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European Association of Urology

Kidney Cancer

Efficacy of Second-line Targeted Therapy for Renal Cell Carcinoma According to Change from Baseline in International Metastatic Renal Cell Carcinoma Database Consortium Prognostic Category

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Article info

Article history:
Accepted September 30, 2016

Associate Editor:
Giacomo Novara

Keywords:
Carcinoma
Renal cell
Database
Follow-up studies
Logistic models

Abstract

Background: We hypothesized that changes in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic category at start of second-line therapy (2L) for metastatic renal cell carcinoma (mRCC) might predict response.
Objective: To assess outcomes of 2L according to type of therapy and change in IMDC prognostic category.
Design, setting, and participants: We performed a retrospective review of the IMDC database for mRCC patients who received first-line (1L) VEGF inhibitors (VEGFi) and then 2L with VEGFi or mTOR inhibitors (mTORi). IMDC prognostic categories were defined before each line of therapy (favorable, F; intermediate, I; poor, P). Data were analyzed for 1516 patients, of whom 89% had clear cell histology.
Intervention: All included patients received targeted therapy for mRCC.
Outcome measurements and statistical analysis: Overall survival (OS), time to treatment failure, and response to 2L were analyzed using Cox or logistic regression.
Results and limitations: At start of 2L, 60% of patients remained in the same prognostic category; 9.0% improved (3% I → F; 6% P → I); 31% deteriorated (15% F → I or P; 16% I → P). Patients with the same or better IMDC prognostic category had a longer time to treatment failure if they remained on VEGFi compared to those who switched to mTORi (adjusted hazard ratio [AHR] ranging from 0.33 to 0.78, adjusted $p < 0.05$). Patients who deteriorated from F to I appeared more likely to benefit from switching to mTORi

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http://dx.doi.org/10.1016/j.eururo.2016.09.047

(median OS 16.5 mo, 95% confidence interval [CI] 12.0–19.0 for VEGFi; 20.2 mo, 95% CI 14.3–26.1 for mTORi; AHR 1.53, 95% CI 1.04–2.24; adjusted $p = 0.03$).
Conclusions: Changes in IMDC prognostic category predict the subsequent clinical course for patients with mRCC and provide a rational basis for selection of subsequent therapy.
Patient summary: The pattern of treatment failure might help to predict what the next treatment should be for patients with metastatic renal cell carcinoma.

1. Introduction

Multiple effective treatments are now available for advanced clear-cell renal cell carcinoma (RCC). These include agents that inhibit signaling through the VEGF pathway (VEGFRi) and related signaling molecules [1–6]; inhibitors of the PI3K/AKT/mTOR pathway (mTORi) [7] [8]; and, more recently, cabozantinib [9,10] (a small-molecule dual inhibitor of VEGFR2 and c-met) and nivolumab (anti-PD1 monoclonal antibody) [11]. Current evidence indicates that VEGFRi are preferable in the first-line setting for advanced RCC with favorable or intermediate risk [12] and most clinicians use sunitinib or pazopanib for these patients [13]. Second-line options after progression on first-line VEGFRi include alternative VEGFRi drugs [4], mTORi [8,12], nivolumab [11], and cabozantinib [9,10]. Discussions about the appropriate best choice of agents in the first- or second-line settings are commonplace in the clinic.

Currently, no known clinical or biological factors predict which type of treatment or specific agent might be optimal after the first-line setting. Previous studies have investigated parameters that emerge after initiation of first-line treatment, such as the development of toxicity [14], the duration of first-line therapy [15,16], the magnitude of the clinical response [17], and drug pharmacokinetics [18]. Pre-existing hypertension appears to be associated with better cancer outcomes for patients receiving VEGFi [19,20]. Risk models using clinical and laboratory data are prognostic but not predictive of response. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk model [21] uses six factors: anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky performance status <80%, and <1 yr from diagnosis to initiation of targeted therapy. IMDC prognostic categories are favorable (no prognostic factors), intermediate (one or two prognostic factors), and poor (three or more prognostic factors).

Failure of first-line advanced RCC VEGFi therapy unrelated to toxicity can occur as one of several clinical patterns. Cancers that show minimal or no response to therapy and continue to progress are likely to be primarily refractory to VEGFi and less likely to respond to another drug of the same class, although that remains possible. Other cancers may respond initially and then fail with a pattern of rapid progression. A catastrophic biological or genomic event has probably occurred in these cancers such that they have evolved resistance mechanisms to VEGFi. Optimal treatment for these cancers might best involve mechanisms of action other than VEGFi, such as mTORi, PD1 inhibition, or drugs that target VEGF resistance. A third group of cancers may regress or stabilize and then slowly progress, eventually passing a clinical threshold at which a decision is made to switch to a second-line agent. These cancers have demonstrated sensitivity to VEGFi and do not exhibit evidence of catastrophic failure, perhaps indicating that an alternative VEGFi might still be of value.

The IMDC prognostic risk model has also been validated in the second-line setting [22]. We hypothesized that the state of sensitivity to VEGFi at the time of commencement of second-line therapy correlates with the pattern of clinical failure; that uncontrolled growth would result in clinical deterioration; and that a surrogate for both of these processes might be observed changes from baseline in IMDC prognostic category as a reflection of the current biology of the cancer. We further hypothesized that for patients commencing second-line therapy and who have stable or improving IMDC prognostic categories, outcomes might be better if VEGFi were used; conversely, patients with worsening IMDC prognostic category might benefit by changing to a drug with a different mechanism of action, such as mTORi.

2. Patients and methods

2.1. Study population

The IMDC consists of 28 tertiary cancer centers that contribute data on patients with mRCC treated with targeted therapy. This population includes adult patients with mRCC of all histologic subtypes who received targeted therapy (VEGFi or mTORi) between April 2003 and July 2015. All individual centers received local approval from the appropriate institutional review board or research ethics board.

The database was locked for the current study in August 2015 with 4824 patients included. Of these, 2219 patients had received a secondary therapy after stopping first-line VEGFi. Prognostic category information at commencement of both first- and second-line therapy was available for 1520 patients. Four patients were excluded because the treatment start date was unknown ($n = 1$) or the patients were lost to follow-up after initiation of second-line treatment ($n = 3$). The final analysis involved 1516 patients.

2.2. Statistical analysis

The primary objective was to assess the outcomes of second-line therapy according to type of therapy and change in IMDC prognostic category from start of first-line to start of second-line therapy. Overall survival (OS) was defined as time from initiation of second-line therapy to death or censoring of patients at last follow-up. Time to treatment failure (TTF) was defined as time from initiation of second-line therapy to progression, treatment cessation, death, or censoring at last follow-up. Progression

Please cite this article in press as: Davis ID, et al. Efficacy of Second-line Targeted Therapy for Renal Cell Carcinoma According to Change from Baseline in International Metastatic Renal Cell Carcinoma Database Consortium Prognostic Category. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.09.047