Original Article

Pazopanib together with 6–8 cycles of sintilimab followed by single use of pazopanib in the second-line treatment of advanced renal cell carcinoma

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Background: The aim of the study was to investigate the temporary combination of anti-PD-1 plus targeted therapy followed by single targeted therapy in advanced renal cell carcinoma (RCC) as second-line therapy.

Methods: A total of 17 patients from Fudan University Shanghai Cancer Center (FUSCC) with advanced clear cell RCC were enrolled. They were treated with sunitinib (50 mg/day; 2 weeks on and 1 weeks off) as first-line therapy. After progression of the disease, sintilimab (200 mg iv/q3w) in combination with pazopanib (800 mg/day) were used. After 6–8 cycles of immunotherapy, patients were treated with pazopanib only. Cox proportional hazards models was used to evaluate the risk factors.

Results: Three patients reached partial response (PR) after second-line treatment, while 12 patients remained stable. Two patients had progressive disease and 1 of them died due to disease progression. The median progression-free survival (PFS) for second-line therapy was 12.2 months. Cox analysis revealed that IMDC score (HR: 0.041, P=0.01) was the only factor that was correlated with progression free survival.

Conclusions: Tyrosine kinase inhibitors (TKIs), together with 6–8 cycles of immune checkpoint inhibitor (ICI) agents followed by the single use of a TKI, are a feasible way to treat metastatic clear cell RCC (ccRCC) patients as second-line treatment.

Keywords: Immune checkpoint inhibitors (ICIs); renal cell carcinoma (RCC); tyrosine kinase inhibitors (TKIs); pazopanib; sintilimab

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Introduction

Renal cell carcinoma (RCC) is common in urological cancer. It accounts for about 3–5% of all newly diagnosed cancers (1). Every year, approximately 403,262 patients with RCC are diagnosed and 175,098 patients die of the disease. Among them, 30% of patients were diagnosed with advanced or metastatic disease, and 20–40% of patients with RCC had metastasis even after nephrectomy. It is estimated that their 5-year survival is only 10% (1,2). Among the histological subtypes, 75% of cases present with clear cell (cc) histology, which is the best studied subtype of RCC (3).

Over the past 20 years, there have been significant changes in the treatment of patients with RCC (4). Before the arrival of immunotherapeutic agents which target the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis, the VEGF receptor tyrosine kinase

Table 1 Patient characteristics

Characteristics	Values
No.	17
Median age, years	62
Gender, n (%)	
Male	16 (94.1)
Female	1 (5.9)
Metastatic site, n	
Lung	12
Bone	5
Lymph nodes	3
Liver	1
Others	3
IMDC, n (%)	
Favorable	2 (11.8)
Intermediate	13 (76.5)
Poor	2 (11.7)
Surgery, n (%)	
Yes	7 (41.2)
No	10 (58.8)
PFS1	10.2 months
PFS2	12.2 months

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PFS, progression-free survival; PFS1, time from the use of sunitinib to disease progression; PFS2, time from the use of second-line therapy to disease progression.

inhibitors (TKIs) were widely used (2). In recent studies, anti-PD-1/PD-L1 combined with targeted therapy have been proven to be effective in advanced RCC patients. In the KEYNOTE-426 study, the overall survival (OS) and progression-free survival (PFS) of pembrolizumab combined with axitinib were significantly longer than those of sunitinib, and the objective response rate was also higher (5).

Sintilimab is an anti-PD-1 antibody independently developed in China. It binds to PD-1 and blocks the binding and interaction between PD-1 and its ligands (PD-L1 and PD-L2), thus restoring the endogenous anti-tumor T cell response. It is used in various solid tumors in China (6). Pazopanib is a TKI that is broadly used in the first-line treatment of advanced RCC. It shows non-inferiority to sunitinib with respect to PFS (7).

However, combination therapy with anti-PD-1/PD-L1 plus targeted therapy greatly increases the financial burden of patients, despite the increase in adverse events. The long-term use of both anti-PD-1/PD-L1 and targeted therapy seems impossible for families with low salaries. From this perspective, we aimed to find a more cost-effective way to treat advanced RCC patients with a temporary combination of anti-PD-1/PD-L1 plus targeted therapy followed by single targeted therapy.

We present the following article in accordance with the STROBE reporting checklist (available at: http://dx.doi.org/10.21037/tau-21-338).

Methods

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Fudan University Shanghai Cancer Center (FUSCC) Ethical Committee (No. 050432-4-1911D). Written informed consent from each patient was obtained. We retrospectively reviewed patients with advanced RCC treated with anti-PD-1/PD-L1 and targeted therapy from FUSCC. The sites of metastases were confirmed by an experienced radiologist using whole body enhanced CT or MRI. Clinicopathological characteristics including age, gender, metastatic sites, and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group were obtained from electronic records (*Table 1*). IMDC risk score was determined by the following 6 risk factors that were present: time from initial diagnosis to randomization of less than 1 year, Karnofsky performance status score of less than 80, hemoglobin levels below the lower limit of the normal range, platelet count above the upper limit of the normal range, absolute neutrophil count above the upper limit of the normal range, and corrected serum calcium level above the upper limit of the normal range (8). The patients were followed up every 3 months by telephone or outpatient follow-up. Blood tests of complete blood count, liver and kidney function and thyroid function were performed once a month to monitor adverse events. Tumor recurrence, progression, metastasis, and death were recorded.

Statistical analysis

OS was defined as the period from the date of diagnosis to the date of death or the last follow-up. PFS referred to

Table 2 The overall response rates

Best overall response	No. (%)
CR	0 (0)
PR	3 (17.6)
SD	12 (70.6)
PD	2 (11.8)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3 Total adverse events

Adverse events	Grade 1–2	Grade 3	Total
Nausea	4	0	4
Liver dysfunction	3	0	3
Diarrhea	2	1	3
Hand-foot syndrome	2	0	2
Fever	2	0	2
Hypothyroidism	2	0	2
Hypertension	1	1	2
Interstitial pneumonia	1	0	1

the time from the beginning of treatment to recurrence or metastasis of the disease. Cox proportional hazards models was used to calculate adjusted hazard ratio (HR) with 95% confidence intervals (95% CIs). The above data were analyzed by SPSS 20 software.

Results

Patient characteristics

We retrospectively analyzed the clinical data of 17 patients with metastatic clear cell RCC (ccRCC) who were treated with sunitinib (50 mg/day; 2 weeks on and 1 weeks off) as first-line therapy. After progression of the disease, all patients were treated with sintilimab (200 mg iv/q3w) in combination with pazopanib (800 mg/day). After 6–8 cycles of immunotherapy, the patients were treated with pazopanib only.

The median age of the patients was 62 years old. The median (range) duration of follow-up for all patients was 24.1 months (13.2–56.0 months). Among them, 16 were male, and 7 patients went through nephrectomy before the use of sunitinib. IMDC scores and metastatic sites are listed in *Table 1*.

PFS for both first-line and second-line therapy

For first line use of sunitinib, the median PFS was 10.2 months (95% CI, 3.9 to 16.5 months). For second-line use of sintilimab with pazopanib, the median OS and PFS were not reached. Three patients reached partial response (PR) after second-line treatment, while 12 patients remained stable. Two patients had progressive disease and 1 of them died due to disease progression (*Table 2*). The median PFS for second-line therapy was 12.2 months (95% CI, 8.9 to 15.5 months).

Adverse events

No single all-cause adverse events (AE) of grade 4/5 occurred. The most common AE (*Table 3*) was nausea (grade 1–2: 4 cases), followed by liver dysfunction (grade 1–2: 3 cases), diarrhea (grade 1–2: 2 cases; grade 3: 1 case), hand-foot syndrome (grade 1–2: 2 cases), fever (grade 1–2: 2 cases), hypothyroidism (grade 1–2: 2 cases), hypertension (grade 2: 1 case; grade 3: 1 case), and interstitial pneumonia (grade 1: 1 case).

Relative factors that affect success of the combination treatment plan

In univariate Cox proportion hazard ratio analysis, IMDC score (HR: 0.041, P=0.01), and the history of renal surgery (HR: 4.102, P=0.018) were significantly correlated with prognosis. A reduced model was used in multivariate cox proportion hazard ratio analysis. Variables that were insignificant in univariate analysis were excluded in the multivariate analysis. The results indicated that IMDC score (HR: 0.041, P=0.01) was the only factor that was correlated with progression free survival (*Table 4*).

Discussion

The new data provided by immune checkpoint inhibitor (ICI) agents and new combination strategies represent a revolution in RCC management, which will lead to an evolving scenario and may further influence clinical decision-making.

A total of 861 previously untreated patients with metastatic ccRCC were randomly selected in the KEYNOTE-426 study. Patients were treated with

Table 4 Univariate and multivariate analyses to predict progression free survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender	0.867 (0.111–6.793)	0.892	–	–
Male				
Female				
Age (years)	1.006 (0.960–1.553)	0.807	–	–
IMDC	0.041 (0.004–0.468)	0.01	0.077 (0.007–0.914)	0.042
Low risk				
Intermediate risk				
High risk				
Metastatic sites			–	–
Lung	1.897 (0.626–5.752)	0.258	–	–
Bone	2.359 (0.797–6.981)	0.121	–	–
Lymph nodes	1.150 (0.317–4.176)	0.832	–	–
Others	0.996 (0.271–3.661)	0.995	–	–
Surgery	4.102 (1.270–13.248)	0.018	3.327 (0.948–11.667)	0.061
Yes				
No				

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; HR, hazards ratio; CI, confidence interval.

pembrolizumab plus axitinib or sunitinib. Compared with sunitinib, the combined treatment reduced the risk of death by 47%. The median PFS in the combination group was 15.1 months, which was significantly longer than 11.1 months in the sunitinib group (HR 0.69, 95% CI, 0.57–0.84, P<0.001). ORR in the combined treatment group was higher than that in the control group [59.3% (95% CI, 54.5–63.9) *vs.* 35.7% (95% CI, 31.1–40.4), P<0.001] (5).

In the JAVELIN Renal 101 study, 886 patients with previously untreated advanced RCC were enrolled. The study evaluated the efficacy of avelumab plus axitinib or sunitinib alone. In the overall population, for the combination therapy group the median PFS was 13.8 months and for the sunitinib group the median PFS was 7.2 months (HR 0.61, 95% CI, 0.47–0.79, P<0.001). For those with PD-L1-positive tumors, ORR was higher in the avelumab plus axitinib group than in the control group (55.2% *vs.* 25.5%) (9).

IMmotion151 evaluated the efficacy of atezolizumab plus bevacizumab IV every 3 weeks verses sunitinib in advanced RCC patients with clear cell or sarcomatoid histology as first-line therapy. The median PFS was longer in the combination group than in the control group (11.2 *vs.* 7.7 months, HR 0.74, 95% CI, 0.57–0.96, P=0.0217) among patients with PD-L1-positive tumors. OS was not reached (10).

Despite the promising results, there is no study that can determine whether for those patients who need long term use of systemic therapy, should we use combination therapy the whole time or should we modify the treatment strategy for a less aggressive one. On the other hand, all the clinical trials of combination therapy have focused on the first-line treatment of advanced RCC. There is no solid evidence that shows promising results in the second-line treatment.

According to National Comprehensive Cancer Network (NCCN) guideline, cabozantinib is recommended as second-line therapy for advanced renal cell carcinoma. The recommendation is based on METEOR trial, which showed estimated median PFS for patients randomized to cabozantinib was 7.4 months (11). As for single use of pazopanib as second-line therapy, a prospective phase II trial enrolled 56 patients who had previously received first-line treatment with sunitinib (n=39) or bevacizumab (n=16).

The trial showed that the median PFS was 7.5 months (95% CI, 5.4–9.4 months) (12). In our study, the PFS for combination therapy was 12.2 months, which is almost 5 months longer than the standard treatment.

In this study, we treated patients with half-year combination therapy followed by single-use targeted therapy as the second-line therapy. Most of the patients remained stable after this treatment strategy. We chose pazopanib as the maintenance treatment because it did not need intravenous administration and it has less adverse events, leading to better patient compliance. According to a large non-inferiority study (COMPARZ) of sunitinib versus pazopanib in the first line therapy of advanced RCC, these two drugs have a similar efficacy profile and a differentiated safety profile. Pazopanib was associated with less hand-foot syndrome, less fatigue, less thrombocytopenia, and less alteration in taste than sunitinib. However, patients treated with pazopanib had more transaminase elevation than sunitinib (13). Our study showed that combination therapy was a feasible way to treat patients. TKIs, together with 6–8 cycles of ICI agents followed by the single use of a TKI, are well accepted by patients and it also reduces patients' financial burden. One study in China on the cost-effectiveness of pembrolizumab plus axitinib versus sunitinib in the first-line treatment of metastatic RCC showed that pembrolizumab plus axitinib provided an additional 2.461 LYs (1.650 QALYs). The total cost per patient was US$178,725 for pembrolizumab plus axitinib and US$87,693 for sunitinib (14). It is evident that despite its significant treatment effect, combination therapy has a greater cost. Our treatment modality could reduce patients' economic burden. As for the AEs, all AEs were manageable. One of the strengths of our study was that patients were treated with combination therapy as the second-line treatment, which was not investigated by previous studies.

There are some limitations in our research. Our study included only a limited population of patients from a single center. In addition, this is a retrospective study. Further multicenter and prospective research is therefore required.

Conclusions

TKIs, together with 6–8 cycles of ICI agents followed by the single use of a TKI, are a feasible way to treat metastatic ccRCC patients as second-line treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at: http://dx.doi.org/10.21037/tau-21-338

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-21-338). The authors reported that study is supported by Novartis Pharmaceuticals Corporation in editing the medical writing of the report. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Fudan University Shanghai Cancer Center (FUSCC) Ethical Committee (No. 050432-4-1911D). Written informed consent from each patient was obtained.

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