Preliminary study on the efficacy of pazopanib combined with toripalimab as first-line therapy for metastatic renal cell carcinoma: Real-world data from a single center

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Abstract. The present study aimed to explore the clinical efficacy and safety of pazopanib combined with toripalimab as first-line therapy for metastatic renal cell carcinoma (mRCC), providing a reference for clinical decision-making. In the present study, clinical data from 22 patients with mRCC who received pazopanib combined with toripalimab treatment at Shanxi Province Cancer Hospital (Taiyuan, China) were retrospectively collected. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and drug safety were analyzed. Among the 22 patients (17 men and 5 women), the median age was 63.5 years. In terms of pathological classification, 19 patients (86.4%) had clear cell RCC. The organs with metastasis mainly included the lungs, lymph nodes, bones, liver and brain. According to the International Metastatic Renal Cell Carcinoma Database Consortium risk classification, 13.6% (3 patients) were classified as favorable-risk, 77.3% (17 patients) were classified as intermediate-risk and 9.1% (2 patients) were classified as poor-risk. A total of 6 patients (27.3%) discontinued treatment due to adverse events (AEs), which included hypertension, proteinuria, elevated transaminases and hypothyroidism. The median follow-up time was 14 months (range, 3-24 months). The overall ORR was 36.36% and the DCR was 77.27%. The median PFS time was 17.1 months (range, 5.9-22.6), while the median OS was not reached. Common AEs included fatigue (27.27%), nausea/vomiting (18.18%), diarrhea (31.82%), hypertension (31.82%), proteinuria (22.73%), elevated transaminases (63.64%), hypothyroidism (18.18%), hand-foot skin reaction (22.73%), rash (9.09%) and leukopenia (13.64%). In conclusion, in the present small, single-center, retrospective real-world study, pazopanib combined with toripalimab as first-line therapy for mRCC showed preliminary signs of efficacy with manageable AEs. These real-world observations suggested that the combination may be feasible and warrants further prospective investigation; however, no clinical recommendation can be made based on the present data. Further prospective randomized controlled trials are needed.

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Abbreviations: RCC, renal cell carcinoma; mRCC, metastatic RCC; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; ccRCC, clear cell RCC; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor; PD-1, programmed death 1; ECOG, Eastern Cooperative Oncology Group; ICIs, immune checkpoint inhibitors; CTLA-4, cytotoxic T lymphocyte associated antigen-4; PD-L1, programmed death ligand 1; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; irAEs, immune-related adverse events

Key words: pazopanib, toripalimab, combination therapy, metastatic renal cell carcinoma, efficacy

Introduction

Renal cell carcinoma (RCC), a malignant tumor originating from renal tubular epithelial cells, is characterized by high heterogeneity and variable pathological types; its global incidence has been increasing annually, particularly among males aged 50 to 70, although in recent years, the affected population has gradually become younger (1,2). The notable pathological features of RCC include its high invasiveness and propensity for metastasis. Notably, ~30% of patients present with distant metastases at initial diagnosis, and even after surgical treatment for localized RCC, there is still a 20-50% risk of RCC progressing to metastatic RCC (mRCC), which has a poor prognosis (3,4). At this stage, surgery is no longer the primary treatment and medication becomes crucial.

In recent years, with the in-depth study of the pathogenesis of RCC, targeted therapy and immunotherapy have made notable progress in the treatment of advanced RCC, becoming important means of precision medicine. Particularly, the roles of the vascular endothelial growth factor (VEGF) and mTOR) pathways in RCC have been elucidated: VEGF signaling

promotes tumor angiogenesis to support tumor growth and metastasis, while mTOR regulates cell proliferation and amplifies VEGF expression, making targeted therapy a crucial strategy for advanced renal cancer (5). Pazopanib, a VEGF receptor tyrosine kinase inhibitor (TKI), can inhibit multiple receptors closely related to tumor angiogenesis, cell proliferation and migration, effectively suppressing tumor angiogenesis and achieving antitumor effects (6). Multiple clinical studies have confirmed that pazopanib demonstrates significant efficacy in prolonging progression-free survival (PFS) and overall survival (OS) in patients with mRCC, and is feasible and safe as a first-line treatment option (7-9). Although pazopanib has shown notable effects in RCC treatment, the efficacy of single targeted therapy is still limited for some patients with refractory mRCC.

With the development of immunotherapy, the combined application of immunotherapy and targeted therapy has become a research hotspot (10,11). Rallis *et al* (12) comprehensively reviewed the potential application value of combining targeted therapy with immunotherapy for the treatment of mRCC in the future. Toripalimab, a programmed death 1 (PD-1) inhibitor, has demonstrated good safety and efficacy; it exerts antitumor effects by relieving the immunosuppression in the tumor microenvironment and activating T cell immune responses against tumors (13). Studies have shown that the combination of PD-1 inhibitors with targeted drugs has achieved positive results in the treatment of mRCC (14-16). However, at present, there are few studies on the treatment of Chinese patients with mRCC using pazopanib combined with toripalimab, and there is a lack of real-world data. Therefore, there is an urgent need to further investigate the therapeutic effects, clinical adverse events (AEs) and the impact on survival of this combination therapy.

The aim of the present study was to retrospectively analyze the clinical data of patients with mRCC who received the treatment regimen of pazopanib combined with toripalimab at Shanxi Province Cancer Hospital (Taiyuan, China). Efficacy indicators such as objective response rate (ORR), disease control rate (DCR), PFS and OS, as well as the occurrence of AEs were assessed. The results of the present study may offer preliminary real-world data that could help generate hypotheses and inform the design of future prospective trials, rather than serving as a direct reference for clinical decision-making.

Materials and methods

Data collection. Patients with mRCC who received first-line treatment with pazopanib combined with toripalimab at Shanxi Province Cancer Hospital from January 2021 to December 2023 were selected and stratified into the favorable-, intermediate- and poor-risk groups according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk criteria. Patients with 0 adverse prognostic factors were classified as favorable-risk, those with 1-2 factors as intermediate-risk, and those with ≥3 factors as poor-risk (16). The present study was approved by the Ethics Committee of Shanxi Province Cancer Hospital (Taiyuan, China; approval no. KY2023106), and all patients provided informed consent for the use of their clinical data.

Inclusion criteria were as follows: i) Pathologically confirmed clear cell RCC (ccRCC) or non-clear cell RCC; ii) imaging indicates local progression or distant metastasis; iii) measurable lesions according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (16); iv) estimated survival time ≥12 weeks to allow 3-month follow-up for efficacy evaluation; v) Eastern Cooperative Oncology Group (ECOG) (16) performance status score of 0 or 1; and vi) good function of major organs, including absolute neutrophil count ≥1.5x10^9/l, platelets ≥100x10^9/l, hemoglobin ≥90 g/l, creatinine ≤130 μmol/l, alanine aminotransferase and aspartate aminotransferase ≤60 U/l, prothrombin time ≤13s, activated partial thromboplastin time ≤35 sec and left ventricular ejection fraction ≥50%.

Exclusion criteria: i) Patients who had previously received targeted therapy or immune checkpoint inhibitors (ICIs) such as PD-1, cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and programmed death ligand 1 (PD-L1); ii) inclusion in other interventional clinical studies; and iii) patients that required long-term systemic hormone therapy or any other immunosuppressive drug therapy, excluding inhaled hormone therapy.

Treatment method. All patients were administered pazopanib 800 mg orally once daily and toripalimab 240 mg intravenously once every 3 weeks. The dose of pazopanib was adjusted based on patient tolerance and adverse reactions. For grade 3 AEs according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (16), the pazopanib dose was reduced to 600 mg once daily; for grade 4 AEs, pazopanib was temporarily suspended until the AE resolved to grade ≤1, after which it was resumed at 600 mg. Administration of toripalimab was temporarily suspended for grade 2-3 immune-related AEs (irAEs) and permanently discontinued for grade 4 or recurrent grade 3 irAEs. These criteria were based on the drug package inserts and institutional clinical practice guidelines. Symptomatic treatment was provided during the treatment period, and medication was continued until tumor progression, patient death or loss to follow-up.

Evaluation of efficacy, survival and follow-up

Efficacy. Imaging examinations using CT or MRI were conducted before treatment and after 2 cycles of treatment, followed by subsequent monitoring every 3 months, to evaluate efficacy according to the RECIST 1.1. Complete response (CR) was defined as complete disappearance of all target lesions, no emergence of new lesions and normalization of tumor marker levels, which persisted for at least 4 weeks; partial response (PR) was defined as a reduction of at least 30% in the sum of the maximum diameters of all target lesions, which also persisted for at least 4 weeks; progressive disease (PD) was defined as an increase of at least 20% in the sum of the maximum diameters of all target lesions or the appearance of new lesions; stable disease (SD) was defined as a decrease in the sum of the maximum diameters of all target lesions that did not meet the criteria for PR or an increase that did not meet the criteria for PD. ORR was calculated as follows: (CR + PR)/total number of cases x100%; DCR was calculated as follows: (CR + PR + SD)/total number of cases x100%.

Survival status. Patients were followed up to record their disease outcomes and survival status. PFS was defined as the time from the start of the combined pazopanib + toripalimab treatment until the first occurrence of disease progression or patient death, with the discontinuation of the pazopanib plus toripalimab treatment or the first occurrence of disease progression serving as the event endpoint. OS was defined as the time from the start of the combined pazopanib plus toripalimab treatment until patient death or the end of follow-up.

Follow-up. Follow-up was conducted, which included assessing patient survival, blood routine, liver and kidney function, coagulation tests, imaging examinations, efficacy and adverse reactions to medication.

Statistical analysis. SPSS 25.0 software (IBM Corp.) was used for statistical analysis of the data. Median was used to describe the age distribution of patients, and rates (%) were used to describe baseline patient data and the occurrence of AEs. The median survival time was used to describe PFS and OS. Waterfall plots were used to visualize the best percentage changes in target lesion size from baseline, summarizing therapeutic responses. The Kaplan-Meier survival analysis method and the log-rank test was employed to estimate OS and PFS. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of general characteristics. A total of 22 patients (17 men and 5 women) were included in the present study. The age range of the patients was from 40 to 79 years old (median age, 63.5 years) and their body mass index ranged from 18.6 to 31.7 (mean value, 21.9). According to the ECOG scoring criteria, 19 patients had a score of 0 and 3 patients had a score of 1. In terms of pathological classification, 19 patients were diagnosed with ccRCC, accounting for 86.4%, while the remaining 3 patients had papillary RCC (2 cases) and chromophobe RCC (1 case). Based on the 8th edition of American Joint Committee on Cancer clinical Tumor Node Metastasis staging system for RCC (16), the number and proportion of patients in each stage were as follows: 4 cases (18.2%) in stage cT2a, 2 cases (9.1%) in stage cT2b, 6 cases (27.3%) in stage cT3a, 8 cases (36.4%) in stage cT3b and 2 cases (9.1%) in stage cT3c. Regarding lymph node metastasis, 16 patients (72.7%) were in the N0-x stage, and 6 patients (27.3%) were in the N1 stage. In total, 17 patients had previously undergone nephrectomy, while 5 had not. Additionally, 13 patients had cancer on the left side, 8 on the right side and 1 patient had bilateral renal cancer. Of all patients, 10 had metastasis to only one organ, while 12 had metastasis to two or more organs. The organs with metastases included the lungs (15 cases, 68.2%), lymph nodes (10 cases, 45.5%), bones (8 cases, 36.4%), liver (3 cases, 13.6%), brain (2 cases, 9.1%) and other sites (2 cases, 9.1%). According to the IMDC risk stratification, 3 patients were classified as favorable-risk (13.6%), 17 as intermediate-risk (77.3%), and 2 as poor-risk (9.1%). Furthermore, 6 patients discontinued treatment due to AEs (27.3%). Please see Table I for a summary of the general characteristics of the patients included in the present study.

Table I. General characteristics of the 22 included patients.

Characteristic	Value
Median age, years (range)	63.5 (40-79)
Sex, n (%)	
Male	17 (77.3)
Female	5 (22.7)
BMI, kg/m^2 (range)	21.9 (18.6-31.7)
ECOG score (%)	
0	19 (86.4)
1	3 (13.6)
Baseline cTNM, n (%)	
cT2a	4 (18.2)
cT2b	2 (9.1)
cT3a	6 (27.3)
cT3b	8 (36.4)
cT3c	2 (9.1)
N0-x	16 (72.7)
N1	6 (27.3)
Prior nephrectomy, n (%)	
Yes	17 (77.3)
No	5 (22.7)
Metastatic organs, n (%)	
1 organ	10 (45.5)
≥2 organs	12 (54.5)
Major metastatic organs, n (%)	
Lung	15 (68.2)
Lymph node	10 (45.5)
Bone	8 (36.4)
Liver	3 (13.6)
Brain	2 (9.1)
Other	2 (9.1)
Side, n (%)	
Left	13 (59.1)
Right	8 (36.4)
Bilateral	1 (4.5)
With tumor thrombus, n (%)	5 (22.7)
Histology, n (%)	
ccRCC	19 (86.4)
Other	3 (13.6)
Sarcomatoid features, n (%)	
Yes	2 (9.1)
No	20 (90.9)
IMDC classification, n (%)	
Favorable	3 (13.6)
Intermediate	17 (77.3)
Poor	2 (9.1)
Discontinuation of therapy due to AEs, n (%)	
Yes	6 (27.3)
No	16 (72.7)

AEs, adverse events; BMI, body mass index; ccRCC, clear cell renal cell carcinoma; cTNM, clinical Tumor Node Metastasis; ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

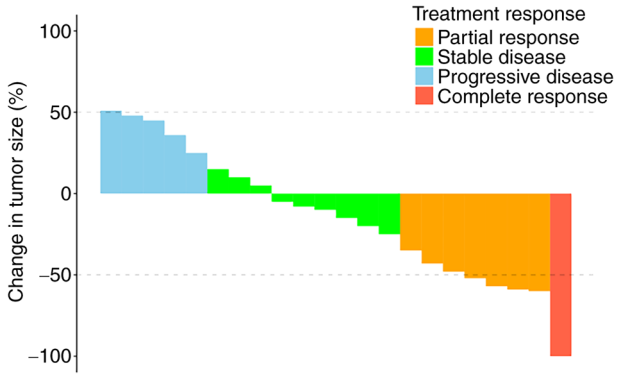

Figure 1. Waterfall plot of the best change from baseline in target lesion size. Each bar represents an individual patient (n=22). The dashed line indicates a 30% reduction from baseline (partial response threshold).

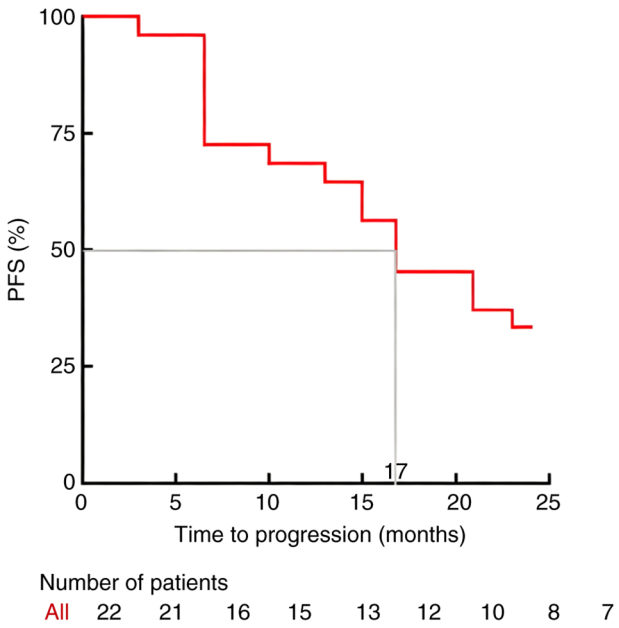

Figure 2. Kaplan-Meier curve for PFS. The median PFS was 17.1 months (range, 5.9-22.6). Ticks represent censored patients. All 22 patients received pazopanib plus toripalimab. PFS, progression-free survival.

Comparison of efficacy. In the present study, as of the follow-up in March 2024, 17 patients were still undergoing treatment. Among all patients, 1 achieved a CR (4.55%), 7 achieved a PR (31.82%), 9 had SD (40.91%) and 5 had PD (22.73%) (Fig. 1). The overall ORR was 36.36% (8/22) and the DCR was 77.27% (17/22).

Survival analysis. The median follow-up time in the present study was 14 months (range, 3-24 months). The median PFS time was 17.1 months [range, 5.9-22.6; Fig. 2], but the median OS time was not reached. Due to the limited follow-up duration of 14 months, OS data are not available; therefore, PFS served as the primary efficacy endpoint in this preliminary analysis. At 2 years, most patients had controlled disease, with only 5 patients experiencing disease progression. The PFS stratified by IMDC risk criteria is shown in Fig. 3. There was a significant difference in PFS across risk groups (log-rank P<0.001). Patient in the favorable-risk group showed the most

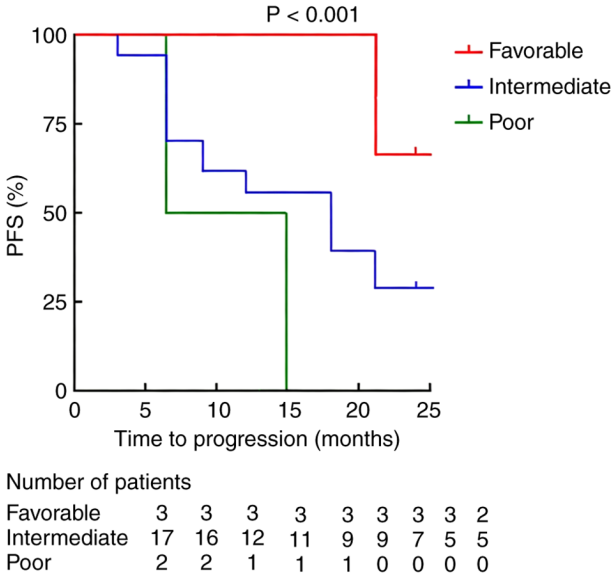

Figure 3. PFS stratified by IMDC risk group: Favorable (n=3), intermediate (n=17) and poor (n=2). Log-rank test showed a significant difference among groups (P<0.001). Patients with a lower IMDC risk had a longer PFS time. PFS, progression-free survival; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

favorable outcomes, with no events occurring before 20 months and a 24-month PFS rate of 66.7%. In contrast, patients in the intermediate-risk group had a gradual decline in PFS, reaching a 24-month PFS rate of 28.6%. Patients in the poor-risk group had the shortest PFS, with all patients experiencing disease progression by 15 months.

Comparison of AEs. The incidence of AEs of all grades was 81.82% (Table II). Most of these AEs were grade 1-2, with 6 patients experiencing grade 3-4 reactions, leading to treatment interruption. Among these patients, 3 had elevated transaminases. After discontinuing pazopanib for 4-6 weeks and receiving symptomatic and supportive treatment, their levels returned to the normal range (ALT, AST ≤40U/l). Subsequently, the pazopanib dose was resumed at 600 mg and continued until the data cutoff date, with 1 patient achieving PR, 1 maintaining stability and 1 experiencing PD. The remaining 3 patients were considered to have irAEs. After discontinuing toripalimab and receiving symptomatic, supportive and hormonal treatment, these patients showed notable improvement. Then, they continued treatment with pazopanib monotherapy until the data cutoff date, with 2 patients maintaining SD and 1 experiencing PD.

Discussion

In recent years, the incidence of RCC has continued to rise globally, with a 5-year mortality rate reaching 30-40% (1,2). According to statistics, factors such as sex, obesity, chronic kidney disease, smoking and hypertension are known risk factors for RCC (17). When RCC progresses to the advanced stage and metastasizes, it is referred to as mRCC. The common sites of metastasis include the liver, lungs, adrenal glands, bones, skin and even the brain (2). The progression to mRCC often indicates a poor prognosis for patients, with

Table II. Incidence of AEs.

AEs	Grade		Total, n (%)
	1-2, n	3-4, n	
Any	12	6	18 (81.82)
Fatigue	6	0	6 (27.27)
Nausea/vomiting	4	0	4 (18.18)
Diarrhea	7	0	7 (31.82)
Hypertension	6	1	7 (31.82)
Proteinuria	4	1	5 (22.73)
Elevated transaminases	11	3	14 (63.64)
Hypothyroidism	3	1	4 (18.18)
Hand-foot skin reaction	5	0	5 (22.73)
Rash	2	0	2 (9.09)
Leucopenia	3	0	3 (13.64)

AEs, adverse events.

a potentially significant reduction in survival time (2). The underlying mechanism of mRCC development involves inactivation of the von Hippel-Lindau tumor suppressor gene, which promotes the upregulation of crucial proteins such as VEGF, platelet-derived growth factor, transforming growth factor and other proteins related to neovascularization (18). These factors play pivotal roles in the development and metastasis of tumors (19).

Immunotherapy, which activates the immune system to inhibit tumor growth and dissemination, has emerged as a new hope in the treatment of mRCC (20). PD-1/PD-L1 and CTLA-4 inhibitors are commonly used ICIs. ICIs targeting PD-1/PD-L1 have made significant breakthroughs in the field of oncology. Toripalimab, which targets PD-1, has been approved for first-line clinical treatment of multiple malignancies (21,22), and significantly prolongs PFS without introducing new safety concerns compared with existing treatment regimens. In a Phase I clinical study of toripalimab for advanced melanoma and urological tumors, 5 patients with advanced renal cancer who had progressed after previous conventional treatments were enrolled. Among them, 2 patients achieved confirmed PR and 1 patient had SD, resulting in an overall ORR of 33% and a DCR of 50%. These findings initially demonstrated the antitumor activity of toripalimab in advanced renal cancer (23).

Targeted therapy, characterized by its high specificity and relatively milder side effects, has become a cornerstone in the treatment of renal cancer. Commonly used targeted drugs in renal cancer primarily inhibit tumor growth by affecting tumor angiogenesis. Representative drugs in this category include sorafenib, sunitinib, everolimus and pazopanib, which exert their tumor-suppressing effects through different pathways (24-30). In particular, pazopanib targets tyrosine kinases to block the formation of new blood vessels in tumors, thereby inhibiting the further proliferation and migration of tumor cells, ultimately suppressing tumor growth and dissemination (31,32). Multiple studies have shown evidence of pazopanib's positive response as a first-line treatment for mRCC. For instance, Park *et al* (33) reported that pazopanib treatment resulted in a PFS time of 8 months compared with placebo, and a PFS of 11 months compared with sunitinib. Joshi *et al* (34) reported that, in a continuous treatment study of 28 patients with mRCC in India, the overall clinical benefit rate (PR + SD) was 76%, with a median PFS time of 5.9 months. In a single-center retrospective study of 40 patients with mRCC treated with three different TKIs (sunitinib, pazopanib and sorafenib), Rudresha *et al* (35) reported that the median PFS and OS times for patients treated with pazopanib were 11.2 and 20.1 months, respectively.

In recent years, the combination of targeted therapy and immunotherapy has achieved certain efficacy in the field of oncology. For instance, a study by Hedegaard *et al* (36) reported the results of a Phase III clinical trial where the combination of axitinib and pembrolizumab was used to treat advanced renal cancer, showing significant improvements in OS and PFS compared with axitinib alone. The KEYNOTE-426 study (37) focused on the combined application of pembrolizumab with axitinib, using sunitinib as a comparator, for first-line treatment of advanced ccRCC. This long-term follow-up study demonstrated that the immune-targeted combination therapy significantly improved the PFS and OS times of patients, with the median OS time in the combination therapy group reaching 45.7 months, exhibiting a significant advantage over the 40.1 months in the sunitinib group [hazard ratio (HR), 0.73; 95% CI 0.60-0.88; P<0.001]. The JAVELIN Renal-101 study (38) evaluated the efficacy of avelumab combined with axitinib in patients with advanced RCC. Although this combination therapy showed a significant advantage in PFS, particularly among patients with PD-L1-positive tumors, the OS in the overall patient population did not reach statistical significance. However, in the high-risk patient subgroup, the combination therapy group demonstrated a significant improvement in OS, providing a new perspective and basis for the application of immune-targeted combination therapy

in specific patient populations. Furthermore, the CheckMate 9ER study (39) explored the combined therapy of cabozantinib with nivolumab, comparing its effectiveness with sunitinib in patients with advanced RCC and bone metastases. The combination therapy significantly prolonged the PFS time in both patients with and without bone metastases, and the ORR was also significantly higher than that of the sunitinib group. Notably, for patients with bone metastases, the median PFS time of the combination therapy reached 18.2 months, far exceeding the 4.4 months in the sunitinib group (HR, 0.38; 95% CI, 0.25-0.59). Compared with studies conducted abroad, this type of research in China is scarce. The latest domestic research was the RENOTORCH study (40), jointly led by Professor Guo Jun from Peking University Cancer Hospital and Professor Huang Yiran from Renji Hospital (School of Medicine, Shanghai Jiao Tong University), which aimed to evaluate the efficacy and safety of the PD-1 immunotherapy drug toripalimab (developed in China) combined with axitinib as first-line treatment for patients with unresectable or mRCC, compared with sunitinib. The present study showed that the median PFS time in the toripalimab + axitinib group reached 18.0 months, while that in the sunitinib monotherapy group was 9.8 months, representing a nearly two-fold extension (HR, 0.66; 95% CI 0.490-0.864; P=0.0034). The ORR in the combination group was 56.7%, significantly higher than the 30.8% in the sunitinib monotherapy group. Although the median OS data are not available, the combination therapy group demonstrated a clear OS benefit trend, with a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.40-0.92) and 1-year and 2-year OS rates of 90.5 vs. 81.9% and 71.8 vs. 63.2%, respectively.

Despite the existence of numerous associated studies (36-40), to the best of our knowledge, there is currently a paucity of clinical research on toripalimab for the treatment of patients with mRCC, especially the first-line treatment of mRCC with the combination of pazopanib and toripalimab. The results of the present study are not directly comparable to those from large phase III trials such as KEYNOTE-426 (41) (pembrolizumab + axitinib) or CheckMate 9ER (nivolumab + cabozantinib), which were randomized, controlled studies and included hundreds of patients (39). These trials provided high-level evidence supporting the superiority of immune-TKI combinations over sunitinib. By contrast, the present single-arm, retrospective analysis of 22 patients can only offer hypothesis-generating observations. Direct cross-trial comparisons should be avoided and the present findings should be viewed as complementary real-world data rather than confirmatory evidence. The present study aimed to explore the clinical application effect of this combination therapy by treating patients with mRCC with pazopanib + toripalimab and observing the clinical efficacy and occurrence of adverse reactions.

In the present study, among all patients, there was 1 case of CR, 7 cases of PR, 9 cases of SD and 5 cases of PD. The overall ORR was 36.4%, indicating that approximately one-third of patients experienced positive treatment outcomes; the DCR was 77.3%, suggesting that the condition of most patients was somewhat controlled. Given the small sample size, these rates should be interpreted as descriptive statistics only; that is, no comparative inferences can be drawn. Treatment was interrupted due to AEs in 27.3% of patients, with half of these patients having their pazopanib dosage reduced to 600 mg. However, given the small sample size, no definitive conclusion can be drawn regarding the impact of dose reduction on efficacy; the observation that some patients maintained disease control after reduction to 600 mg is hypothesis-generating and warrants further investigation. Regarding PFS, the decline in the PFS curve became gradual over time, which may be related to the time required for immunotherapy to take effect. In the initial stages of immunotherapy, the immune system may not be fully activated, requiring time to activate and expand T cells within the body to achieve sufficient numbers and activity to effectively kill tumor cells. This process involves multiple steps, including T-cell recognition, activation, proliferation and migration, all of which require time to complete.

In the present study, the safety profile during treatment revealed that common AEs included primarily fatigue (27.27%), nausea/vomiting (18.18%), diarrhea (31.82%), hypertension (31.82%), proteinuria (22.73%), elevated transaminases (63.64%), hypothyroidism (18.18%), hand-foot skin reaction (22.73%), rash (9.09%) and leukopenia (13.64%). Most patients experienced mild to moderate (grade 1-2) AEs, although some reported severe (grade 3-4) AEs such as hypertension, proteinuria, elevated transaminases and hypothyroidism. Among these, liver function abnormalities due to elevated transaminases were the most frequent AE, occurring in up to 63.64% of patients. Xu *et al* (42), through pharmacogenetic analysis, found that this elevation in transaminases was associated with the mechanism of pazopanib-induced liver injury. Ezponda *et al* (43) confirmed that pazopanib could improve PFS in patients with advanced non-lipogenic soft tissue sarcoma but could also trigger the occurrence of chronic active hepatitis. These findings further explain the higher incidence of liver function abnormalities and highlight the need to carefully consider appropriate dose titration of pazopanib in this combination therapy strategy.

In summary, within the constraints of the present small retrospective cohort, the combination of pazopanib and toripalimab showed preliminary signs of activity in the first-line treatment for mRCC, with a median PFS time of 17.1 months and a generally manageable safety profile. These real-world observations do not provide comparative evidence of benefit over standard therapies and should not be overinterpreted. The safety data were consistent with previous reports, but attention should be paid to the hepatotoxicity of pazopanib and the rational determination of its dosage.

The present study has several limitations that must be considered when interpreting the results. First, it is a retrospective, single-arm, single-center analysis with a small sample size (n=22), which notably limits the statistical power and generalizability of the findings. Second, no comparator group (such as pazopanib monotherapy or other standard first-line regimens) was included, making it impossible to determine the true added benefit of toripalimab. Third, the median follow-up of 14 months is relatively short for assessing OS in mRCC; therefore, OS data remained immature, and PFS was the primary focus of the present preliminary report. Fourth, the limited

sample size precluded robust subgroup analyses (such as by IMDC risk groups or metastatic burden) and the reported 95% CIs for ORR and DCR should be interpreted with caution. Fifth, as a real-world study, potential selection bias and unmeasured confounders (such as performance status changes and concomitant medications) cannot be excluded. Consequently, these findings should be regarded as exploratory and hypothesis-generating, not as definitive evidence of efficacy. Prospective randomized controlled trials are essential to validate the role of pazopanib plus toripalimab in the first-line treatment of mRCC.

In conclusion, in the present real-world, single-center, retrospective study of 22 patients, first-line pazopanib combined with toripalimab for mRCC showed exploratory, hypothesis-generating signs of efficacy with a safety profile that appeared manageable. Owing to the lack of a control group and the small sample size, no definitive conclusions regarding superiority over existing standard therapies can be drawn. These observations support the feasibility of the combination and highlight the need for further prospective randomized controlled trials, but they do not justify current clinical recommendations.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BW designed the study, acquired funding, performed data collation and wrote the manuscript. TX, HL, XH and KW analyzed and interpreted the data. BW, TX, HL, XH and KW revised the manuscript. XH and KW supervised the study. BW and KW confirm the authenticity of all the raw data. All the authors have contributed to this manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Shanxi Cancer Hospital (approval no. KY2023106), and all patients provided written informed consent for the use of their clinical data. The study adhered to the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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