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Outcomes for Patients with Metastatic Renal Cell Carcinoma Achieving a Complete Response on Targeted Therapy: A Registry-based Analysis

Tomas Buchler [a,*], ***Zbynek Bortlicek*** [b], ***Alexandr Poprach*** [c], ***Tomas Pavlik*** [b], ***Veronika Veskrnova*** [a], ***Michaela Honzirkova*** [a], ***Milada Zemanova*** [d], ***Ondrej Fiala*** [e], ***Katerina Kubackova*** [f], ***Ondrej Slaby*** [c], ***Marek Svoboda*** [c], ***Rostislav Vyzula*** [c], ***Ladislav Dusek*** [b], ***Bohuslav Melichar*** [g], ***on behalf of the Czech Renal Cancer Cooperative Group***

[a] *Department of Oncology, Thomayer Hospital and Charles University First Faculty of Medicine, Prague, Czech Republic;* [b] *Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic;* [c] *Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic;* [d] *Department of Oncology, General University Hospital and Charles University First Faculty of Medicine, Prague, Czech Republic;* [e] *Department of Oncology, University Hospital, Pilsen, Czech Republic;* [f] *Department of Oncology, Motol University Hospital and Charles University Second Faculty of Medicine, Prague, Czech Republic;* [g] *Department of Oncology, Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic*

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Abstract

Background: It is currently not known whether treatment with anti–vascular endothelial growth factor agents for metastatic renal cell carcinoma (mRCC) can be safely discontinued in patients achieving a complete response (CR).
Objective: To assess outcomes for patients with mRCC achieving CR on targeted therapy (TT) and the survival of patients discontinuing TT after CR.
Design, setting, and participants: A national registry was used to identify patients achieving CR during first-line TT using bevacizumab, sunitinib, sorafenib, or pazopanib.
Outcome measurements and statistical analysis: Relationships with outcomes were analysed using a log-rank test.
Results and limitations: A total of 100 patients achieving CR were identified out of 2803 patients. The median time to CR was 10.1 mo. Median progression-free survival (PFS) from TT initiation was 3.8 yr (95% confidence interval [CI] 2.9–4.6 yr) and the 5-yr overall survival (OS) was 80% (95% CI 70–91%). Patients discontinuing TT within 1 mo after achieving CR and those continuing TT beyond CR had similar OS (CI for difference in 2-yr post-CR OS –13% to 19%; $p = 0.3$) and PFS (CI for difference in 2-yr post-CR PFS –29% to 17%; $p = 0.7$). The limitations include the retrospective, registry-based data analysis.
Conclusions: Achievement of CR on TT for mRCC was associated with excellent long-term prognosis. No significant differences in post-CR survival were observed between patients discontinuing TT after the date of CR and those who continued on TT, although the wide CIs cannot exclude important differences between the groups.
Patient summary: According to this registry-based analysis, patients with metastatic renal cancer with no signs of disease (complete response) after treatment with targeted agents experience excellent long-term survival even if the treatment does not continue beyond the date of complete response.

* Corresponding author. Department of Oncology, Thomayer Hospital, Videnska 800, 140 59 Prague, Czech Republic. Tel. +420 2 61082637; Fax: +420 2 61082522.
E-mail address: tomas.buchler@ftn.cz (T. Buchler).

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1. Introduction

Targeted therapy is the mainstay in management of patients with metastatic renal cell carcinoma (mRCC). Current first-line options for mRCC patients with good and intermediate prognosis according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria [1] include agents directed against the vascular endothelial growth factor (VEGF) and its receptor signalling. However, mRCC is considered incurable by systemic therapy, and prolonged treatment with anti-VEGF agents, in addition to considerable costs, exposes patients to significant toxicities. There is currently no consensus on whether treatment holidays can be granted to a subpopulation of patients who achieve a complete response (CR) or long-term control of the disease on anti-VEGF therapy.

The aim of the present study was to evaluate outcomes in the population of mRCC patients who achieved CR on first-line anti-VEGF therapy in the real-world clinical setting. Specifically, continued exposure to targeted therapy after the date of CR was assessed and correlated with progression-free survival (PFS) and overall survival (OS).

2. Patients and methods

2.1. Patients and treatment

As of October 31, 2014, the total population of mRCC patients included in the RENIS registry was 2904. In total, 2803 patients were treated with first-line anti-VEGF agents (1834 with sunitinib, 594 with sorafenib, 306 with pazopanib, and 69 with bevacizumab in combination with interferon-α). Patients previously treated with cytokines were included in the present analysis, and cytokines were not considered a separate line of treatment. Only patients who reached CR during first-line targeted treatment with these four anti-VEGF agents were included in the analysis. In addition, targeted therapy had to continue at least until the date of CR to exclude patients with CR after metastasectomy following targeted treatment.

2.2. The RENIS registry

The RENIS registry was used as a data source for this retrospective analysis. The registry has been described elsewhere [2]. In brief, the RENIS registry comprises epidemiological and clinical data as well as detailed information about diagnosis, histology, staging, and treatment and its toxicity. The registry is updated twice yearly and covers approximately 95% of patients treated with targeted agents for mRCC outside of clinical trials in the Czech Republic. The registry is approved by the institutional boards of the participating institutions.

2.3. Definition of outcomes and statistical analysis

Intervals and methods for imaging evaluation were not predefined, but imaging every 3–4 mo was required by the health insurance companies for reimbursement of the treatment costs and recommended by the national guidelines. The response evaluation was performed according to RECIST 1.1 criteria, but repeated imaging was not required to confirm CR. The CR date was defined as the date of the scan first demonstrating CR.

OS was calculated from the date of CR to death due to any cause. PFS was defined as the time from date of CR to first documented relapse or death due to any cause. For patients with subsequent treatment, we also computed PFS from the date of relapse. PFS rather than time to progression was selected as one of the endpoints in accordance with the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products guidelines because most deaths in the population of patients with mRCC are expected to occur in relationship to the cancer or its treatment, and the objective of the present study was to assess a particular treatment strategy rather than activity of a drug [3,4]. Both outcome measures (OS and PFS) were estimated using the Kaplan-Meier method and all main estimates included 95% confidence intervals (CIs). Landmark analysis with 1-, 3-, and 6-mo landmarks was carried out to compare survival between patients stopping therapy for reasons other than progression or death and those continuing the treatment. Patients who relapsed, died, or were lost to follow-up during the landmark period were excluded from the comparison. The significance of differences in baseline categorical parameters between two groups was estimated using Fisher's exact test. Comparisons of survival endpoints were carried out using the log-rank test. All p values reported are two-sided, and $p < 0.05$ was considered statistically significant.

3. Results

3.1. CR is rare in mRCC treated with targeted therapy

Of 2803 patients with data for first-line VEGF-targeted therapy, 100 achieved CR as the best response to the first-line treatment. The majority of patients with CR received sunitinib ($n = 84$), while nine were treated with sorafenib, four with pazopanib, and three with bevacizumab/interferon-α. The median follow-up from first-line targeted therapy initiation was 3.3 yr. Baseline patient characteristics are listed in Table 1. The distribution of metastases at the time of targeted therapy initiation is shown in Supplementary Table 1. There were 26, nine, and 11 patients with lung-only, lymph node–only, and lung and lymph node–only metastatic disease, respectively.

3.2. Achievement of CR is associated with prolonged OS and PFS

The median time from initiation of first-line targeted therapy to CR was 10.1 mo and the number of patients with CR increased almost linearly until approximately 20 mo after treatment initiation (Supplementary Fig. 1).

CR was associated with prolonged PFS and OS. Median PFS from the initiation of targeted therapy was 3.8 yr (45.1 mo), while the median OS was not reached in the present cohort; the 5-yr OS from targeted therapy initiation was 80% (Fig. 1).

The median PFS from the CR date for the whole cohort was 2.3 yr (95% CI 1.2–3.3), with 5-yr OS of 71% (95% CI 53–89%; Fig. 2). The time to CR was not associated with subsequent PFS ($p = 0.9$).

There were 36 patients who had been treated with cytokines prior to receiving targeted therapy, including five receiving cytokines as adjuvant therapy and 31 treated for advanced or metastatic disease. OS and the time to CR were not associated with previous cytokine therapy ($p = 0.7$ and $p = 0.4$, respectively).

By the data cutoff, 15 patients had died. In all cases the cause of death was specified as cancer-related and had been preceded by detection of disease relapse.