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Efficacy of targeted therapies after PD-1/PD-L1 blockade in metastatic renal cell carcinoma

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Abstract ***Background:*** Monoclonal antibodies that target the programmed death-1 (PD-1)/programmed death-ligand 1(PD-L1) pathway have shown antitumour activity in metastatic renal cell carcinoma (mRCC) and are currently being developed in first-line (in combination) and in previously treated patients. The efficacy targeted therapy (TT) after PD-1/PD-L1 blockade is still unknown.
Methods: Medical records of mRCC patients treated with investigational PD-1 or PD-L1 inhibitors at 4 academic institutions were reviewed. Patients who received subsequent treatment with TT were selected to collect outcome measures of subsequent TT.
Results: Of 99 patients who received PD-1/PD-L1 blockade as part of clinical trials, 56 patients have received subsequent therapy: 44 patients received vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) inhibitors and 12 received mammalian target of rapamycin (mTOR) inhibitors as first subsequent TT. Median

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follow up, from the start of subsequent TT was 16.1 months (range: 0.2, 30.6 months). TT post PD-1/PD-L1 blockade was administered as second-line, third-line or beyond third-line in 9 (16%), 24 (43%) and 23 patients (41%) respectively. Median time to treatment failure on subsequent TT was 6.6 months (range: 0.2+, 23.0). 1-year and 2 year overall survival from the initiation of subsequent TT was 58% (95% confidence interval (CI): 41–72%) and 36% (95% CI: 18–54%), respectively.

Conclusion: Both VEGF/VEGFR and mTOR inhibitors demonstrate antitumour activity following PD-1/PD-L1 blockade.

1. Introduction

Metastatic renal cell carcinoma (mRCC) accounts for 16,000 deaths in the United States and 37,000 in the European Union in the year of 2015 [1]. Overall, seven targeted therapies have been approved since 2005 and include agents targeting the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, four VEGF receptor tyrosine kinase inhibitors (VEGFR TKI) namely sunitinib, sorafenib, pazopanib and axitinib, and finally, two inhibitors of the mammalian target of rapamycin (mTOR): everolimus and temsirolimus. Efforts to improve patient outcome through combination therapy with approved agents have failed to extend overall survival (OS) [2].

An improved understanding of the immune response to cancer has led to the development of monoclonal antibodies that block immune checkpoints (e.g. CTLA-4 and PD-1). These agents have been shown to restore and enhance the antitumour immune response and have produced promising results in many tumours including mRCC [3,4]. The activity signals of PD-1/PD-L1 inhibitors in mRCC have been reported in phase I and II studies for nivolumab (Bristol-Myers Squibb Company, Princeton, NJ) and MPDL3280A (Genentech, South San Francisco, CA) [5–13]. NCT01668784 recently showed an overall survival benefit for nivolumab over everolimus in patients in the VEGF-refractory setting. In the first line setting, MPDL3280A is being combined with bevacizumab (NCT01984242).

Despite the encouraging results seen in these phase I/II trials of immune checkpoint blockers including response rate in the range of 10–36% [6,10,12,13] and intriguing median overall survival ranging from 18.2 to 25.5 months in the different cohorts of the largest phase II with nivolumab in previously treated patients, it is expected that many patients will require additional systemic therapy after PD-1/PD-L1 pathway blockade. Subsequent therapies are likely to be de facto the 'available' targeted agent that has not been yet used. Whether these changes will impact the efficacy of subsequent therapies including VEGFR TKI or mTOR inhibitors is still unknown. The objective of this work is to assess the efficacy of targeted therapies after PD-1/PD-L1 blockade in patients with mRCC.

2. Patients and methods

2.1. Study population

Ninety-nine mRCC patients enrolled in clinical trials of PD-1 or PD-L1 inhibitors at four institutions (Dana Farber Cancer Center, Boston; Institut Gustave Roussy, Villejuif; Beth Israel Deaconess Medical Center, Boston; and Tom Baker Cancer Center, Calgary) were retrospectively collected. Fifty-six patients who received subsequent treatment with targeted therapies at the same institutions were included in this study.

Baseline patient characteristics including demographic, pathological and prognosis classification according to the International Metastatic RCC Database Consortium (IMDC) criteria [14] were retrospectively collected from medical records. Outcome measures were also retrieved from medical chart reviews including time to treatment failure (TTF), investigator-assessed best response (RECIST 1.1) and OS.

All centres obtained local institutional review board approval before data collection in this retrospective study. Uniform data templates were used to ensure consistent data collection at each institution. Patients may have received subsequent targeted therapy as part of clinical trials or with the standard of care according to national cancer guidelines.

2.2. Statistical analysis

The primary objective of this study was to characterise clinical outcomes (TTF and OS) of mRCC patients treated with targeted therapies after progression on PD-1/PD-L1 inhibitors. TTF was defined as the time period between treatment initiation and drug cessation due to progression, toxicity, patient refusal, death, or censored at last follow-up. OS was defined as the time period between the start of the first subsequent targeted therapy initiation and date of death, or censored at last follow-up. Distributions of TTF and OS were estimated using the Kaplan Meier methodology; 1- and 2-year OS