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First-line pazopanib in patients with advanced non-clear cell renal carcinoma: An Italian case series

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Abstract

BACKGROUND
Non-clear cell (ncc) metastatic renal-cell carcinoma (RCC) has dismal results with standard systemic therapies and a generally worse prognosis when compared to its clear-cell counterpart. New systemic combination therapies have emerged for metastatic RCC (mRCC), but the pivotal phase III trials excluded patients with nccRCC, which constitute about 30% of metastatic RCC cases.

AIM
To provide a piece of real-life evidence on the use of pazopanib in this patient subgroup.

METHODS
The present study is a multicenter retrospective observational analysis aiming to assess the activity, efficacy, and safety of pazopanib as first-line therapy for advanced nccRCC patients treated in a real-life setting.

RESULTS
Overall, 48 patients were included. At the median follow-up of 40.6 mo, the objective response rate was 27.1%, the disease control rate was 83.3%, and the median progression-free survival and overall survival were 12.3 (95% confidence interval [CI]: 3.6-20.9) and 27.7 (95%CI: 18.2-37.1) mo, respectively. Grade 3 adverse events occurred in 20% of patients, and no grade 4 or 5 toxicities were found.

CONCLUSION
Pazopanib should be considered as a good first-line option for metastatic RCC with variant histology.

Key Words: Pazopanib; Non-clear cell; Kidney cancer; Renal-cell carcinoma; Variant histology; Tyrosine kinase inhibitors

Core Tip: Non-clear cell metastatic renal-cell carcinoma (nccRCC) has dismal results with standard systemic therapies and a poor prognosis. Few therapeutic molecules have

been explicitly tested in nccRCC patients. We retrospectively collected 48 advanced nccRCC patients treated with pazopanib in the first-line setting, offering promising findings of quite good response rate (27%), progression-free survival around 12 mo, and overall survival around 28 mo. In light of these results, we suggest that pazopanib can be a good treatment choice in this subgroup of patients, pending the results of ongoing clinical trials with new therapeutic combinations.

INTRODUCTION

Non-clear cell renal-cell carcinoma (nccRCC) represents a heterogeneous group of tumors with distinct genomic and metabolic features. Therefore, its clinical behavior can be benign to indolent and even highly malignant with high metastatic potential[1].

Of note, non-clear mRCC has dismal results with standard systemic therapies and a generally worse prognosis when compared to its clear-cell counterpart, as demonstrated in a large study by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), showing a worse overall survival (OS) for patients with nccRCC compared to ccRCC patients [12.8 mo (95%CI: 11.0-16.1) *vs* 22.3 mo (20.7-23.5)][2].

Recent advances have offered the availability of new systemic therapies for metastatic RCC (mRCC), such as immunotherapy-based combinations with the current recommendation in the first-line setting[3-6]. These combinations, all forecasting the use of anti-PD-1/PD-L1 immune checkpoint inhibitors (ICIs), have been investigated in phase III randomized clinical trials (RCTs) enrolling patients with clear-cell RCC (ccRCC) or at least a clear-cell component in the tumor histology. Nevertheless, conventional clear-cell RCC accounts for only 70% of renal cortical tumors that metastasize, preventing to provide evidence for 30% of mRCC patients still lacking indication for the most productive therapeutic solutions. About nccRCC, international guidelines still recommend that such patients should be preferentially referred to clinical trials.

The previous gold-standard first-line therapies for mRCC, represented by anti-vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs) used as a single agent, have been in part investigated in nccRCC patients. In particular, sunitinib was tested in two prospective trials (the ESPN trial and the ASPEN trial) initially planned to show the superiority of the mammalian target of rapamycin inhibitor everolimus over sunitinib as first-line therapy. Both studies, on the contrary, finally supported the use of sunitinib as a primary systemic approach in this population of patients[7,8]. On the other hand, other TKIs have been approved in the first-line setting for all-mRCC histologies, including the alternative with pazopanib, which demonstrated similar efficacy and even better safety profile when compared to sunitinib in randomized trials[9,10]. Nevertheless, little evidence is available about using this drug in nccRCC patients, with a consequent reluctance to prescription in clinical practice, notwithstanding the drug's good profile, also suitable for frail and elderly patients[11,12].

Given the unmet oncological need for evidence for the systemic approach to nccRCC, the present report of a retrospective multicenter case series aims to provide a piece of real-life evidence on the use of pazopanib in this patient subgroup.

MATERIALS AND METHODS

Study population and setting

The present study is a retrospective, observational analysis aiming to assess the

activity, efficacy, and safety of pazopanib as first-line therapy for advanced nccRCC patients treated in a real-life setting at multiple Italian institutions. The principal inclusion criteria were the diagnosis of nccRCC, including papillary RCC (pRCC), chromophobe RCC (chRCC), RCC with Xp11 translocation, RCC with undefined histology, and mixed-histology RCC with mostly ncc component; receiving the first dose of pazopanib between June 2012 and June 2015; > 18 years old; measurable disease at the computed tomography (CT) scans performed according to clinical practice at the treating centers. Data were collected between February 2017 and February 2018.

Study endpoints

The primary objective was to assess the outcome of patients in terms of objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), OS, and tolerability as co-primary endpoints. PFS was defined as the time between pazopanib initiation and disease progression or death; OS was defined as the time between pazopanib initiation and death or the date of the last follow-up visit for alive patients; DCR as responses plus stable diseases. Objective responses (complete, CR; partial, PR; stable, SD; progressive disease, PD) were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[13] and assessed every 2-3 mo according to clinical practice.

Treatment-related adverse events (TRAEs) were recorded as clinical practice according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (in use at the time of the study conduct)[14].

The characteristics of patients were collected, and their correlation with the outcome was explored.

The study was reviewed and approved by the Local Ethics Committee of Parma (Italy). All study participants provided informed written consent before study enrollment.

Statistical analysis

Descriptive statistics are used to summarize the data. PFS and OS were estimated using the Kaplan-Meier method with 95% confidence intervals (CI) and compared using the log-rank test. Univariate and multivariate analyses were performed by using Cox proportional hazards models. The comparison between categorical endpoints was performed using the chi-square test. Significance levels were set at a 0.05 value, and all *P* values were two-sided. SPSS Statistics 24.0 software (IBM Corporation, Armonk, NY, United States) was used to conduct the statistical analyses.

RESULTS

From January 2011 to January 2017, 48 consecutive patients were included in 20 Italian centers. The median follow-up was 40.6 mo (95%CI: 22.3-58.9). The characteristics of patients are reported in Table 1. The median age was 70 (range, 27-86) years, and most patients were male (75.0%). Fifteen patients (31.3%) had distant metastases at disease onset. The majority of patients had pRCC (50.0%) or chRCC (18.8%) as histology. Most patients had previously received nephrectomy (85.4%), and seven (14.6%) had metastasectomy. Thirty-seven patients (77.1%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0. All IMDC risk groups were represented in the study population.

The median duration of treatment was 9.1 (range, 0.6-52.5) mo, and eight patients (16.7%) were still receiving pazopanib at the time of the last follow-up. Twenty-eight patients (58.3%) received a second-line therapy (four received nivolumab and three cabozantinib).

In 17 cases (35.4%), the starting dose of pazopanib was primarily reduced because of the patient conditions (age and/or comorbidity): Ten patients started with 600 mg, and seven patients started with 400 mg. Secondary dose reductions or temporary treatment discontinuations due to TRAEs were required in 19 cases (39.6%), mainly due to grade (G) 3 hepatic toxicity, fatigue, and diarrhea. G3 TRAEs occurred in 20.8% of patients, G1-2 in 81.2%, and no G4 toxicity was observed (Table 2).

PR was achieved in 13 patients (27.1%), and no CR was observed. Twenty-seven patients (56.3%) obtained SD; the DCR was 83.3%, whereas six patients (12.5%) had PD as the best response (while 4.2% were not evaluable). Neither ORR nor DCR was significantly correlated with any of the following parameters: Sex, histology, grading, sarcomatoid component, initial pazopanib dose, ECOG PS, and IMDC risk group.

Table 1 Characteristics of patients, *n* (%)

Baseline characteristic	*n* = 48
Age, median (range)	70 (27-86)
Sex	
Males	36 (75)
Females	12 (25)
Histology	
Papillary	24 (50)
Chromophobe	9 (10.8)
Xp11 translocation	1 (2.1)
Unclassified	6 (12.5)
Mixed[1]	8 (16.7)
Grade (Fuhrman/ISUP)	
1-2	6 (12.5)
3	15 (31.3)
4	4 (8.3)
NA	23 (47.9)
Stage at diagnosis	
I-III	33 (68.8)
IV	15 (31.3)
Previous nephrectomy	
Yes	41 (85.4)
No	7 (14.6)
Metastasectomy	
Yes	7 (14.6)
No	41 (85.4)
ECOG PS	
0	37 (77.1)
1	11 (22.9)
IMDC score risk group	
Good	19 (39.6)
Intermediate	25 (52.1)
Poor	2 (4.2)
NA	2 (4.2)
Starting dose of pazopanib	
800 mg	31(64.6)
600 mg	10 (20.8)
400 mg	7 (14.6)

[1]Four tumors had mixed histology (clear-cell/papillary) with papillary histology prevalence and four tumors had mixed histology (clear-cell/chromophobe) with chromophobe histology prevalence.

NA: Not assessed/available; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ISUP: International Society of Urological Pathology.

Table 2 Adverse events according to Common Terminology Criteria for Adverse Events (version 4.0)

Adverse event	Grade 1/2, *n* (%)	Grade 3, *n* (%)
Fatigue	24 (50.0)	
Diarrhea	15 (31.3)	2 (4.2)
Mucositis	9 (18.8)	
Hypertransaminasemia	7 (14.6)	4 (8.3)
Thrombocytopenia	6 (12.5)	
Anemia	15 (31.2)	2 (4.2)
Neutropenia	5 (10.4)	
Hypothyroidism	15 (31.3)	
Disgeusia	5 (10.4)	1 (2.1)
Cutaneous toxicity[1]	8 (16.7)	
Nausea/vomiting	14 (29.2)	
Heart failure	1 (2.1)	
Renal failure	5 (10.4)	1 (2.1)
Other[2]	16 (33.3)	

[1]Including discoloration of hairs and cutis, hand-foot syndrome, and dermatitis.

[2]Including bleeding, sleepiness, hypertrigliceridemia, hypophosphoremia, hyperbilirubinemia, loss of appetite/hyporexia, dyspepsia/epigastralgia, and hypertension.

Most cases of primary refractory (PD as best response) were pRCC. Table 3 shows the responses according to the histology.

Median PFS and OS were 12.3 (95%CI: 3.6-20.9) and 27.7 (95%CI: 18.2-37.1) mo, respectively (Figure 1, Table 3).

In the univariate analysis, no factors (among sex, previous nephrectomy, histology, grading, metastatic disease at diagnosis, previous metastasectomy, IMDC risk group, ECOG PS, and initial pazopanib dose) were significantly associated with PFS. Conversely, factors significantly associated with a better OS were IMDC group (P = 0.011), previous nephrectomy (P = 0.002), previous metastasectomy (P = 0.008), absence of metastatic disease at diagnosis (P = 0.014), and subsequent therapy with cabozantinib or nivolumab (P = 0.049).

Notwithstanding the limit of multivariate analysis in such a small sample size, it was performed for OS, and only the absence of metastatic disease at diagnosis (hazard ratio = 8.49, 95%CI: 1.76-40.90; P = 0.008) maintained a positive impact on OS.

DISCUSSION

The present analysis reported the most extensive case series, to our knowledge, treated with the TKI pazopanib as first-line systemic therapy for advanced nccRCC patients.

The activity and efficacy outcomes are in line with those reported by two prior series from the literature, with an ORR around 27%, a good DCR (over 80%), an mPFS over 1 year, and a good mOS of 27.7 mo. Compared to the other older reports, our study also included patients receiving new-generation drugs as second-line after pazopanib (*i.e.*, nivolumab or cabozantinib), suggesting (in the univariate analysis) this choice as significantly associated with improved survival and providing some evidence for these treatment sequences in nccRCC.

Regarding safety, pazopanib was generally well-tolerated, with G3 TRAEs occurring only in 20% of patients and no G4-5 toxicities. The AE-related discontinuations and the initial dose reductions were relatively frequent. Still, no impact on the outcome was evidenced for the latter choice, often preferable for frail patients with hepatic impairment or cardiovascular comorbidities.

The limitations of our report are represented by the retrospective nature, the heterogeneous follow-up time (with a wide range, but a good median value), the lack of central independent revision for the histological samples (nccRCC histology based on

Table 3 Objective response rate, progression-free survival, and overall survival outcomes

Effectiveness outcome	All patients (*n* = 48)	Papillary RCC (*n* = 24)	Chromophobe RCC (*n* = 9)
Response rate (RECIST 1.1), *n* (%)			
Partial responses	13 (27.1)	6 (25.0)	2 (22.2)
Complete responses	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease	27 (56.3)	14 (58.3)	5 (55.5)
Progressions of disease	6 (12.5)	3 (12.5)	1 (11.1)
Not evaluable	2 (4.2)	1 (4.2)	1 (11.1)
Disease control rate	40 (83.3)	20 (83.3)	7 (77.8)
PFS			
Median (mo) (95%CI)	12.3 (3.6-20.9)	-	-
Rate of patients progression free at 6 mo	67.8%	-	-
Rate of patients progression free at 12 mo	49.0%	-	-
OS			
Median (mo) (95%CI)	27.6 (18.3-37.1)	-	-
Rate of patients alive at 12 mo	82.7%	-	-
Rate of patients alive at 24 mo	62.0%	-	-

RCC: Renal cell carcinoma; PFS: Progression free survival; OS: Overall survival; RECIST 1.1: Response Evaluation Criteria in Solid Tumours version 1.1.

the original diagnosis), and the limited number of patients receiving new-generation drugs (such as cabozantinib or nivolumab) in other treatment lines. On the other hand, the present analysis corroborates with the largest sample size two previous similar retrospective case series, providing herein clean data for pure first-line setting (as a difference *vs* Matrana *et al*[12]), and supporting the use of pazopanib as a single agent for nccRCC patients with advanced disease.

A further single-TKI alternative could be available in the next future as a primary choice for the subgroup of pRCC patients, represented by the third generation TKI cabozantinib. Currently approved as a first-line treatment option for ccRCC patients with poor- or intermediate-risk according to the IMDC model, this drug was investigated in a prospective study as a first- or second-line TKI for advanced pRCC. It demonstrated improved PFS (median 9.0 mo, 95%CI: 6-12) *vs* the comparator sunitinib (5.6 mo, 95%CI: 3-7; HR = 0.60, 95%CI: 0.37-0.97, *P* = 0.019) and ORR (23% *vs* 4% for sunitinib, *P* = 0.010), at the cost of quite manageable toxicity and a toxic death reported [15].

Beyond TKIs, the advent of immunotherapy has finally landed also in the field of nccRCC, reporting initial findings from prospective monotherapy trials. The single-arm phase II Keynote-427 trial investigated the efficacy and safety of single-agent pembrolizumab, a PD-1 inhibitor, in advanced nccRCC. In this study, 71.5% of patients had confirmed pRCC, 12.7% had chRCC, and 15.8% had unclassified RCC histology. Overall, the ORR was 26.7% (28.8% for papillary, 9.5% for chromophobe, and 30.8% for unclassified RCC); the mPFS was 4.2 mo (95%CI: 2.9-5.6), and the mOS was 28.9 mo. The toxicity was manageable, with 69.7% of patients reporting TRAEs; nevertheless, two deaths were reported as treatment-related[16]. These findings are pretty encouraging about the activity of immunotherapy in variant histologies. Anyway, the activity seems in line with those reported herein for pazopanib (similar ORR). In contrast, the efficacy appears relatively poor in terms of mPFS compared with that reported with TKIs in ours and similar populations. On the other hand, the OS outcome was similar.

Another first-line trial (Checkmate-920) recently investigated an immunotherapy combining ipilimumab and nivolumab (anti-CTLA-4 and anti-PD1 respectively) in a nccRCC treatment-naïve population. The first results reported relatively high rates of G3 (92.3%) and G4 (36.5%) toxicities (but without toxic deaths), ORR of 19.6%, and mPFS of 3.7 mo (95%CI: 2.7-4.6)[17]. The SUNNIFORECAST trial, a phase II randomized study currently ongoing with the same combination *vs* standard of care for previously untreated nccRCC patients, will provide further evidence about this
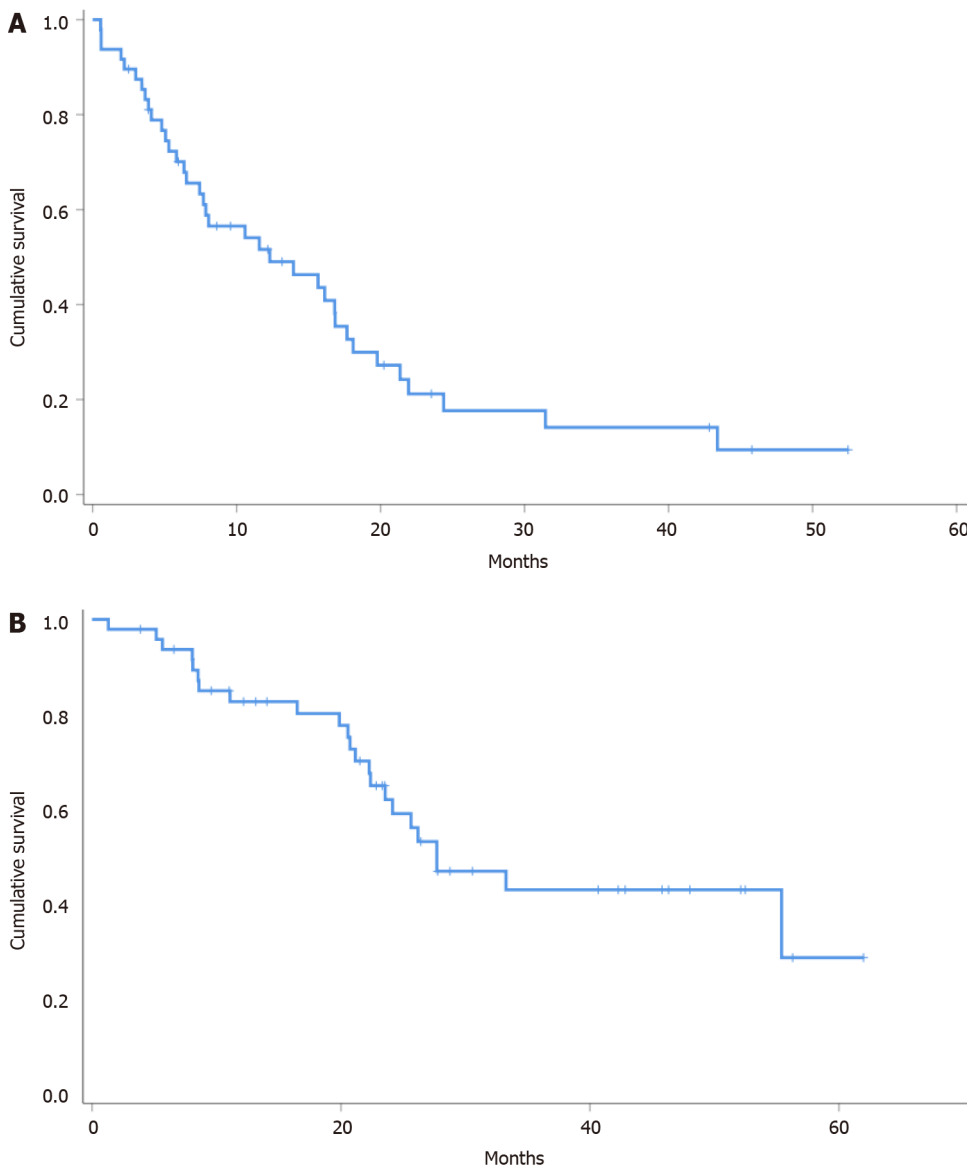
Figure 1 Progression-free survival (A) and overall survival (B) of the study population.

exclusive immunotherapy strategy (NCT03075423).

CONCLUSION

On the one hand, RCC with sarcomatoid features (irrespective of the primary histology) indeed gains excellent benefit from immunotherapy compared to TKIs[18]. On the other hand, RCC with variant histology still needs a TKI-based approach, with new generation TKIs, possibly combined with ICIs in future trials.

Meanwhile, the single-agent options should include pazopanib, favored by excellent manageability in terms of safety, and supported by high feasibility and excellent cost-effectiveness, especially for elderly patients.

ARTICLE HIGHLIGHTS

Research background

Non-clear cell metastatic renal-cell carcinoma (nccRCC) has dismal results with standard systemic therapies and a generally worse prognosis when compared to its clear-cell counterpart.

Research motivation

We aimed to provide a piece of real-life evidence on the use of pazopanib in this patient subgroup.

Research objectives

To assess the activity, efficacy, and safety of pazopanib as first-line therapy for advanced nccRCC patients treated in a real-life setting.

Research methods

This was a multicenter retrospective observational analysis.

Research results

The objective response rate with pazopanib was 27.1%, the disease control rate was 83.3%, and the median progression-free survival and overall survival were 12.3 (95%CI: 3.6-20.9) mo and 27.7 (95%CI: 18.2-37.1) mo, respectively. Grade 3 adverse events occurred in 20% of patients, and no grade 4 or 5 toxicities were found.

Research conclusions

Pazopanib should be considered as a good first-line option for metastatic RCC with variant histology.

Research perspectives

Pazopanib warrants further development in metastatic RCC with variant histology.

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