Research Report

Targeted Therapies Following First-Line Immune Checkpoint Inhibitor Combination in Metastatic Renal Cell Carcinoma: A Single Center Experience

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Abstract.

Background: Both late and early phase immune checkpoint inhibitor (CPI) combination trials indicate an impending role of combinations in the first-line treatment of metastatic renal cell carcinoma (mRCC). Sequencing the options following failure of CPI combinations is an emerging conundrum.

Objective: To present our single-center clinical experience with targeted therapies (TT) following first-line CPI combinations.

Methods: mRCC patients who received TT following failure of a combination regimen with CPI were identified from an institutional database. Clinical information including tumor characteristics, survival outcomes, and adverse events was retrieved from medical records. Descriptive statistics and Kaplan-Meier survival functions were performed.

Results: Of 11 patients identified, median age was 63 (31–79) and 8 (73%) patients were male. First-line treatment was a CPI and TT combination in 7 (64%) patients while the rest received combination of two CPIs. The majority of patients (82%) were intermediate risk category at the initiation of targeted therapies. TTs utilized included cabozantinib (46%), lenvatinib and everolimus (27%), sunitinib (18%), and temsirolimus (9%). Best response was stable disease for 10 (91%) and partial response for 1 (9%) patient. In a median follow up of 9.1 months (range, 4.9–34.1), median progression free survival was 7.7 (95% CI 4.6–10.8) months. Progression has occurred in 7 patients, and 3 patients remain on treatment. One patient discontinued treatment due to toxicity.

Conclusions: In our report, TTs demonstrate effective disease control and safety. Further exploration in prospective setting is warranted.

Keywords: Targeted therapy, immunotherapy, renal cell carcinoma, checkpoint inhibitor

INTRODUCTION

Renal cell carcinoma is the seventh most common solid cancer type worldwide. Approximately 15000 cancer related deaths occur due to renal cell carcinoma each year [1]. Within the last 15 years, dynamic advances in cancer research led to an expansion of the treatment armamentarium for metastatic

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renal cell carcinoma (mRCC) [2]. Previously, the only evidence based treatment approach was conventional immunotherapy that included interleukin-2 and interferon alfa. Immune activation was effective in a small subset of patients [3]. Targeted therapies (TT) acting via vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) pathway blockade were first introduced, with VEGF-inhibitors doubling the progression free survival (PFS) over existing standards [4].

Recently, immunotherapy has been established as a standard in this disease [2]. Nivolumab, a programmed death-1 (PD-1) inhibitor, was the first CPI with activity in second-line treatment following TTs [5]. Perhaps the most groundbreaking advance was the results of the CheckMate214 study where the efficacy of nivolumab and ipilimumab was compared to sunitinib in first-line treatment of intermediate and poor risk patients. The combination demonstrated an absolute overall survival (OS) benefit over sunitinib [6]. Furthermore, patient reported outcomes were recently published confirming the better tolerability of the combination CPI over sunitinib [7].

Efficacy of the two different strategies led to the investigation of combined approaches in order to foster efficacy and tolerability. To date, two phase 3 studies were published comparing CPI and TT combination with sunitinib in first-line setting. Firstly, the Immotion151 study met the primary endpoint of PFS with combination of bevacizumab, a VEGF receptor inhibitor and atezolizumab, a programmed cell death-ligand 1 (PD-L1) directed checkpoint inhibitor (CPI), over sunitinib [8]. Subsequently, in the Javelin Renal 101 study, axitinib, a VEGF-TKI and avelumab, a PD-L1 directed CPI combination demonstrated PFS benefit over sunitinib across patients from all risk categories [9]. More recently, the results of Keynote-426 trial were positive, with the PD-1 inhibitor pembrolizumab and axitinib in combination showing a superior PFS, OS and response rate compared to sunitinib [10]. Several other early phase studies employing the combined CPI and TT approach have shown promise [11–13].

Considering the efficacy of combined approaches, another shift in treatment algorithm for mRCC is anticipated. However, the sequencing strategies after failure of first-line combinations have not been examined prospectively. Therefore, the question regarding how to juxtapose several available treatment options has been emerging in clinical practice. We conducted a retrospective analysis to examine outcomes with second-line targeted therapies following treatment failure with a combination of two CPIs or a CPI and TT in patients with mRCC.

MATERIALS AND METHODS

Patient selection and data collection

Patients who received first-line combination treatment with immune checkpoint inhibitor for treatment of metastatic renal cell carcinoma at the City of Hope Comprehensive Cancer Center Medical Oncology department between April 2014 and January 2019 were retrospectively identified using an institutional database. Those who were treated with a second-line TT following the CPI combination were included in the final analysis. Patient characteristics in first and second-line treatment initiation, response to treatment, survival and adverse event information were retrieved from the medical records.

This retrospective study was approved by the Institutional Review Board of the City of Hope Comprehensive Cancer Center. Confidentiality of study subjects was protected in compliance with the regulations of Health Insurance Portability and Accountability Act.

Statistical analyses

The International mRCC Database Consortium (IMDC) model was utilized for first and second-line prognostic risk calculation and categorization of patients. Response to treatment was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Median, range and standard deviation were calculated using descriptive statistics. PFS and OS with 95% confidence interval were evaluated by Kaplan-Meier survival function. All analyses were performed using SPSS software 23 (IBM SPSS Statistics for Mac, version 23.0, Armonk, NY: IBM Corp).

RESULTS

Patient characteristics in first-line

In total, 11 patients received second-line TT following first-line CPI combination. Median age at the time of the first-line treatment initiation was 63 (range, 31–79), and 73% of participants were male. The majority of patients, 7 (64%), were in an intermediate prognostic risk category while there were two patients in favorable and poor prognostic groups

each. First-line treatment was CPI and TT combination in 7 patients; CPI and CPI combination in four patients. The entire cohort received first-line CPI combination by means of clinical trial enrollment. First-line CPI resulted in disease control in 6 (54%) patients in contrast to the 5 (46%) patients whose best response was progressive disease. Median duration of CPI combination was 2.76 months (range, 5.0–49.9). Two patients discontinued first-line treatment due to immune related toxicities (nephropathy and myasthenia gravis, respectively). The remaining 9 patients had progression of their disease that resulted in transition to second-line targeted treatment (Table 1).

Patient characteristics in second-line

At the time of second-line targeted treatment initiation, 9 (82%) patients were in an intermediate risk category and there was one patient in favorable and poor risk categories each. The median interval between first-line treatment discontinuation and second-line initiation was 23 days (range, 0–80

Table 1
Patient and tumor characteristics during first-line treatment with checkpoint inhibitor combination

	N = 11 (%)
Age, median (range)	63 (31–79)
Gender	
Female	3 (27%)
Male	8 (73%)
Stage at the time of diagnosis	
Stage I–III	4 (36%)
Stage IV	7 (64%)
Nephrectomy	
Yes	9 (82%)
First-line prognostic group (IMDC)	
Favorable	2 (18%)
Intermediate	7 (64%)
Poor	2 (18%)
First-line treatment	
CPI + TT	7 (64%)
CPI + CPI	4 (36%)
Best response to first-line treatment	
Partial response	2 (18%)
Stable disease	4 (36%)
Progressive disease	5 (46%)
Duration of treatment with first-line CPI treatment	
Median (range) (in months)	2.8 (1.3–25.9)
Reason to stop first-line treatment	
Progression	9 (82%)
Toxicity	2 (18%)
CPI: Checkpoint inhibitor, TT: Targeted therapy	

Table 2
Patient and tumor characteristics during second-line targeted therapy

	N = 11 (%)
Second-line prognostic group (IMDC)	
Favorable	1 (9%)
Intermediate	9 (82%)
Poor	1 (9%)
Second-line treatment	
Cabozantinib	5 (46%)
Lenvatinib + everolimus	3 (27%)
Sunitinib	2 (18%)
Temsirolimus	1 (9%)
Site of metastasis, second-line	
Lung	9 (82%)
Lymph node	6 (55%)
Bone	3 (27%)
Soft tissue	3 (27%)
Liver	1 (9%)
Pleura	1 (9%)
Pancreas	1 (9%)
Peritoneum	1 (9%)
Skin	1 (9%)
Adrenal	1 (9%)

days). Five patients received cabozantinib, 3 patients received lenvatinib and everolimus combination, 2 patients received sunitinib and 1 patient received temsirolimus. Most frequent metastatic sites at the second-line treatment initiation were lung, lymph node, bone and soft tissue, present in 9 (82%), 6 (55%), 3 (27%) and 3 (27%) patients, respectively (Table 2).

Clinical outcome

Starting with the initiation of the first-line TT, median follow-up was 9.1 months (range, 4.9–34.1). At the time point of the data cut off, each patient had at least one response evaluation. Median time to treatment response was 2.6 months, ranging between 1.2 and 4.2 months. The majority of the population, 10 (91%) had stable disease as their best response to treatment. One patient demonstrated partial response 7 weeks after initiation of cabozantinib. No complete responses were observed within the cohort. At the data cut off three patients were still on second-line TT. The remaining 8 (73%) patients discontinued the treatment; seven due to progression of the disease and one due to toxicity (Grade 3 mucositis and fatigue). Median PFS with the second-line targeted therapies was 7.7 months (95% CI, 4.6–10.8) (Table 3). A swimmer plot of the included patients and PFS function can be appreciated in Figs. 1 and 2 respectively.
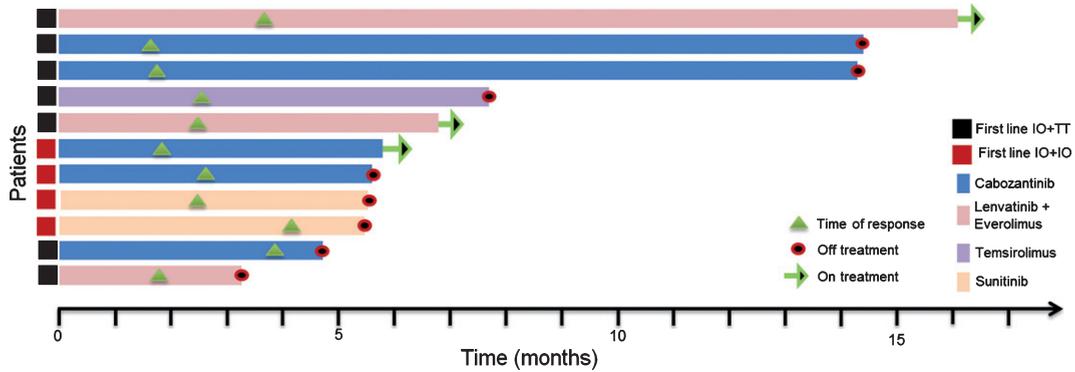
Fig. 1. Swimmers plot for the response evaluable patients.
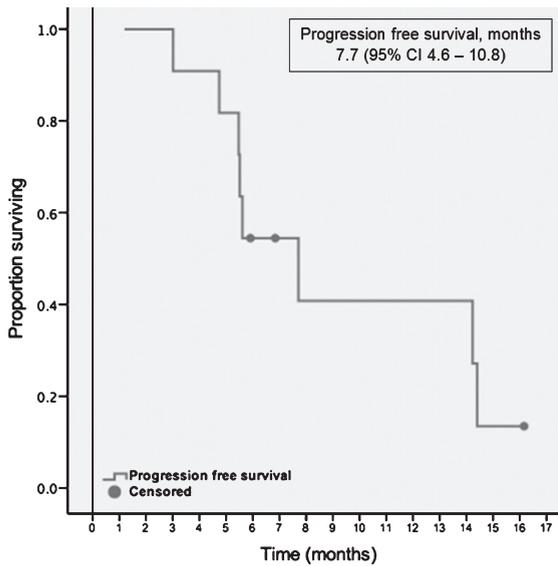
Fig. 2. Progression free survival with second-line targeted therapies.
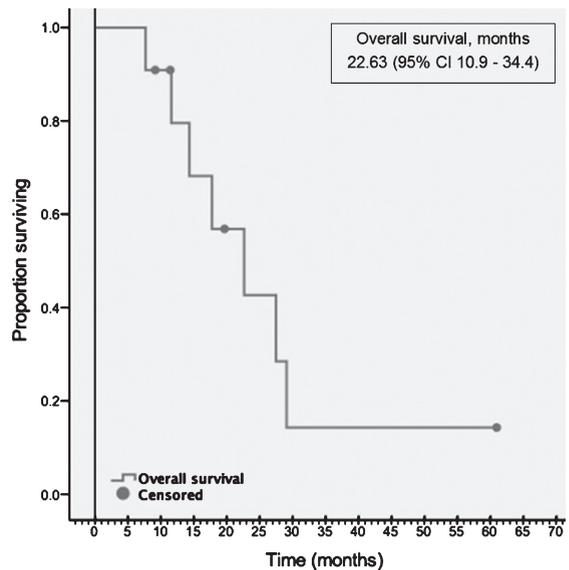
Fig. 3. Overall survival.

Following second-line TT, 4 patients received one more line of subsequent TT. One patient received one line of TT and one line of CPI subsequently. At the data cut off, 4 (36%) patients were alive, and OS was 22.6 months (10.9–34.4) (Fig. 3).

Adverse events

During the second-line treatment with targeted therapies, 6 (54%) of patients experienced adverse events. The most commonly observed adverse events were fatigue, stomatitis, hand food syndrome, and diarrhea. Three (27%) patients had grade 3 adverse events. Grade 3 adverse events in two patients were managed with dose reduction but not resulted in treatment discontinuation. One patient experienced grade 3 mucositis and fatigue with the lenvatinib and everolimus combination that resulted in treatment discontinuation (Table 4).

DISCUSSION

Our results demonstrate that mRCC patients benefited from TT at the second-line setting after exposure to a CPI in combination with a CPI or a TT; specifically, disease control was achieved in the entire cohort. However, the overall response rate was 9%. Despite the high disease control rate, responses were not durable and disease progression had eventually occurred resulting in a PFS of 7.7 months this appears similar to the PFS in second-line historical trials of TTs used in our dataset [14–16]. The safety

Table 3
Response to second-line targeted therapy and survival

	N = 11 (%)
Best response to second-line treatment	
Response evaluable	11 (100%)
Stable disease	10 (91%)
Partial response	1 (9%)
Complete response	0
Progressive disease	0
Objective response rate	9%
Disease control rate	100%
Progression free survival, months	7.7 (95% CI 4.6–10.8)
Second-line treatment stopped	8 (73%)
Reason to stop second treatment	
Progression	7 (88%)
Toxicity	1 (12%)
Overall Survival, months	22.7 (95% CI 10.9–34.3)

Table 4
Side effect profile of targeted therapies in second-line setting

	Total N (%)	Grade 1-2 N (%)	Grade 3-4 N (%)
All	6 (54%)	5 (45%)	3 (27%)
Fatigue	5 (45%)	5 (45%)	1 (9%)
Stomatitis	3 (27%)	2 (18%)	1 (9%)
Hand foot syndrome	2 (18%)	1 (9%)	1 (9%)
Diarrhea	2 (18%)	2 (18%)	–
Nausea - vomiting	1 (9%)	1 (9%)	–
Cytopenia	1 (9%)	–	1 (9%)
Hypertension	1 (9%)	–	1 (9%)

profile was overall similar to previous studies with targeted therapies. Unexpected toxicities were not encountered. The majority of the adverse events were manageable and only one patient required treatment discontinuation due to toxicity.

To date, a number of reports aiming to examine the effect of second-line targeted therapies after CPIs have been presented or published. Two included patients who received CPI and TT combination in first-line [17, 18]. Barata et al. reported outcomes of 41 patients who progressed on nivolumab/ipilimumab, axitinib/avelumab or bevacizumab/atezolizumab [17]. First subsequent TT was cabozantinib, axitinib, pazopanib or sunitinib. Objective response rate was 29%, and disease control rate was 83%. Median PFS was 6.4 months. No difference in PFS was seen in patients received first-line dual CPI versus VEGF-TKI plus CPI. Characteristics and survival outcomes were comparable to the present study.

A similar analysis was conducted at the MD Anderson Cancer Center. Shah et al. reported their experience with VEGF-TKIs following progression on nivolumab alone or in combination with ipili-

mumab or bevacizumab [18]. In total, 43 patients who were treated with pazopanib, axitinib or cabozantinib were included. Objective response rate was 43% with one complete response. The rest of the cohort responded to treatment with stable disease as their best response, resulting in a disease control rate of 100%. Median PFS was 10 months, which is the longest among other studies reported to date.

Outcomes with second-line VEGF-TKIs after nivolumab/ipilimumab failure in CheckMate214 was more recently published, using data from 12 participating institutions [19]. VEGF-TKIs used included sunitinib, axitinib, pazopanib or cabozantinib. Objective response rate was 36%, and stable disease was the best response in 39% of patients. Median PFS was 8 months. PFS did not differ for first generation versus second generation TKIs (namely, sunitinib and pazopanib versus axitinib and cabozantinib).

Few studies have investigated the role of individual targeted therapies in the post-CPI setting. Ornstein et al. prospectively studied axitinib in an individualized dose titration schema and reported favorable tolerability and anti-tumor activity with an ORR of 38.7% and median PFS of 9.2 months [20]. A retrospective analysis of 69 patients who received cabozantinib at second or further lines following progression on a CPI-containing regimen yielded evidence of the safety and activity of cabozantinib [21].

In comparison to the other cited experiences, our study has a lower response rate, but the clinical benefit rate remains at 100%. Differing outcomes from these studies could be secondary to biologic characteristics. Recent data indicates that patients bearing *PBRM1* alteration, for instance, may have particular sensitivity to CPI [22]. In contrast, mutations in *TSC1/2* and *MTOR* have been well documented to confer sensitivity to mTOR inhibitors [23]. More recently, molecular signatures have been identified in the Immotion150 trial, for instance, an angiogenic signature was deciphered that identified patients with selective benefit from angiogenesis inhibition as opposed to CPI therapy [24]. Although the effect of genomic characteristics on treatment response has been exclusively studied in the front line setting, a similar association can be anticipated throughout the disease course. In these relatively small cohorts, biologic differences could drive variations in clinical outcome.

Several limitations to this report should be acknowledged. The study was retrospective with a small sample size. Furthermore, the limited follow-up may challenge our estimates of PFS and potentially underestimate latent responses. Despite these

limitations, the clinical relevance of the question encouraged us to present our experience.

In conclusion, our data indicates that second-line targeted therapies in patients who progressed on CPI combinations appear to be safe and efficacious. Varying response rates and PFS estimates between existing studies can also be attributed to heterogeneous treatment types used. In an effort to address these important questions, prospective studies with larger patient cohorts are needed.

ACKNOWLEDGMENTS

None.

DISCLOSURES

Authors have no conflict of interest to report.

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