JBUON 2021; 26(6): 2571-2576
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

First-line pazopanib in metastatic renal cell carcinoma: Multicenter experience

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Summary

Purpose: *To investigate the efficacy and safety of pazopanib in the first line treatment of metastatic renal cell carcinoma in an everyday oncology practice population.*

Methods: *Patients aged 18 years and older and histopathologically diagnosed with renal cell carcinoma between 2012 and 2020 were included in the study. All patients received pazopanib treatment at a daily dose of 800 mg. Radiological response was assessed every 12 weeks using abdominal and thoracic CT. The side effects were graded using National Cancer Institute Criteria (CTCAE v4.).*

Results: *A total of 84 patients were included. The median age was 61 years (range: 37-87). There were 59 (70.2%) males and 25 (29.8%) females. The objective response rate (ORR: CR + PR) was 26.6%, while the disease control rate (DCR: CR + PR + SD) was 77.4% . Median progression-free survival (PFS) was 14.4 months (95%Cl, 8.0-20.7). The median overall survival (mOS) was 23.9 months (95%CI, 5.9-41.8). When compared, the MSKCC favorable group had a median OS of 37.8 vs. 22 and 6.5 months for the intermediate and poor risk groups, respectively (p=0.179). Multivariate analysis for OS revealed that more than 2 metastatic sites (p=0.025) and clear cell histology (p=0.015) were predictors of poor and improved survival, retrospectively.*

Conclusions: *The results of this study revealed that patients with metastatic clear cell RCC outside the context of a randomized clinical study confirmed the efficacy and safety of pazopanib used as a first-line treatment in real-life conditions.*

Key words: *pazopanib, renal cell carcinoma, MSKCC risk stratification, real life data, side effects*

Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney, comprising approximately 90% of all cases. The most common (80%) pathologic subtype of RCC is clear cell carcinoma, while papillary, chromophobe, and collecting duct tumors have lower frequency. The mean age at diagnosis is 64 years, with a male to female ratio of 2:1 [1-3].

Nearly a third of the cases have metastatic disease at the time of diagnosis. On the other hand, a third of the resectable patients with locally advanced disease develop metastases during the course of their disease [4,5]. The 5-year OS rate in patients with metastatic renal cell carcinoma (mRCC) is around 12% [6].

Angiogenic dysregulation plays an important role in the pathogenesis of RCC. Increased expression and receptor number of vascular endothelial growth factor (VEGF) as well as the increase in platelet derived growth factor receptors (PDGFR) have been implicated in tumor growth [2,3]. Elevated expression of these factors is associated

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Received: 29/09/2020; Accepted: 25/11/2020

with increased angiogenesis, more advanced tumor stage, aggressive phenotype, and poor survival [7,8]. Pazobanib is an oral agent that inhibits VEGF 1, 2, 3 receptors, PDGFR alpha and beta receptors, and stem cell factor receptors (c-kit) [9].

In a study by Steinberg et al (VEG105192) pazopanib and placebo were compared in treatment-naive or 1st line cytokine treatment-failed patients. The progression-free survival (PFS) was 9.2 vs. 4.2 months (HR=0.46, p<0.001), 11.1 vs. 2.8 months (HR=0.40; p<0.0001), and 7.4 vs. 4.2 months (HR=0.54; p<0.001) in the overall population, in treatment-naive patients, and in those with previous cytokine therapy, respectively. Based on these results, pazobanib was granted approval in this indication [10].

In the COMPARZ study by Motzer et al involving metastatic RCC patients, first-line treatment with pazopanib and sunitinib were compared, and no significant differences in PFS, OS, and response rate (RR) were found between the two treatments. There was a statistically insignificant trend toward better safety with regard to treatment toxicity in the pazopanib arm [11].

Similarly, pazopanib demonstrated comparable efficacy to sunitinib in the PISCES study. However, pazopanib was associated with better results in terms of safety and quality of life (QoL) assessments [12].

In light of these data, there has been an increased use of pazopanib in the first-line treatment of renal clear cell carcinoma. The National Comprehensive Cancer Network (NCCN) recommends the use of pazopanib in the first-line treatment of metastatic clear cell renal carcinoma. In contrast with pivotal studies, advanced age, poor prognostic characteristics, and/or poor performance status are felt to be common reasons of predilection for pazopanib in real-life conditions [13]. In this multicenter study, we investigated the efficacy and safety of pazopanib in the first line treatment of metastatic RCC.

Methods

A total of 84 patients aged 18 years and older and histopathologically diagnosed with RCC between 2012 and 2020 at the departments of Medical Oncology in University of Health Sciences, Umraniye Research and Training Hospital, University of Health Sciences, Dr. Lütfi Kırdar Kartal Research and Training Hospital, Medical Faculty of Tokat Gaziosmanpasa University and Medical Faculty of Trakya University, were included. The study protocol was approved by the Ethics Committee at the University of Health Sciences Umraniye Research and Training Hospital. Patients with secondary primary cancer were excluded. All patients received pazopanib treatment at a daily dose of 800 mg. Subsequent dose reduction to toxicity were recorded. Prior to treatment, routine biochemical and hematologic parameters were examined and a baseline computed tomography images of the abdomen and thorax were obtained. Also, bone scintigraphy and cranial magnetic resonance imaging (MRI) were performed in symptomatic patients. All patients underwent follow-up examinations every 4 weeks. The treatment was continued until progression according to the Response Criteria in Solid Tumors (RECIST) or until serious toxicity. Radiological response was assessed at every 12 weeks using abdominal and thoracic CT examinations. Additionally, bone scintigraphy was performed in patients with bone metastases. The side effects were graded using National Cancer Institute Criteria (CTCAE v4.).

The primary endpoint of the study was PFS, which was defined as the time from the start of pazopanib treatment to disease progression or death, whichever came first. The secondary endpoints included the OS rate and toxicity. OS was defined as the time from the start of pazopanib treatment to death.

Statistics

Quantitative variables were analyzed using proportions. Categorical variables were analyzed chi square test. Survival distributions, including PFS and OS were estimated by the Kaplan–Meier method, and treatment differences were compared using the log-rank test. Univariate and multivariate analyses were by Cox proportional hazards method to predict the hazards ratios for the association between clinicopathologic features and mortality. SPSS version 17.0 software was used for all analyses and p<0.05 was considered statistically significant.

Results

Patient characteristics

A total of 84 patients who were treated with pazopanib 800 mg/day were included. Table 1 summarizes the patient demographic and clinical characteristics.

The median age was 61 years (range: 37-87). There were 59 (70.2%) male and 25 (29.8%) female patients. The distribution of tumor subtypes included clear cell in 71 (84.5%), papillary in 8 (9.5%), sarcomatoid in 2 (2.4%), and other subtypes in 3 (3.6%) patients. Sixty-four patients (76.2%) underwent nephrectomy prior to therapy. At the time of diagnosis 47 patients (56%) had stage 4 disease. Based on Memorial Sloan-Kettering Cancer Center (MSKCC) risk stratification, 21 (25%), 50 (59.5%), and 13 (15.5%) patients belonged to favorable, intermediate, or poor prognostic group, respectively. The most common sites of metastasis included lungs in 59.5%, bones in 39.3%, and adrenals in 14.3% of the patients.

Efficacy and safety

Partial response (PR), stable disease (SD), and progressive disease (PD) were determined in 22 (26.2%), 43 (51.2%) and 19 (22.6%) patients. The objective response rate (ORR: CR + PR) was 26.6%, while the disease control rate (DCR: CR + PR + SD) was 77.4% (Table 2). The median PFS was 14.4 months (95 % CI, 8.0-20.7) (Figure 1). Patients in the MSKCC favorable group had a median PFS of 16.9 vs 8.9 and 5.7 months for the intermediate and poor risk groups (p=0.226). A statistically significant PFS difference was found in multivariate analyses favoring patients with clear cell histology compared with non-clear cell variants (HR 0.47, 95% CI 0.24-0.91; p=0.026) (Table 3).

The median overall survival (mOS) was 23.9 months (95% CI, 5.9-41.8) (Figure 2). When compared, MSKCC favorable group had a median OS of 37.8 vs. 22 and 6.5 months for the intermediate and poor risk groups, respectively (p=0.179). Multivariate analysis for OS revealed that more than 2 metastatic sites (p=0.025) and clear cell histology (p=0.015) were predictors of poor and improved survival, retrospectively. (HR 1.88, 95% CI 1.08-3.25, p=0.025 ; HR 0.40, 95% CI 0.19-0.84, p=0.015, respectively) (Table 4).

Table 1. Baseline patient demographic and clinical characteristics

Characteristics	*Patients (n=84) n (%)*
Age	
Median, years (range)	61 (37 - 85)
<65	50 (59.5)
≥65	34 (40.5)
Sex	
Male	59 (70.2)
Female	25 (29.8)
ECOG PS	
0-1	71 (84.5)
>1	13 (15.5)
Metastatic disease at diagnosis	
Yes	47 (56.0)
No	37 (44.0)
MSKCC/Motzer Score*	
Favorable	21 (25.0)
Intermediate	50 (59.5)
Poor	13 (15.5)
Prior nephrectomy	
Yes	64 (76.2)
No	20 (23.8)
Histology	
Clear cell carcinoma	71 (84.5)
Papillary	8 (9.5
Sarcomatoid variant	2 (2.4)
Other	3 (3.6)
Number of metastatic sites	
<2	49 (58.3)
≥2	35 (41.7)
Most common metastatic sites	
Lung	50 (59.5)
Bone	33 (39.3)
Adrenal	12 (14.3)
Liver	10 (12.0)
Cranial	6 (7.1)
Other	16 (19.0)

n: number of patients, ECOG PS: Eastern Cooperative Oncology Group Performance Status.
*Memorial Sloan-Kettering Cancer Center.

Table 2. Objective response with Pazopanib in our study population

Response	*Patient (n=84) n (%)*
Best response	
CR	0
PR	22 (26.2)
SD	43 (51.2)
PD	19 (22.6)
ORR (CR + PR)	22 (26.2)
DCR (CR + PR + SD)	65 (77.4)

n: number of patients, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: objective response rate, DCR: disease control rate.

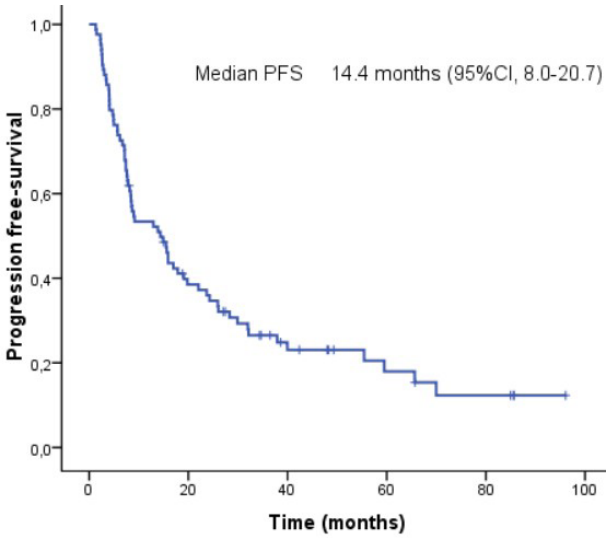

Figure 1. Kaplan-Meier curve of median PFS of patients treated with Pazopanib.

Treatment-associated adverse effects were mostly grade 1 or 2. Diarrhea, hypertension, hair depigmentation, nausea, stomatitis, and vomiting occurred in 28%, 25%, 32%, 10%, 15%, and 15% of the patients, respectively. A 25% dose reduction was required in 12 of 84 patients (15%) due to side effects. Also, dose reductions were done in 3 patients with grade 3 hypertension, in 2 patients with grade 3 thrombocytopenia, in 4 patients with grade 3 diarrhea, and in 3 patients with fatigue (Table 5).

Discussion

This study was designed to evaluate the efficacy and tolerability of patients with metastatic renal carcinoma who were treated with pazopanib as first-line therapy. The median PFS was 14.4 months (95% CI, 8.0-20.7).

In a pivotal phase III trial involving 290 patients (treatment naïve: 155 patients) the reported mPFS and mOS were 11.1 and 22.9 months, respectively. In that study, 42% and 58% of the patients had an ECOG PS 0 and 1, respectively. In the COMPARZ study comparing pazopanib and sunitinib as a first-line treatment, the reported mPFS was 8.4 months and mOS was 28.3 months. Seventy-five percent of the patients had ECOG PS 0 and 25 had ECOG PS 1 or above. In the current study, none of the patients had received treatment prior to pazopanib use. ECOG PS 0 and 1 patients comprised 84.5% of the overall study population, while 15.5% had an ECOG PS 1 or above. In the COMPARZ study the response to therapy was evaluated up to 24 weeks, with monthly intervals [11]. In our study, objective response was assessed every 12 weeks. Thus, our mPFS might be longer than that reported in pivotal studies due to a number of factors including the ECOG PS in the study population, response assessment frequency, or the retrospective design.

Table 3. Multivariate adjusted Cox model for progression-free survival

	Progression-free survival		
	*HR**	*(95%CI)*	*p value*
ECOG PS			
>1	1.56	(0.83-2.94)	0.164
Histology			
Clear cell	0.47	(0.24-0.91)	0.026
Number of metastatic sites			
≥ 2	1.64	(0.99-2.72)	0.055

HR: hazard ratio; 95%CI: 95% confidence interval.

Table 4. Multivariate adjusted Cox model for overall survival

	Overall survival		
	*HR**	*(95%CI)*	*p value*
ECOG PS			
>1	1.69	(0.90-3.18)	0.106
MSKCC/Motzer Score			
≥2	1.56	(0.82-2.96)	0.179
Histology			
Clear cell	0.40	(0.19-0.84)	0.015
Number of metastatic sites			
≥2	1.88	(1.08-3.25)	0.025

HR: hazard ratio; 95%CI: 95% confidence interval.

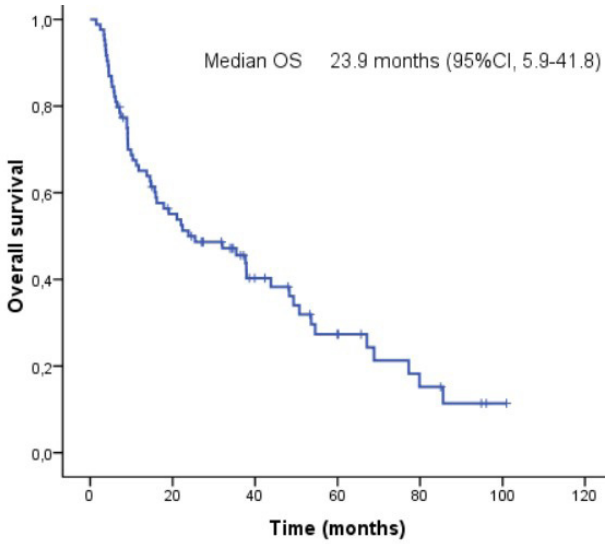

Figure 2. Kaplan-Meier curve of median OS of patients treated with Pazopanib therapy.

Table 5. Maximum grade toxicity recorded per patient (n=84)

	Grade 1-2 n (%)	*Grade 3-4 n (%)*
Diarrhea	24 (28)	4 (4)
Hair depigmentation	38 (32)	0
Hypertension	29 (25	3 (3)
Anemia	21 (18)	0
Neutropenia	1 (1)	0
Thrombocytopenia	11 (10)	2 (2)
Stomatitis	17 (15)	0
Nausea	11 (10)	0
Vomiting	17 (15)	0
Fatigue	17 (15)	3 (3)
Hepatic	11 (10)	0
Skin	11 (10)	0

In Matrana study [14] assessing real-life data similar to the design of our study, the mPFS was 13.7 months, while Galvis et al [17] in their study involving 104 patients (treatment naïve 77 patients) found the mPFS as 13 months, and in RELACS [18] study mPFS was reported to be 4 months. The median OS in the present study was 23.9 months (95% CI, 5.9-41.8). In MSKCC favorable patients, the mOS was 37.8 months vs. 22 and 6.5 months in intermediate and poor prognosis groups. Again, in Matrana study [14] based on real-life conditions, mOS was 29.1 months, with mOS of 35.4, 23.1 and 7.9 months in those with favorable, intermediate, and poor prognostic groups, respectively. Median OS was 22.2 months in both the study by Ruiz-Morales [15] and the research of Perez et al [20] with mOS still not being reached in the favorable prognostic group of the latter. Similarly, in a phase III pivotal study, the reported mOS was 22.9 months [21]. Among patients included in the present study, 25% and 15.5% had a MSKCC class of favorable and poor prognosis, respectively. On the other hand, in Matrana study [14] 31% of the patients had favorable prognostic factors and 25% had poor prognostic factors, while in the COMPARZ study [11] (mOS, 28.3 months) the proportion of patients with favorable prognostic features was higher, while the rate of those with poor prognostic factors was lower, probably accounting for better mOS result as compared to that in our study.

In the COMPARZ and VEG105192 studies, the response rates for pazopanib vs. placebo were 31% and 30%, respectively [11,21]. In one study by Sabrina et al ORR was 30.3% and DCC 72.7% [22]. In the PRINCIPAL study, the ORR observed among treatment naïve patients was 31.6% [16]. In the current study, the resultant ORR of 26.2% and DCR of 77.4% were consistent with the aforementioned data.

With regard to safety, we observed a slightly better tolerability profile than that in most of the previous studies, with no patients experiencing grade 4 toxicity. In 12 patients, a dose reduction of 25% was required due to grade 3 toxicities. No patient discontinued treatment as a result of side effects. The most common side effect was hair depigmentation, which occurred in 32% of the subjects. Similar rates of hair color alterations were reported in 38% and 43% of the patients in the pivotal phase III study and in the study by Thomas, respectively [19,21]. Diarrhea and hypertension were observed in 32% and 28% of our study participants unlike the rates in the phase III pivotal study which were 52% and 40%, respectively [21]. The corresponding rates in the COMPARZ study [11] were even higher, i.e. 63% and 46%, respectively, while 22.8% of the patients in the PRINCIPAL study [16] experienced hypertension. In the study by Matrana [14], similar to our observations, diarrhea was reported in 39% and hypertension in 21% of the study population. In the pivotal study [21], 53% of the patients had hepatic toxicity vs. 10% in our study. However, in the PRINCIPAL study [16] 11% of the patients were reported to have hepatic toxicity, similar to our findings.

In summary, the results of this study examining patients with metastatic clear cell RCC outside the context of a randomized clinical study confirm the efficacy and safety of pazopanib used as a first-line treatment in real-life conditions. The algorithm for the therapeutic agents used in the treatment of metastatic RCC is rapidly evolving, necessitating prospective randomized trials to better define the role of newer agents.

Missing or inadequate data in patient files is certainly a limiting factor due to the retrospective nature of the study and as in all retrospective studies, there might have been some internal selection bias. Also, the small sample size is another limitation of our work.

Ethical approval

The study was performed according to the institutional ethical standards (University of Health Sciences, Umraniye Training and Research Hospital, Number: B.10.1.TKH.4.34.H.GP.0.01) and the Helsinki Declaration.

Informed consent

Formal consent was not required as the study was retrospective.

Conflict of interests

The authors declare no conflict of interests.

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