not have access to reimbursed third-line treatment. The aim of this study was to characterize the use of targeted therapy in a third-line setting and to determine if the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria can stratify patients into different risk groups to help us choose individuals that may benefit more from TTT.

2. Materials and methods

2.1. Patient population

Twenty-five international cancer centers in Canada, USA, Denmark, Greece, South Korea, Australia, New Zealand, Japan, Singapore, and Belgium provided consecutive patient data collected from hospital and pharmacy records using uniform database software and templates between 2005 and July 2015.

All patients were diagnosed with mRCC of any type and had been treated with at least one approved VEGF or mTOR targeted therapies (sunitinib, sorafenib, pazopanib, bevacizumab, axitinib, temsirolimus, or everolimus). Previous immunotherapy was allowed but not counted as a first line of therapy. This study received institutional review board approval from each participating center.

2.2. Statistical analysis

Statistical analyses were performed with SAS version 9.4 (Cary, NC, USA). Kaplan-Meier curves were constructed to determine OS and PFS. OS was defined as time from initiation of TTT to death, or censored at last follow-up, with the exception of one analysis that defined OS as time from cessation of second-line therapy to death or censor in order to compare those that did receive TTT and those that did not. PFS was defined as the time from initiation of TTT until death, progression based on Response Evaluation Criteria in Solid Tumors guidelines, cessation of TTT, or censored at last follow up [11].

Cox regression analyses were used to determine the statistical association between OS and the six factors included in the IMDC prognostic model: (1) Karnofsky Performance Score (KPS) $<$80%, (2) time from diagnosis to initiation of targeted therapy $<$1 yr, (3) hypercalcemia, (4) anemia, (5) neutrophilia, and (6) thrombocytosis [12]. In TTT analysis these variables were all collected at the initiation of third-line therapy (except for time to diagnosis to initiation of first line targeted therapy $<$ 1 yr). In the analysis comparing those that received TTT and those that did not, the prognostic criteria were all collected at second-line therapy initiation (with the exception of diagnosis to initiation of first line targeted therapy $<$ 1 yr).

A case deletion method was used to handle missing values in all explanatory variables in the Cox regression models. Patients were stratified based on their IMDC prognostic risk factors and analyzed for OS and PFS.

3. Results

3.1. Patient characteristics and treatments

Of 4824 patients treated with first-line targeted therapy, 2534 (52.5%) received second-line therapy, and 1012 (21%)

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