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Categories of response to first line vascular endothelial growth factor receptor targeted therapy and overall survival in patients with metastatic renal cell carcinoma

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KEYWORDS
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Abstract ***Introduction:*** Sequential use of targeted therapy (TT) has improved overall survival (OS) of patients with metastatic renal cell carcinoma (mRCC). The value of objective response (OR) as compared to stable disease (SD) is unclear. We aimed to investigate OR of first-line TT and its impact on OS.

Material and methods: Retrospective analysis of OS among 331 mRCC patients with a first-line assessment according to RECIST 1.0. Characteristics between objective responders (complete response [CR] or partial remission [PR]), patients with SD and non-responders (progressive disease [PD] and toxicity [Tox]) were compared with the Chi-square test and the Kruskal–Wallis test. Kaplan–Meier analysis of OS and progression-free survival (PFS). Cox model analysis of Predictors of OS .

Results: Best response was CR, PR, SD, PD and Tox in 9 (2.7%), 61 (18.4%), 167 (50.5%), 80 (24.2%) and 14 (4.2%) patients respectively resulting in an OR rate of 21%. Median OS in months: CR 63.2; PR 37.6; SD 35.9; PD 14.6; TOX 22.5 ($p < 0.0001$). Median PFS for responders was 14.8, 11.5 for patients with SD and 2.5 for non-responders ($p < 0.0001$). Similarly median OS was 38.7, 35.9 and 15.5 ($p < 0.00001$). Primary resistance and a first-line PFS <6 months were the strongest independent predictors of OS. The achievement of OR as compared to SD did not impact OS.

Conclusions: In our cohort of unselected patients OR was not associated with superior OS as compared to SD.

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1. Introduction

The sequential use of vascular endothelial growth factor (VEGF)-receptor targeted therapy (TT) has improved the overall survival (OS) of patients with metastatic renal cell carcinoma (mRCC) compared to the era of cytokine therapy. The receptor tyrosine kinase inhibitor (rTKI) Sunitinib (Sun) is the most common first-line treatment [1–3]. Pazopanib (Paz), bevacizumab in combination with interferon (Bev) and Tivozanib proved to be alternative treatment options [4–6]. Inevitably the majority of patients develops treatment resistance and requires further sequential therapy treated with VEGF inhibitors (VEGFi) or mTOR inhibitors [7,8].

The value of objective response (OR) on OS of mRCC patients as compared to disease stabilization under first-line TT is unclear. Previous studies have investigated the role of first line progression-free survival (PFS) or response to first line treatment in smaller subsets of patients or were limited to certain TT substances [9,10]. One of the largest studies investigated the association of OS and tumour response in a subset of 468 patients undergoing phase-I-trials [11]. This study demonstrated an almost linear association between change in tumour size and survival questioning the concept of categorical response evaluation. Another study in a large cohort of 1065 patients treated with Sun within clinical trials clearly showed an association of objective response and an improved OS [12].

The aim of our study was to investigate the OR of first-line TT and its impact on OS in a large academic cohort of unselected mRCC patients.

2. Material and methods

2.1. Patients' selection

We retrospectively reviewed mRCC patients treated with at least one first line TT substance at two large academic centres between 2005 and 2012. All patients with a measurable first-line response according to standard Response Evaluation Criteria in Solid Tumours (RECIST v.1.0) [13] were included. Sun, Sorafenib (Sor), Bev, Temsirolimus (Tem), Everolimus (Ev) and other TTs such as Paz, Lapatinib or Axitinib were allowed. These substances were applied according to the approval status, within a clinical trial or as compassionate use.

Immunotherapy was the only therapy allowed prior to first TT treatment. Sun was administered daily as 50 mg orally over 4 weeks followed by a 2-week washout period. Stepwise dose reductions by 12.5 mg. Sor was administered continuously at a full dose of 400 mg orally twice a day with allowed dose reduction by 200 mg. Dosing for EV was 10 mg daily (dose reductions to 5 mg daily) and 25 mg weekly for Tem. All other first or subsequent sequence therapy agents were given in standard doses with standard dose reductions allowed in the case of toxicity or according to clinical trial protocols. All agents were given until progression, death, or intolerable toxicity. Response assessment by computed tomography or magnetic resonance imaging scans was performed every 8–12 weeks. Toxicity was graded according to the Common Toxicity Criteria for Adverse Events (CTCAE v.4.0).

2.2. Statistics

Characteristics between objective responders (complete response [CR] or partial remission [PR]), patients with stable disease [SD] and non-responders (progressive disease [PD] and toxicity [Tox]) were compared with the chi-square test and the Kruskal–Wallis test. Main characteristics were age, gender, Memorial Sloan-Kettering Cancer Centre (MSKCC) criteria according to Motzer et al. [14] and Eastern Cooperative Oncology Group performance group. PFS and OS were estimated using the Kaplan–Meier method. Cox proportional hazards models were applied to explore predictors of inferior OS/risk of death in univariate- and multivariable-adjusted analyses. Predictors of OS were further tested in stratified Kaplan–Meier analyses whenever appropriate. All statistical calculations were performed using SPSS v.20 (IBM Corp., Somers, NY, USA) considering a p value <0.05 statistically significant.

3. Results

3.1. Patients' characteristics

A total of 21 patients were excluded from analysis because of no measurable disease, and 139 patients (42%) were treated within clinical trials during their targeted (sequence) therapy. Finally, a total of 331 patients with a measurable response to first TT were included in the study. Of these 70 patients were categorised as responders, 167 had a SD and 94 patients were non-responders with PD or Tox. Overall 90.1% of patients underwent nephrectomy before TT. Table 1 depicts the main patients' characteristics of the study population by response group. SD patients were older with a median age of 65.3 years (interquartile range [IQR]: 55.3–71.1) versus 61.8 years (IQR: 54.6–67.3) and 60.4 years (IQR: 54.1–69.1) for responders and non-responders $p = 0.032$). Non-responders more often fell into the poor prognosis category according to MSKCC (13.8% versus 4.3% and 1.8%; $p = 0.002$), and more often had a death (DIT)- or toxicity-induced termination (TIT) of first line treatment compared to responders and SD (DIT: 6.4% versus 0% and 0% $p = 0.001$; TIT: 23.4% versus 10.0% and 10.8% $p = 0.048$ respectively). Responders underwent