Original Article

The efficacy of subsequent therapy after failure of anti-PD-1 antibody in metastatic renal cell carcinoma

Yu Zhou^, Baozhen Ma, Quanli Gao, Lingdi Zhao

Department of Immunotherapy, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China

Contributions: (I) Conception and design: Y Zhou, L Zhao; (II) Administrative support: Q Gao; (III) Provision of study materials or patients: Y Zhou, L Zhao; (IV) Collection and assembly of data: Y Zhou, B Ma; (V) Data analysis and interpretation: Y Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Lingdi Zhao, MD. Department of Immunotherapy, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, 127 Dongming Road, Zhengzhou 450003, China. Email: lingdi1010@126.com.

Background: The optional regimens of subsequent therapy after failure of anti-programmed cell death protein-1 (PD-1) antibody in metastatic renal cell carcinoma (mRCC) remain to be explored. There are reports of the efficacy of single-agent vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) in patients with mRCC after failure of anti-PD-1 antibody therapy. However, it is not clear whether it is beneficial for patients to receive anti-PD-1 antibody as post-progression treatment. It has great significance to explore whether continuous application of anti-PD-1 antibody is beneficial for patients with mRCC whose diseases progressed to the state of pre-anti-PD-1 therapy. The purposes of this study are to explore the efficacy and safety of subsequent treatment on whether to continue using anti-PD-1 antibody therapy for patients who have progressive mRCC after prior treatment with anti-PD-1 antibody.

Methods: The clinical data of patients with mRCC from the Department of Immunotherapy in the Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital from February 1, 2019 to December 31, 2021 were analyzed retrospectively. The primary endpoints were the objective response rate (ORR) and progression-free survival (PFS). The ORR and disease control rate (DCR) were estimated with Fisher's exact test. PFS and overall survival (OS) were assessed using the Kaplan-Meier method and log-rank tests. The associations between potential prognostic variables and PFS were evaluated with univariate and multivariate Cox regression analyses. A P value of less than or equal to 0.05 was deemed as statistically significant.

Results: A total of 35 patients were included in this study, during which 19 received VEGFR-TKI monotherapy and 16 received the VEGFR-TKI plus anti-PD-1 antibody therapy. Until the last follow-up on June 30, 2022, 19 patients experienced progressive disease (PD), five were in remission, and 11 kept stable disease (SD). After a median follow-up of 28.7 [95% confidence interval (CI): 17.0–35.6] months, the median PFS (mPFS) was 11.6 months for the VEGFR-TKI group and 9.1 months for the VEGFR-TKI plus anti-PD-1 antibody group [hazard ratio (HR) =0.81, 95% CI: 0.32–1.03, P=0.44]. Median OS (mOS) were 16.9 and 11.2 months respectively (HR =0.99, 95% CI: 0.44–2.27, P=0.90). The ORRs were 26.3% and 0% (P=0.049), and the DCRs were 47.4% and 43.8% (P=0.55) respectively. Treatment-related adverse events (TRAEs) occurred in 14 patients (73.7%) in the VEGFR-TKI group and 14 patients (87.5%) in the VEGFR-TKI plus anti-PD-1 antibody group (P=0.42); grade 3/4 TRAEs occurred in two patients (10.5%) and six patients (37.5%) respectively (P=0.11).

Conclusions: VEGFR-TKI monotherapy is an efficacious regimen for patients with mRCC whose diseases progressed on previous anti-PD-1 antibody therapy, and continuous anti-PD-1 therapy after failure of anti-PD-1 antibody could not provide additional clinical benefit but increased the incidence of TRAEs.

Keywords: Metastatic renal cell carcinoma (mRCC); anti-programmed cell death protein-1 antibody (anti-PD-1

^ ORCID: 0000-0002-9778-9639.

antibody); vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI); subsequent therapy; resistance

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Introduction

Background

Renal cell carcinoma (RCC) originates from renal tubular epithelium and is one of the most common malignant tumors in the urinary system, accounting for 80% and 90% of all renal malignant tumors (1). The most common subtypes of RCC include clear cell type (65–70%), papillary type (15–20%) and chromophobe cell type (5–7%) (2). It was estimated that there would be about 430,000 new cases and 179,000 deaths of RCC worldwide each year (3). In the United States, it is estimated that there will be 79,000 new cases and 13,920 deaths of kidney cancer in 2022 (4), and its incidence and mortality are increasing year by year (3). About 20% to 50% of patients develop disease progression despite surgical resection (5), and the five-year survival rate of metastatic RCC (mRCC) is only about 12% (6). Epidemiological studies have found that smoking, obesity and hypertension are risk factors for the occurrence and development of RCC, and genetic factors also account for a large proportion (5,7). For example, autosomal dominant mutations in Von Hippel-Lindau (VHL) gene can easily lead to proliferative angiopathy of clear cell RCC (8).

Rationale and knowledge gap

In addition, mRCC is insensitive to traditional radiotherapy and chemotherapy (9). RCC has always been regarded as a solid tumor with strong immunogenicity and immunoreactivity, rich in immune cells infiltration, including macrophages and T lymphocytes (10,11). So immunotherapy has a great advantage for mRCC. Systemic therapies for mRCC have changed dramatically in recent years with the development of immune checkpoint inhibitors (ICIs) especially anti-programmed cell death protein-1 (PD-1) antibodies (12). Based on previous phase III clinical randomized controlled trials (13-17), combination therapies involving double ICIs or anti-PD-1 antibody plus vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) have significantly improved progression-free survival (PFS) and objective response rate (ORR) and have been recommended as first-line choices for mRCC (18,19). In the CheckMate 9ER study, the combination of nivolumab and cabozantinib resulted in a longer median overall survival (OS) and median PFS (mPFS) compared to sunitinib as first-line treatment for mRCC (13). The CLEAR study reported that the ORR of lenvatinib plus pembrolizumab for mRCC was 71%, and the complete response (CR) rate was 16.1% (17); further follow-up results showed that the two-year survival rate for patients with CR was 100% (20). In addition, double ICIs as first-line treatment for mRCC also achieved positive clinical results. In patients with International mRCC Database Consortium (IMDC) intermediate- and poor-risk disease, the ORR of nivolumab plus ipilimumab was 42% and the mPFS was 11.6 months (21).

However, in most patients, the diseases do not respond to anti-PD-1 antibody therapy (primary resistance), and some develop progressive diseases (PD) after a period of remission (acquired resistance). In addition, some patients will have specific reactions such as false progression, disease hyperprogression and so on (22). Because of the adverse events (AEs) of anti-PD-1/programmed death ligand-1 (PD-L1) antibodies, in some cases, the therapy has to be interrupted. Although there are biomarkers for predicting the efficacy of anti-PD-1 antibody in other solid tumors (23), such as PD-L1 expression, tumor mutation burden (TMB) and microsatellite instability (MSI), there are still no effective predictive biomarkers to predict the efficacy of anti-PD-1 antibody in mRCC. The drug resistance mechanism of anti-PD-1 antibodies is complex and changeable, which has not been fully elucidated.

Objective

There is an urgent need to explore effective treatment schemes after drug resistance to prior immunotherapy for these patients. Moreover, it is still not clear whether subsequent continued application of anti-PD-1 antibody in late stage disease can bring clinical benefits for patients with

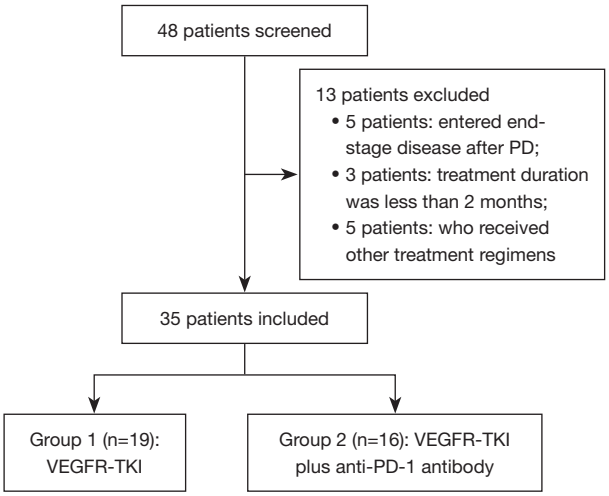

Figure 1 Flowchart of the screening. PD, progressive disease; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; PD-1, programmed cell death protein-1.

mRCC after failure of anti-PD-1 antibody. Therefore, it is necessary to explore the optional regimens of subsequent therapy after failure of anti-PD-1 antibody in mRCC. This retrospective study aimed to investigate the efficacy and safety of targeted agents and immune combination therapy in patients with mRCC whose diseases progressed after anti-PD-1 antibody therapy. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2390/rc).

Methods

Study design and patients

From February 1, 2019 to December 31, 2021, a total of 35 patients from the Department of Immunotherapy in the Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital were enrolled in this retrospective study. The inclusion criteria were as follows: over 18 years old regardless of gender, disease progression on prior anti-PD-1 therapy, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, having received the VEGFR-TKI or the VEGFR-TKI plus anti-PD-1 antibody therapy, and with an expected survival time of over three months. Baseline clinical characteristics were recorded, including histology, metastatic sites, IMDC risk score, ECOG score, and previous immunotherapy regimens and efficacy, safety, as well as treatment-related adverse events (TRAEs). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital (No. 2021-069). The ethics committee waived the requirement of written informed consent for participation.

Outcomes

The primary endpoints were ORR and PFS. ORR was defined as the proportion of patients who achieved a CR or partial response (PR) as their best response, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (24). Disease control rate (DCR) was defined as the ORR plus the percentage of patients with stable disease (SD). PFS was defined as the period between the first subsequent therapy initiation and drug discontinuation due to progression, death, or censored at the last follow-up, whichever occurred first. OS was defined as the time from the first day of subsequent therapy to death from any cause, or the censor of data at the last follow-up. The TRAEs were evaluated concerning incidence and severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Statistical analysis

All calculations were conducted using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) software. PFS, OS, ORR, DCR and the incidence of TRAEs were compared between the different treatment groups using the Fisher's exact test. Kaplan-Meier method and log-rank tests were performed for survival analysis and the associations with potential prognostic factors. Univariate and multivariate Cox proportional hazards model analyses were done to determine the associations between clinical variables and PFS. Variables with a P value ≤ 0.05 in the univariate analysis were used for multivariate analysis. All statistical analyses were two-sided and a P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 35 patients were enrolled in this study. Of these, 19 patients received VEGFR-TKI monotherapy, and 16 patients received the VEGFR-TKI plus anti-PD-1 antibody therapy (*Figure 1*). The last follow-up was

performed on June 30, 2022. The median follow-up duration was 28.7 [95% confidence interval (CI): 17.0–35.6] months. The baseline characteristics of the 35 patients are shown in *Table 1*. Patients were mostly men (77.1%), with a median age of 54 years (range, 30–90 years), of mainly clear cell carcinoma (88.6%), and had an intermediate IMDC prognostic score (80.0%).

Previous treatment with anti-PD-1 antibody

Previous anti-PD-1 antibody therapies were first-line (5.7%) or second-line (94.3%) therapy. Most patients (60%) received prior anti-PD-1 antibody treatment for at least six months (*Table 1*). Three patients achieved a PR (8.6%) as the best response and no CR in these patients. The DCR was 74.3%. The mPFS of prior immunotherapy was 7.3 months for the VEGFR-TKI group and 4.3 months for the VEGFR-TKI plus anti-PD-1 antibody group (95% CI: 4.175–8.425, P=0.02). The median OS (mOS) was 31.8 and 16.5 months respectively (95% CI: 14.072–43.728, P=0.26). The occurrence rate of TRAEs of previous anti-PD-1 antibody was 82.9%, with most being of grade 1/2. TRAEs of any grade occurred in 17 of 19 patients (89.5%) in the VEGFR-TKI group and 12 of 16 patients (75.0%) in the VEGFR-TKI plus anti-PD-1 antibody group (P=0.38); grade 3/4 AEs occurred in four patients (21.1%) and two patients (12.5%) respectively (P=0.67). The most frequent AEs of previous anti-PD-1 antibody were anemia (47.4%) and fatigue (42.1%) in the VEGFR-TKI group, and vomiting (43.8%) and pain (31.3%) in the combination group.

Clinical efficacy

Objective responses were observed in five patients (14.3%) and all five patients were in the VEGFR-TKI group. There was no CR or PR achieved in the combination group. The ORR was 26.3% versus 0% (P=0.049), and the DCR was 47.4% versus 43.8% (P=0.55) respectively (*Table 2*). A waterfall plot of the best overall tumor response is shown in *Figure 2*. The results showed that 68.4% of the patients in the VEGFR-TKI group had tumor target reduction, and the maximum proportion of tumor target reduction was as high as 56.3%, while only 25% of the patients in the combination group showed tumor reduction, and the maximum proportion of tumor target reduction was 20.4%. There were 10 and 9 patients whose diseases progressed in the VEGFR-TKI group and in the VEGFR-TKI plus anti-PD-1 antibody group respectively, and all these patients died. The mPFS was 11.6 months for the VEGFR-TKI group and 9.1 months for the VEGFR-TKI plus anti-PD-1 antibody group (95% CI: 0.32–1.03, P=0.44). The mOS was 16.9 and 11.2 months, respectively (95% CI: 0.44–2.27, P=0.90) (*Figure 3A*,*3B*).

As shown in *Figure 4*, the associations between baseline clinical characteristics and PFS were evaluated. The

Table 1 Baseline clinical characteristics of the patients

Variable	Total	VEGFR-TKI group	VEGFR-TKI plus anti-PD-1 antibody group	P value
Number	35	19 (54.3)	16 (45.7)	
Age (years)	54 [30–90]	60 [40–90]	48.5 [30–75]	0.04
Sex				0.55
Male	27 (77.1)	15 (78.9)	12 (75.0)	
Female	8 (22.9)	4 (21.1)	4 (25.0)	
Histology				0.31
Clear cell type	31 (88.6)	18 (94.7)	13 (81.3)	
Non-clear cell type	4 (11.4)	1 (5.3)	3 (18.7)	
Tumor location				0.52
Left kidney	25 (71.4)	14 (73.7)	11 (68.7)	
Right kidney	10 (28.6)	5 (26.3)	5 (31.3)	

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Total	VEGFR-TKI group	VEGFR-TKI plus anti-PD-1 antibody group	P value
Prior nephrectomy				0.72
Yes	24 (68.6)	14 (73.7)	10 (62.5)	
No	11 (31.4)	5 (26.3)	6 (37.5)	
Sites of metastatic disease				
Lung and pleura	30 (85.7)	18 (94.7)	12 (75.0)	0.16
Liver	8 (22.9)	5 (26.3)	3 (18.7)	0.70
Brain	4 (11.4)	3 (15.8)	1 (6.3)	0.61
Bone	22 (62.9)	10 (52.6)	12 (75.0)	0.29
Adrenal	7 (20.0)	3 (15.8)	4 (25.0)	0.68
Abdominal cavity	4 (11.4)	1 (5.3)	3 (18.7)	0.31
Lymph node	31 (88.6)	17 (89.5)	14 (87.5)	>0.99
Number of metastatic sites				>0.99
≤2	8 (22.9)	4 (21.1)	4 (25.0)	
>2	27 (77.1)	15 (78.9)	12 (75.0)	
ECOG score				0.38
0–1	29 (82.9)	17 (89.5)	12 (75.0)	
2	6 (17.1)	2 (10.5)	4 (25.0)	
IMDC risk score				0.23
Favorable	2 (5.7)	2 (10.5)	0	
Intermediate	28 (80.0)	15 (79.0)	13 (81.3)	
Poor	5 (14.3)	2 (10.5)	3 (18.7)	
Prior immunotherapy				0.66
Anti-PD-1 agent plus VEGFR-TKI	17 (48.6)	9 (47.4)	8 (50.0)	
Anti-PD-1 agent plus CIK	13 (37.1)	9 (47.4)	4 (25.0)	
Anti-PD-1 single-agent	5 (14.3)	1 (5.2)	4 (25.0)	
Prior immunotherapy duration				0.02
<6 months	14 (40.0)	4 (21.1)	10 (62.5)	
≥6 months	21 (60.0)	15 (78.9)	6 (37.5)	
Prior immunotherapy response				0.81
CR/PR	3 (8.6)	1 (5.3)	2 (12.5)	
SD	23 (65.7)	14 (73.6)	9 (56.2)	
PD	9 (25.7)	4 (21.1)	5 (31.3)	

Data are presented as median [range] or n (%). VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; PD-1, programmed cell death protein-1; ECOG, Eastern Cooperative Oncology Group; IMDC, International mRCC Database Consortium; CIK, cytokine-induced killer; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; mRCC, metastatic Renal cell carcinoma.

Table 2 Tumor responses according to RECIST version 1.1

Efficacy	Total	VEGFR-TKI group	VEGFR-TKI plus anti-PD-1 antibody group
PR, n (%)	5 (14.3)	5 (26.3)	0
SD, n (%)	11 (31.4)	4 (21.1)	7 (43.8)
PD, n (%)	19 (54.3)	10 (52.6)	9 (56.2)
ORR (%)	14.3	26.3	0
DCR (%)	45.7	47.4	43.8
mPFS (months)	–	11.6	9.1
mOS (months)	–	16.9	11.2

RECIST, Response Evaluation Criteria in Solid Tumors; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; PD-1, programmed cell death protein-1; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; mPFS, the median progression-free survival; mOS, the median overall survival.

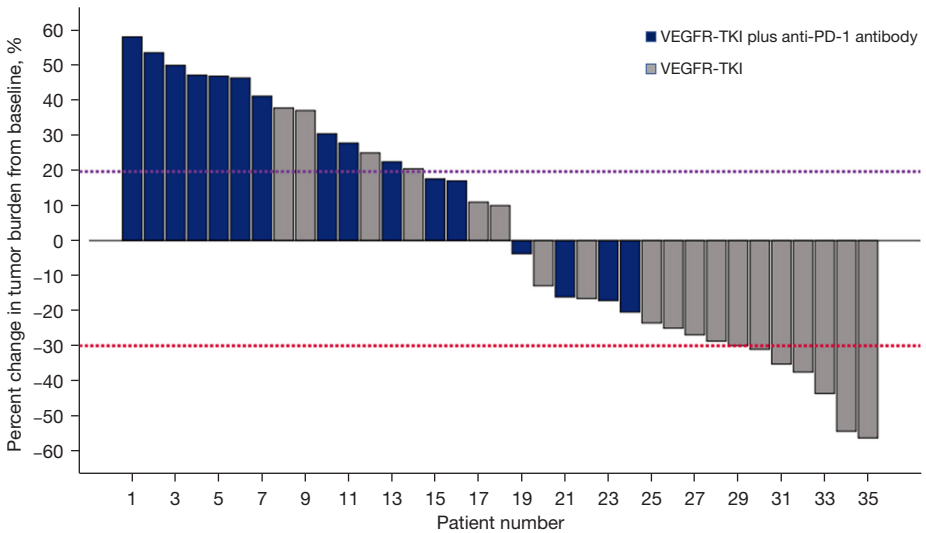

Figure 2 Waterfall plot of best overall response from baseline. VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; PD-1, programmed cell death protein-1.

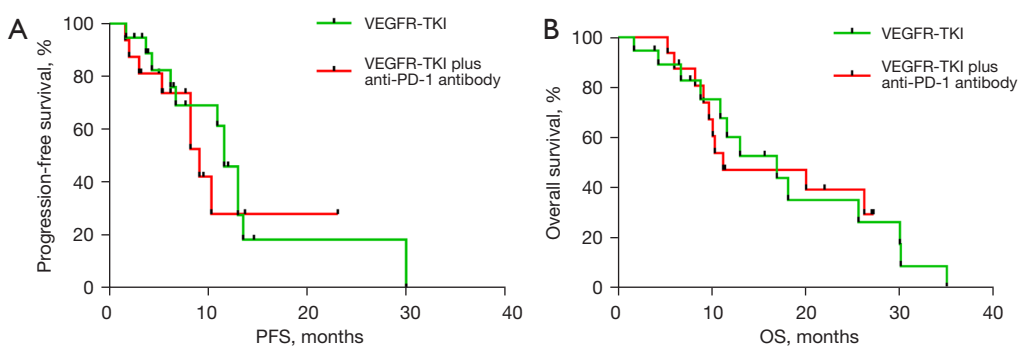

Figure 3 Kaplan-Meier (A) PFS and (B) OS curves of patients treated with VEGFR-TKI alone and combination therapy. VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; PD-1, programmed cell death protein-1; PFS, the progression-free survival; OS, overall survival.

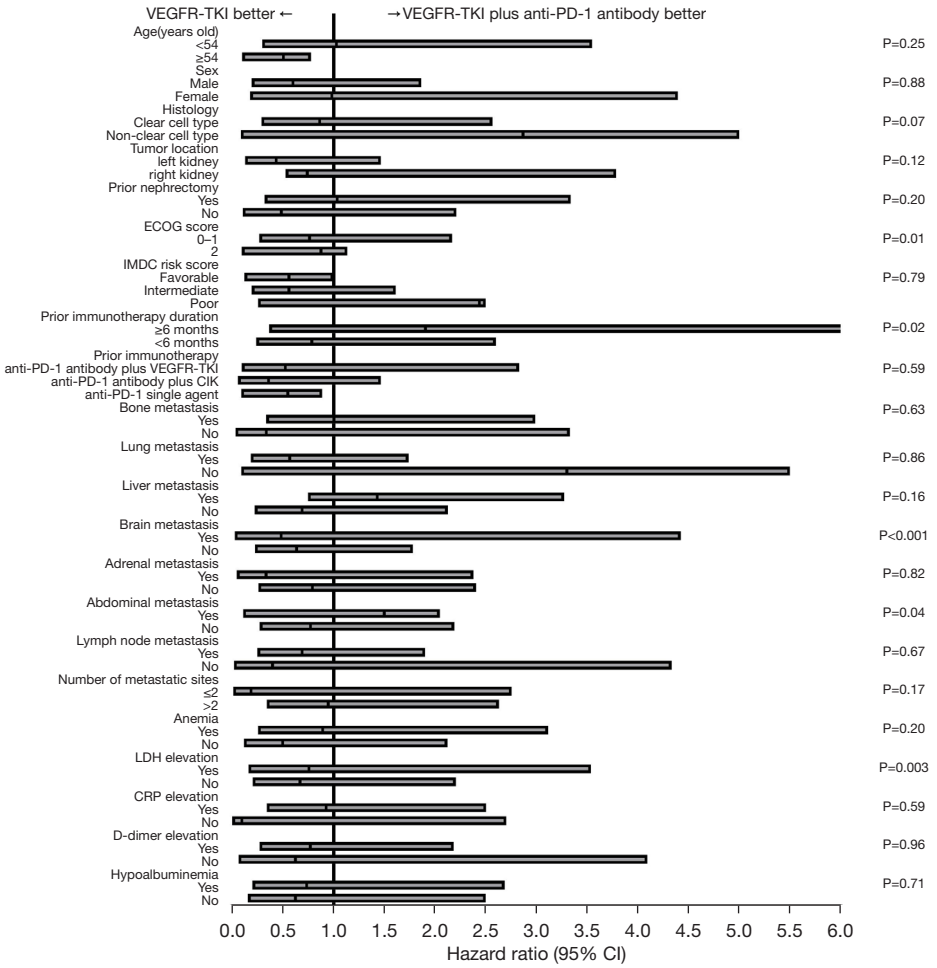

Figure 4 Subgroup analysis of PFS. VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; PD-1, programmed cell death protein-1; ECOG, Eastern Cooperative Oncology Group; IMDC, International mRCC Database Consortium; mRCC, metastatic renal cell carcinoma; CIK, cytokine-induced killer; LDH, lactate dehydrogenase; CRP, C-reactive protein; CI, confidence interval.

results showed that patients whose age over 54 years [hazard ratio (HR) =0.506, 95% CI: 0.100–0.755], with a favorable IMDC risk score (HR =0.561, 95% CI: 0.124–0.998), and those who received anti-PD-1 single-agent as prior immunotherapy (HR =0.550, 95% CI: 0.092–0.887) derived a better survival when receiving VEGFR-TKI monotherapy. In addition, ECOG score (P=0.01), brain metastasis (P<0.001), abdominal metastasis (P=0.04), prior immunotherapy duration (P=0.02), and lactate dehydrogenase (LDH) elevation (P=0.003) were significantly associated with PFS (P<0.05). As shown in *Table 3*, the multivariate Cox regression analyses showed that the independent variables for prediction of PFS were presence of brain metastasis (HR =21.707, P=0.004), prior immunotherapy duration less than six months (HR =0.299, P=0.03) and LDH elevation (HR =0.269, P=0.04).

Safety

TRAEs of any grade occurred in 14 of 19 patients (73.7%) in the VEGFR-TKI group and 14 of 16 patients (87.5%) in the VEGFR-TKI plus anti-PD-1 antibody group (P=0.42); grade 3/4 AEs occurred in two patients (10.5%) and six patients (37.5%) respectively (P=0.11). As shown in *Figure 5*, the most frequent AEs of any grade in the VEGFR-TKI group were anemia (36.3%), hypothyroidism (27.2%), and proteinuria (22.7%). While in the VEGFR-TKI plus anti-PD-1 antibody group, the most frequent AEs were pain (62.6%), hypothyroidism (56.3%), and hypoproteinemia (50%). In the VEGFR-TKI group, one

Table 3 Multivariate analyses according to the associations between clinical characteristics and PFS

Variables	HR	95% CI		P value
		Lower	Upper	
ECOG score, 0–1 *vs.* 2	2.115	0.075	2.988	0.43
Brain metastasis, absent *vs.* present	21.707	2.728	22.732	0.004
Abdominal metastasis, absent *vs.* present	2.614	0.592	11.551	0.21
Prior immunotherapy duration, ≥6 *vs.* <6 months	0.299	0.101	0.886	0.03
LDH elevation, absent *vs.* present	0.269	0.079	0.919	0.04

PFS, the progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

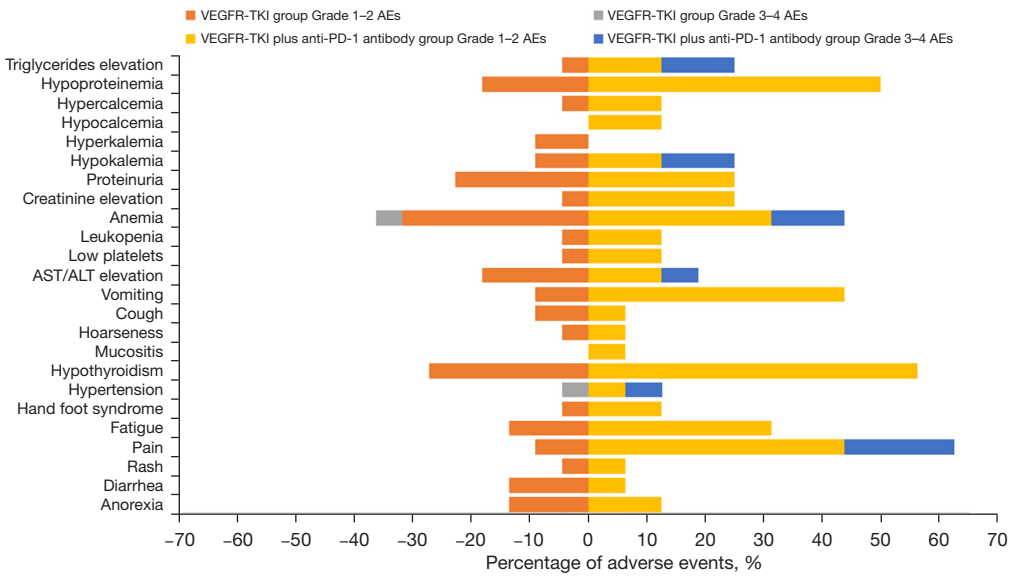

Figure 5 The occurrence rate of grade 1–4 adverse events of any cause during subsequent therapy. VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; AEs, adverse events; PD-1, programmed cell death protein-1; AST, aspartate aminotransferase; ALT, alanine transaminase.

patient developed grade three AE (hypertension) and another one developed grade three anemia, which were well-tolerated by dose-reduction or treatment interruption. In the VEGFR-TKI plus anti-PD-1 antibody group, grade 3/4 TRAEs included pain (18.8%), hypertension (6.3%), aspartate aminotransferase (AST) / alanine transaminase (ALT) elevation (6.3%), anemia (12.5%), hypokalemia (12.5%) and triglycerides elevation (12.5%), which were also well-tolerated by symptomatic treatment. There were no treatment-related deaths occurred. TRAEs leading to treatment discontinuation occurred in 4.5% and 12.5% of the patients in the respective groups.

Discussion

Key findings

This study evaluated the efficacy and safety of subsequent therapeutic regimens after failure of anti-PD-1 antibody in mRCC. The results showed that 68.4% of patients presented with tumor shrinkage in the VEGFR-TKI group, ORR was 26.3% and the mPFS was 11.6 months. In addition, the occurrence rate of grade 3/4 TRAEs in the VEGFR-TKI group (2/19) was lower than that in the combination group (6/16). Furthermore, based on multivariate analysis, the presence of brain metastasis, prior

immunotherapy duration less than six months, and LDH elevation were associated with a shorter PFS.

Comparison with similar researches and explanations of findings

VEGFR-TKIs have improved the prognosis of mRCC as first-line choices in the last two decades. Sorafenib, sunitinib and pazopanib, which target VEGFR were the first to be approved for first-line treatment for mRCC patients. The results of the TIVO-1 clinical study showed that the ORR of sorafenib was 24%, and the mPFS was 9.1 months in the first-line treatment of mRCC (25). A multicenter retrospective study analyzed efficacy of sorafenib in 845 patients with mRCC, the results showed that the mPFS was 11.1 months (26). An early study published in the *New England Journal of Medicine* showed that sunitinib achieved higher ORR (31%) and PFS (11 months) than interferon alpha in the first-line treatment of mRCC (27). The results of a phase IV clinical study in China were similar, with an ORR of 31.1% and the mPFS of 14.2 months in patients with mRCC (28). Another phase III clinical study of pazopanib versus sunitinib (COMPARZ study) showed that ORR was 31% and 25%, and the mPFS was 8.4 months and 9.5 months, respectively. There was no significant difference in the mPFS of the subgroup of 209 Chinese patients (8.3 *vs.* 8.3 months) (29). The results of the Alliance A031203 CABOSUN clinical trial published in the *Journal of Clinical Oncology* (*JCO*) in 2017 showed that the mPFS of cabozantinib versus sunitinib was 8.2 months and 5.6 months, and the ORR was 33% and 12% respectively in the treatment-naive mRCC (30). Based on the results of this clinical trial, cabozantinib was approved in the intermediate and poor risk mRCC patients for the first-line treatment. The efficacy of the VEGFR-TKI monotherapy in our study was similar to that of first-line VEGFR-TKIs therapy, which suggests that prior immunotherapy may not interfere with the efficacy of subsequently single-agent targeted therapy. However, the mechanism of anti-PD-1 antibody therapy affecting the efficacy of follow-up VEGFR-TKI has not been fully clarified, and further exploration is needed in the future.

The anti-tumor effects of targeted therapy following ICIs have been previously reported in mRCC (31-40). A phase II clinical study included 40 patients with mRCC who were treated with axitinib after failure of ICIs. The results showed that the mPFS was 8.8 months (31). The results of a phase II non-randomized study of 38 patients showed that axitinib may improve efficacy (mPFS =9.2 months, ORR =40%) after ICIs therapy, including ipilimumab or nivolumab (31). There is also a phase III multicenter randomized controlled trial (TIVO-3) analyzing the efficacy of tivozanib or sorafenib in patients with mRCC after failure of ICIs therapy. The results showed that the mPFS was 5.6 and 3.9 months, respectively (32). An open label, multicenter, single arm, phase II study designed to assess efficacy of cabozantinib in mRCC patients progressed after an adjuvant or first line anti-PD-1 therapy. After a median follow-up of 11.9 months, mPFS was 8.3 months and mOS was 13.8 months. The results showed that ORR was 37.9% (33). However, few prospective studies can be found in the literature, and there are limitations of patients enrolled in the group. At present, most studies are still retrospective studies. Moreover, a retrospective study explored the efficacy of third-line axitinib after failure of nivolumab in mRCC (34). The mPFS was 12.8 months in 17 patients and the ORR and DCR were 29.4% and 94.1% respectively. In another retrospective study of patients with mRCC who were subsequently treated with VEGFR-TKIs after immune combination therapy, the results showed that 29% of patients achieved PR as the best response and the mPFS was 6.4 months (35). Powles *et al.* have previously demonstrated that cabozantinib was associated with improved ORR, PFS, and OS versus everolimus in patients with mRCC, irrespective of prior therapy, including anti-PD-1 antibody therapy (36). A study enrolled 86 patients with mRCC whose diseases progressed after anti-PD-1 antibody and were subsequently treated with cabozantinib (37). The results showed that the ORR was 36%, the DCR was 79% and the mPFS was 6.5 months. Auvray *et al.* reported on 33 patients who received second-line VEGFR-TKIs after first-line nivolumab plus ipilimumab. The mPFS was eight months with first-generation VEGFR-TKIs and seven months with second-generation VEGFR-TKIs (38). These studies suggested sustained clinical benefits of targeted therapy after immunotherapy in mRCC, which were consistent with our findings. Interestingly, patients with a duration of response more than six months on first-line ICI appeared to have longer durations of response to second-line VEGFR-TKIs (38), which was also consistent with our finding that prior immunotherapy duration over six months may prolong the PFS of subsequent VEGFR-TKI therapy (P=0.03). In addition, there are case reports in patients with mRCC who were treated with axitinib or pazopanib that could reduce the size of tumors after failure of nivolumab

treatment (39).

Immunotherapy rechallenges after failure of anti-PD-1 antibody have been explored in patients with melanoma (40) and non–small cell lung cancer (41). However, there are few studies using single-agent or combined immunotherapy subsequently for patients with mRCC after failure of anti-PD-1 antibody therapy. In the CheckMate 025 trial, 142 patients experienced failure of nivolumab and continued to receive nivolumab. In patients with CR/PR, SD or PD as their best response before first progression, the ORRs of subsequent monotherapy were 28% (8/29), 6% (3/47) and 14% (9/66) respectively (42). The results showed that after anti-PD-1 resistance, continued application of anti-PD-1 antibody monotherapy for some patients may still be effective. However, we can not rule out the possibility that the pseudoprogression of the tumor for the first progression. On the contrary, a case series of two patients with mRCC rechallenged with a different PD-1 inhibitor monotherapy showed no responses (43). In addition, a retrospective study assessed the efficacy of ipilimumab plus nivolumab after prior ICIs in 30 patients with mRCC, which showed an ORR of 17% (44). A subsequent study included 45 patients with mRCC, who also explored the efficacy and safety of ipilimumab plus nivolumab after previous anti-PD-1 antibody treatment. The results showed that ORR was 20%, PR was 13%, and the mPFS was 4 months. The incidence of immune-related adverse events (irAEs) was 64%, of which grade 3 irAEs accounted for 13% (45). In a multicenter prospective study, 45 patients with mRCC received either monotherapy with nivolumab or a combination of double ICIs after receiving ICIs. The results showed that the ORR was 16%, the mPFS was 3.5 months, and the mOS was 24 months (46). In a phase 1b/2 clinical trial of 104 patients with mRCC, the efficacy of pembrolizumab combined with lenvatinib as a posterior line treatment after failed treatment of ICIs was evaluated. The results showed that the ORR was as high as 56% (47). A retrospective study published on Cancer Medicine in 2022 analyzed the efficacy and safety of 85 mRCC patients with any histological components who received second-line or more ICI plus VEGFR-TKIs therapy. The results showed that patients who had previously received only ICI monotherapy had better efficacy after receiving ICI combined with VEGFR-TKIs therapy. The ORR was as high as 50%, and the mPFS was 9.1 months. Patients who had previously received ICI combined with VEGFR-TKIs had poor efficacy after receiving ICI combined with VEGFR-TKIs, with an ORR of 20% and a mPFS of 5.5 months (48). Furthermore, a cohort study included patients with mRCC whose diseases progressed (72%) or experienced toxicities (23%) after prior immunotherapy. These patients subsequently received single-agent ICI (38%), dual ICIs (32%), or ICI plus VEGFR-TKI (19%), and the ORR was 23% in total patients (49). While in our study, subsequent anti-PD-1 antibody plus VEGFR-TKI cannot bring additional clinical benefit to these patients. The reason maybe lie in the patients included in the studies, in Ravi's study, patients who experienced toxicities rather than progression from prior ICIs were included (49), while in our study only patients experienced progression from prior ICIs were included. In addition, it should be pointed out that the patients who were included in our study who received VEGFR-TKIs combined with anti-PD-1 antibody therapy had a short duration of prior anti-PD-1 antibody therapy, indicating that this group of patients are relatively resistant to immunotherapy, and the prognosis of them may be worse, which may also be the reason for the poor efficacy of anti-PD-1 antibody therapy. Another important aspect of immunotherapy retreatment would be in patients who had previously received pembrolizumab as adjuvant therapy after nephrectomy (50). This is poorly studied in the literature, and it is anticipated that an estimable number of patients currently being treated in this setting will be worth studying in the near future.

Limitations, implications and actions needed

Our study has several limitations. First, it is a retrospective study, limited by the patients included, while we included eligible continuous patients which might reduce this kind of errors. Second, the small sample of this study which may influence the results. Third, the patients included in this study have different histological components. Although most of them are clear cell RCC, it is impossible to explore other histological components of RCC because of the limitation of sample size. For example, the recently published SWOG 1500 study shows that cabozantinib is more effective in patients with papillary cell RCC (51), so it is necessary to expand the sample size and analyze the difference of histological components in patients with mRCC treated with different VEGFR-TKIs. Fourth, in this study, the agents of VEGFR-TKIs included axitinib, sunitinib, cabozantinib, lenvatinib and tivozanib. The anti-tumor activity of these agents may be different, which may affect the results. Therefore, there is an urgent need to expand the sample size in order to explore the clinical efficacy of each VEGFR-TKIs medication. Last,

the recent artificial intelligence (AI) and radiogenomic have the ability to help clinicians set the treatment selection, follow-up strategy, and prognosis of the renal cancer. The application of AI and radiomics could predict gene mutation through molecular biomarkers and treatment response in mRCC undergoing immunotherapy (52). In the last few years, almost all of the studies had pursued the approach of combining radiomics features and gene expression in clear cell RCC. Thus, there was a lack of statistics and monitoring of genomics in follow up of our patients (53), which could have the possibility to predict the efficacy of subsequent therapy after failure of anti-PD-1 antibody in mRCC.

Conclusions

VEGFR-TKIs monotherapy is well-tolerated in patients with mRCC whose diseases progressed on previous anti-PD-1 therapy and may be an optional regimen for this kind of patients, while anti-PD-1 combination therapy beyond progression is not. Continuous anti-PD-1 therapy beyond progression from anti-PD-1 antibody could not provide additional clinical benefit but increased the incidence of TRAEs.

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Footnote

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital (No. 2021-069). The ethics committee waived the requirement of written informed consent for participation.

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