ORIGINAL RESEARCH

DOI: 10.37047/jos.2020-76764

A Real-World Comparison of Pazopanib Versus Sunitinib in Metastatic Renal Cell Carcinoma: Focus on Poor-Risk patients, A Single-Center Study

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ABSTRACT Objective: The efficacy of pazopanib and sunitinib are comparable in favorable-to intermediate-risk metastatic renal cell carcinoma (mRCC) patients. However, whether pazopanib or sunitinib have different outcomes in poor-risk patients is unknown. This study aimed to investigate the efficacy of these drugs in a real-world poor-risk patient population. **Material and Methods:** The medical records of 46 mRCC patients treated with sunitinib or pazopanib between 2012 and 2018 in the outpatient clinic in the Department of Medical Oncology, Faculty of Medicine, Eskisehir Osmangazi University were retrospectively evaluated. Risk classification was done based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) system. **Results:** The objective response rate (ORR) was significantly higher in patients treated with pazopanib than in those treated with sunitinib (50% vs. 16.7%; p=0.038). The median progression-free survival (PFS) was six months in the sunitinib group and 9.9 months in the pazopanib group, among poor-risk patients only (p=0.36). However, the median PFS was almost equal between the sunitinib and pazopanib group, among favorable- to intermediate-risk patients (12.4 months vs. 13.9 months; p=0.97). Anemia, elevated liver function tests, hand and foot syndrome, and hyponatremia were higher in patients treated with pazopanib. However, neutropenia and leucopenia were more frequent in patients treated with sunitinib. **Conclusion:** Pazopanib might be an appropriate first-line therapy in poor-risk mRCC due to improved PFS rates and ORRs compared to sunitinib. However, extensive, multi-center, prospective studies are required to support these results.

Keywords: Poor-risk metastatic renal cell carcinoma; sunitinib; pazopanib

Renal cell carcinoma (RCC) is the sixth and the tenth most frequently diagnosed cancer in males and females, respectively. It accounts for 5% and 3% of all oncological diagnoses in men and women, respectively.[1] Approximately 17-30% of RCC patients are diagnosed with advanced disease, and the five-year survival rate of these patients is approximately 8-12%.[2,3]

The Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) have classified RCC according to clinical characteristics into three risk groups: favorable, intermediate, and poor. Previous reports have demonstrated that patients with poor-risk features (according to MSKCC criteria and neutrophil and platelet counts) presented a significantly shorter overall survival (OS) than patients with favorable- to intermediate-risk features, and the two-year survival rate of poor-risk patients did not exceed 7%, while that of the favorable- to intermediate-risk patients was 53-75%.[4,5]

After the immunogenicity of RCC was revealed, cytokine therapies [e.g., interferon alfa (IFN) and interleukin-2] were used to treat metastatic RCC (mRCC) until 2006; however, the objective response rates (ORRs) of these agents were approximately 15-20% with added toxicity rates.[6,7] After the significance of Von Hippel-Lindau (VHL) gene mutations, the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) [PI3K/AKT/ mTOR]

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Peer review under responsibility of Journal of Oncological Sciences.

Received: 29 May 2020 ***Received in revised form:*** 29 Sep 2020 ***Accepted:*** 17 Oct 2020 ***Available online:*** 30 Oct 2020

pathway, and vascular endothelial growth factor [VEGF] expression in RCC were recognized, targeted therapy has been used in both, first-line and subsequent treatments; it has improved survival of mRCC patients.[8]

In 2005, sorafenib was the first VEGF-targeted multi-kinase inhibitor (VEGF-TKI) that was more effective than a placebo in phase III randomized trial.[9] One year later, sunitinib replaced sorafenib because of the better progression-free survival (PFS) and ORR than first-line IFN.[10] Besides, IFN and bevacizumab combination therapy produced longer PFS and a higher ORR as first-line treatment of mRCC, compared to IFN monotherapy in the phase III AVOREN study, despite higher toxicity rates.[11] In 2009, a VEGF-TKI, pazopanib, was approved by the FDA as a first-line treatment for mRCC.[12] Further, the results of a non-inferiority trial comparing first-line sunitinib vs. pazopanib led to the approval of both sunitinib and pazopanib as first-line options for advanced clear cell RCC.[13]

Moreover, incorporating immune checkpoint inhibitors into treatment improved RCC patients' survival by more than two years. Ipilimumab plus nivolumab, as a combination therapy, in comparison to sunitinib, was noted to be superior to sunitinib among intermediate- to poor-risk patients in a phase III study.[14] In contrast, sunitinib was superior to the immunotherapy combination among patients in the favorable-risk subgroup. Cabozantinib was another agent found to be superior to sunitinib in a phase II study involving an intermediate- to poor-risk population.[15]

The first-line treatment for the favorable-risk disease included VEGF-TKIs (i.e., sunitinib or pazopanib) or IFN plus bevacizumab. For intermediate- to poor-risk mRCC, cabozantinib monotherapy and ipilimumab plus nivolumab combination therapy were demonstrated to be superior to sunitinib.[14,15] Pazopanib and sunitinib are available as VEGF-TKI options, and the efficacy of these two agents is comparable according to the COMPARZ non-inferiority trial.[13] Unfortunately, this trial mostly included patients with favorable- to intermediate-risk clear cell mRCC. It is not known whether the efficacy of pazopanib and sunitinib are similar among patients with poor-risk features.

In this study, the authors retrospectively evaluated the efficacy and tolerability of sunitinib and pazopanib in a real-world mRCC patient population, where a large proportion of the patients exhibited poor-risk features.

MATERIAL AND METHODS

This study was carried out after approval was obtained from the Ethics Committee of the Medical Faculty of Eskisehir Osmangazi University (Decision number:25403353-050.99-E.147909: date 24 December 2019, Eskisehir, Turkey). All the investigations were performed according to the guidelines of the Declaration of Helsinki.

The medical records of 46 mRCC patients treated with sunitinib or pazopanib between 2012 and 2018 in an outpatient clinic in the Department of Medical Oncology, Faculty of Medicine, Eskisehir Osmangazi University, were retrospectively evaluated.

Risk classification was performed using the IMDC system, based on the neutrophil and platelet counts, hemoglobin levels, calcium levels, performance score, and metastasis-free interval (Table 1). Both patients on first-line and second-line treatment were included in the study. The patients on second-line treatment were previously treated with IFN monotherapy or IFN plus bevacizumab as first-line therapy. Sunitinib was started as a traditional scheme (50 mg 4 weeks on 2 weeks off treatment) in most patients. After 2016, with the knowledge that the alternative 2/1 sunitinib schedule is safer than the traditional scheme, an alternative 2/1 schedule of sunitinib was preferred for patients older than 60 years.

Pazopanib was administered orally once daily at a dose of 800 mg. Dose reduction was made after recurrent toxicities; sunitinib was first reduced to 37.5 mg and then to 25 mg, while pazopanib was reduced to 600 mg and then to 400 mg depending on the type and severity of the toxicities. The efficacy was evaluated by the ORR, PFS, and OS. The ORR was defined as the number of patients with a partial or complete response based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria.[16] Toxicity was evaluated by thyroid dysfunction, liver enzyme abnormalities, hand and foot syndrome, hypertension, proteinuria, and cytopenia according to WHO toxicity criteria.[17] PFS was defined as the time

TABLE 1: IMDC (International Metastatic Renal Cancer Database Consortium) risk score.

Prognostic factors	Risk groups
Karnofsky Performance Status score less than 80%	Favorable (or low) risk: 0 factors
Anemia	
Hypercalcemia	Intermediate risk: 1-2 factors
Neutrophilia	
Thrombocytosis	Poor (or high) risk: 3-6 factors
Diagnosis to treatment interval less than one year	

between initiation and discontinuation of TKI therapy. OS was defined as the time between initial RCC diagnosis and the last visit or death. Also, OS from TKI therapy initiation to the last visit date or death, whichever came first, was evaluated and was termed as OS-TKI. The survival analyses were compared according to risk group, toxicities, treatment line, age, gender, and other clinical parameters.

Statistical analyses were performed with SPSS version 22 (IBM Corporation, New York, USA). Chi-square or Mann-Whitney U tests were used to compare categorical and continuous variables between the two groups. The Kruskal Wallis test was used to compare variables between more than two groups. Survival analyses were done using the Kaplan-Meier analyses. The log-rank tests were used for survival comparison between the two groups. A value $p<0.05$ was accepted to be statistically significant.

RESULTS

PATIENT CHARACTERISTICS

The medical records of all mRCC patients were evaluated. Of all, 46 patients for whom medical records and follow-up were available were included in the analyses. The patients' median age was 57 years, and clear cell morphology was the predominant histology (36/46, 78.2%). Male patients were more commonly affected than female patients (32/46). Twenty-eight patients had the operable disease at initial diagnosis, and three patients underwent nephrectomy during the advanced stage of the condition. A total of 23 patients received sunitinib, while the other 23 patients received pazopanib. The majority of patients receieved sunitinib according to traditional 4/2 schedule (16/23, 69.5%); in seven patients, sunitinib was initiated as per the 2/1 alternative dose scheme. As a result of the social security insurance payment policies, IFN is still accepted as the first-line therapy for mRCC in the country. However, most medical oncologists usually get permission to use TKIs as first-line treatment due to the possible side effects and probable intolerance to IFN. Out of 46, only twelve patients received TKI as second-line therapy after IFN treatment in the study. Twenty-seven patients had poor-risk mRCC, and nineteen patients had favorable- to intermediate-risk mRCC (three favorable-risk patients and sixteen intermediate-risk patients) according to the IMDC classification. Thirteen patients (48.5%) had at least four metastatic sites. Patients' demographic and clinical characteristics did not differ significantly between the patients treated with pazopanib and those treated with sunitinib (Table 2).

EFFICACY

The median follow-up time was 41.2 months from the initial diagnosis and 29.8 months from TKI initiation.

The ORR was higher in the pazopanib group than in the sunitinib group (43.5%, 10/23 vs. 17.4%, 4/23; $p=0.055$) (Figure 1a). As compared to the response rates of patients treated with sunitinib, patients treated with pazopanib in both the poor-risk (38.5% vs. 14.3%, $p=0.15$) and favorable- to intermediate-risk groups showed higher response rates (50% vs. 22.2%, $p=0.21$) (Tables 3, 4). Twelve patients received TKI as second-line treatment after cytokine therapy. Evaluation of response rates among patients who received this therapy as first-line treatment (n=34 patients), excluding the patients on second-line therapy, revealed that ORR was significantly higher in patients treated with pazopanib than in those treated with sunitinib (50%, 8/16 vs. 16.7%, 3/18; $p=0.038$) (Figure 1b).

TABLE 2: The clinical and demographic features of patients in each study group.

Variable	Sunitinib	Pazopanib	p-value
Gender			
Male	18 (78.3%)	14 (60.9%)	0.2
Female	5	9	
Age			
<60 years	14 (60.9%)	14 (60.9%)	1
≥60 years	9	9	
Histology			
Clear cell	17 (77.3%)	19 (86.4%)	0.72
Non-clear cell	6 (22.7%)	4 13.6%)	
IMDC risk group			
Favorable	2 (8.7%)	1 (4.3%)	1
Intermediate	7 (30.4%)	9 (39.1%)	
Poor	14 (60.9%)	13 (56.5%)	
Metastasis-free interval			
< one year	18 (78.3%)	15 (65.2%)	0.32
≥ one year	5 (21.7%)	8 (34.8%)	
Stage at initial diagnosis			
Metastatic	17 (73.9%)	11 (47.8%)	0.07
Early disease	6 (26.1%)	12 (52.2%)	
Primary tumor side			
Left	10 (43.5%)	12 (52.2%)	0.55
Right	13 (56.5%)	11 (47.8%)	
Nephrectomy			
For advanced disease	2 (8.7%)	1 (4.3%)	0.34
For early disease	12 (52.2%)	16 (69.6%)	
No	9 (39.1%)	6 (26.1%)	
Metastatic sites			
Visceral	15 (65.2%)	19 (82.6%)	0.17
Lymph nodes/bone	8 (34.8%)	4 (17.4%)	
Metastatic site number			
≥4	5 (21.7%)	8 (34.8%)	0.32
<4	18 (78.3%)	15 (65.2%)	
Brain metastasis			
Yes	2 (8.7%)	6 (26.1%)	0.24
No	21 (91.3%)	17 (73.9%)	
Liver metastasis			
Yes	7 (30.4%)	4 (17.4%)	0.30
No	16 (69.6%)	19 (82.6%)	
Lung metastasis			
Yes	12 (52.2%)	14 (60.9%)	0.55
No	11 (47.8%)	9 (39.1%)	
Bone metastasis			
Yes	13 (56.5%)	12 (52.2%)	1
No	10 (43.5%)	11 (47.8%)	

PROGRESSION-FREE SURVIVAL (PFS) ANALYSIS

The median PFS was 10.5 months (range: 7.8-13.1 months, 95% CI). It was longer in favorable- to intermediate-risk patients than in poor-risk patients (favorable-risk: 22.5 months vs. intermediate-risk: 12.4 months vs. poor-risk: 8.2 months; 95% CI; p=0.018; favorable- to intermediate-risk: 13.9 months vs. poor-risk: 8.2 months; 95% CI; p=0.005) (Figure 2). The median PFS did not differ irrespective of whether the patient received TKI as first-line or second-line (10.1 months vs. 10.5 months, respectively; 95% CI; p=0.79) (Figure 3).

The median PFS in patients treated with sunitinib was 8.1 months, while in patients treated with pazopanib, it was 11.7 months (95% CI; p=0.55) (Figure 4a). When the median PFS was compared among poor-risk patients, it was observed to be six months in the sunitinib group and 9.9 months in the pazopanib group (95% CI; p=0.36) (Figure 4b). However, the median PFS was almost equal between the sunitinib and pazopanib groups among favorable- to intermediate-risk patients (12.4 months vs. 13.9 months; 95% CI; p=0.97) (Figure 4c).

OVERALL SURVIVAL (OS) ANALYSIS

At a median 41.2 months of follow-up from initial diagnosis, the median OS was 41.4 months (range: 19.6-63.2 months, 95% CI) (Figure 5a). The median OS did not change with gender or age. However, it was significantly shorter in poor-risk patients than in favorable- to intermediate-risk patients (20.9 months vs. 83.2 months; 95% CI; p<0.0001) (Figure 5b).

The median OS-TKI at a median 29.8 months of follow-up was 23.8 months (range: 18.5-29.1 months; 95% CI) (Figure 6a). The median OS-TKI was 15.5 months and 30.1 months in poor-risk and favorable- to intermediate-risk patients, respectively (95% CI; p=0.001) (Figure 6b).

The median OS-TKI of patients treated with pazopanib was 16.4 months (range: 8.3-24.6 months), and that of patients treated with sunitinib was 28.2 months (range: 14.3-42 months; 95% CI; p=0.096) (Figure 7a). A comparison of the OS-TKI among only poor-risk patients revealed a significantly longer OS-TKI in the sunitinib group than in the pazopanib group (22.4 months vs. 12.6 months 95% CI; p=0.04) (Figure 7b).

SUBSEQUENT THERAPIES

A proportion of 56.5% of patients treated with pazopanib and 34.8% of patients treated with sunitinib could not receive second-line treatment. Most patients

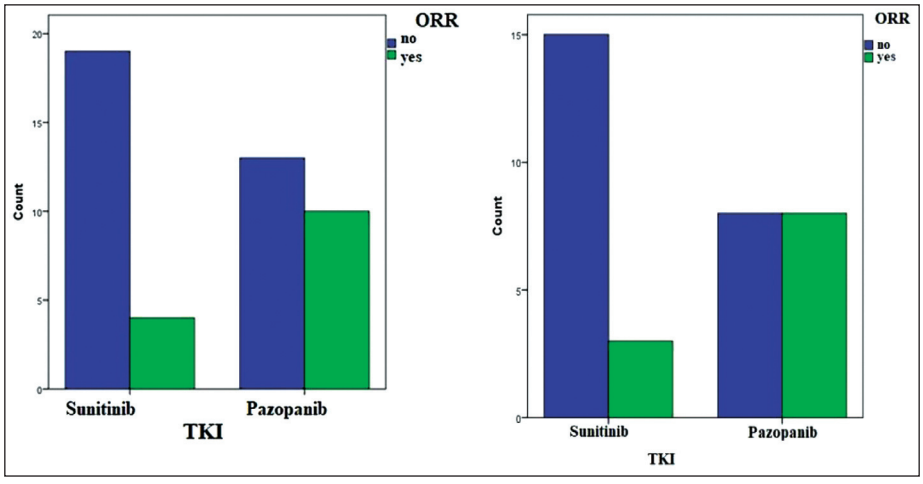

FIGURE 1: a) ORR in the entire patient population according to the TKI received **b)** ORR in patients who received pazopanib or sunitinib as the first-line therapy.

TABLE 3: Response types, according to tyrosine TKI in the entire patient population.

	TKI			
Response to TKİ	**Sunitinib**	**Pazopanib**	**Total**	**p-value**
Partial response	4 (17.4%)	10 (43.5%)	14 (30.4%)	0.055
Stabile response	13 (56.5%)	10 (43.5%)	23 (50%)	
Progression	6 (26.1)	3 (13%)	9 (19.6%)	

TABLE 4: Response types according to TKI in poor-risk patients only.

	TKI			
Response to TKİ	**Sunitinib**	**Pazopanib**	**Total**	**p-value**
Partial response	2 (14.3%)	5 (38.5%)	7 (25.9%)	0.15
Stabile response	8 (57.1%)	5 (38.5%)	13 (48.1%)	
Progression	4 (28.6%)	3 (23.1%)	7 (25.9%)	

(7/11) in the sunitinib group received immunotherapy as second-line therapy, while 2/9 patients in the pazopanib group received immunotherapy as second-line therapy. Only 22.7% of patients in the pazopanib group received third-line treatments in contrast to 60.9% of patients in the sunitinib group. Figure 8 illustrates the subsequent therapies in each case.

TOXICITY PROFILE

A dose reduction was made in 30.4% (7/23) of patients in the sunitinib group (reduced to 25 mg in one patient and 37.5 mg in six patients). Six out of these seven patients received sunitinib with a 4/2 schedule. Among pazopanib treated patients, dose reduction was performed in 21.7% of patients (5/23) (reduced to 400 mg in one patient and 600 mg in 4 patients).

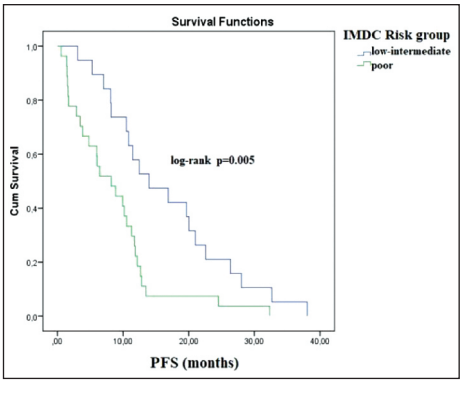

FIGURE 2: The median PFS of study groups according to the IMDC risk classification.

The incidence of anemia, elevated liver function tests, hand and foot syndrome, and hyponatremia was higher in patients treated with pazopanib than in those

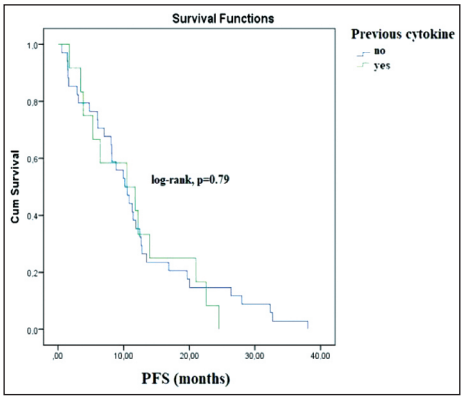

FIGURE 3: The median PFS of patients on TKI therapy according to the treatment line.

treated with sunitinib. However, neutropenia and leucopenia were more frequent in patients treated with sunitinib. Hypothyroidism was the primary thyroid abnormality, while thrombocytopenia was rare. Hypothyroidism and thrombocytopenia were equally seen in both the treatment groups. Most of the toxicities belonged to grade I and II (Table 5). The most prominent grade IV toxicity was neutropenia in the sunitinib group, while that in the pazopanib group were symptomatic acute hyponatremia and anemia.

The patients who developed hypothyroidism and leucopenia had significantly longer PFS than those without these toxicities (13.5 vs. 6.4 months; 95% CI; $p<0.0001$ for hypothyroidism; 12.8 vs. 8.8 months; 95% CI; $p=0.036$ for leucopenia) (Figure 9a and b).

DISCUSSION

This single-center study is a real-life comparison of sunitinib versus pazopanib in a patient population, of which approximately 60% presented with poor-risk features. The first randomized study, including only patients with poor-risk factors, was reported by Hudes et al. in 2007.[18] In their study, the efficacy of first-line IFN versus temsirolimus was compared, and patients treated with temsirolimus had significantly longer OS than those treated with interferon.[18] It is well known that most pivotal studies evaluating the efficacy of VEGF-TKIs in mRCC include favorable- to intermediate-risk patients, while poor-risk mRCC

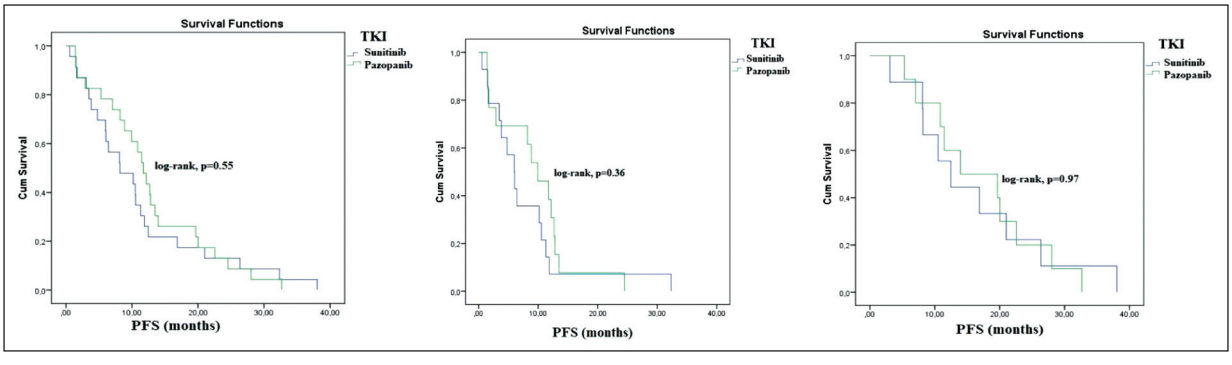

FIGURE 4: The median PFS of sunitinib- vs. pazopanib- treated patients **a)** in the entire group, **b)** in poor-risk patients, **c)** in favorable to intermediate-risk patients.

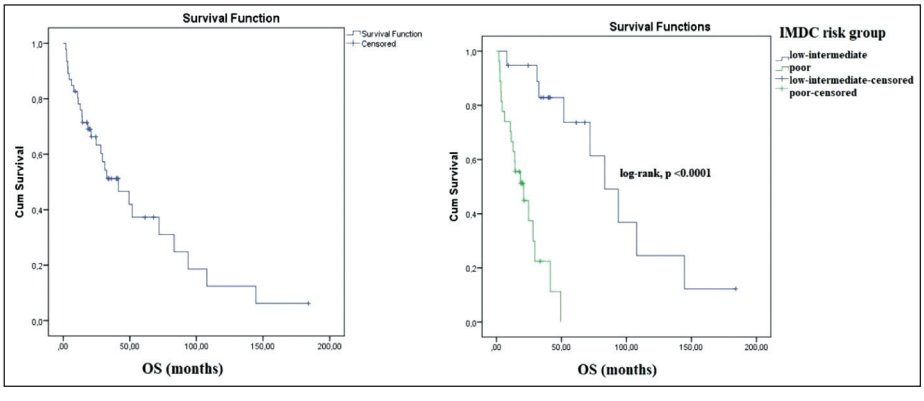

FIGURE 5: a) The OS of the study population; **b)** The OS according to IMDC risk classification.

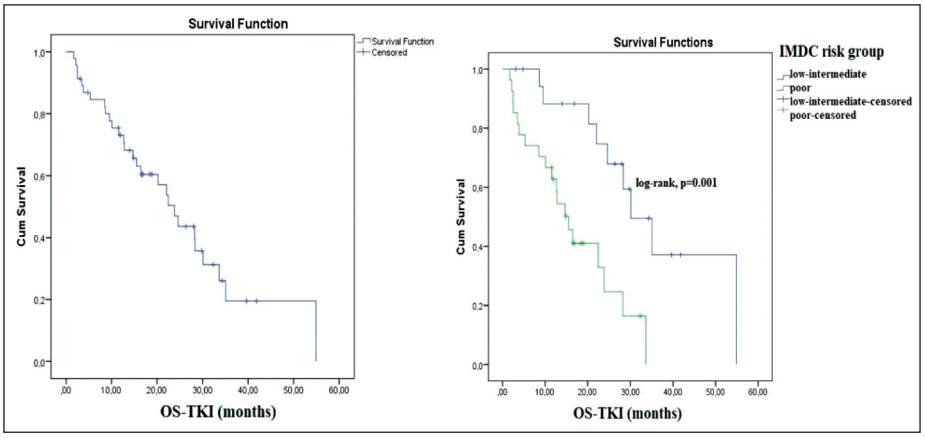

FIGURE 6: a) The OS-TKI of the study population; **b)** The OS-TKI of the study population according to IMDC risk classification.

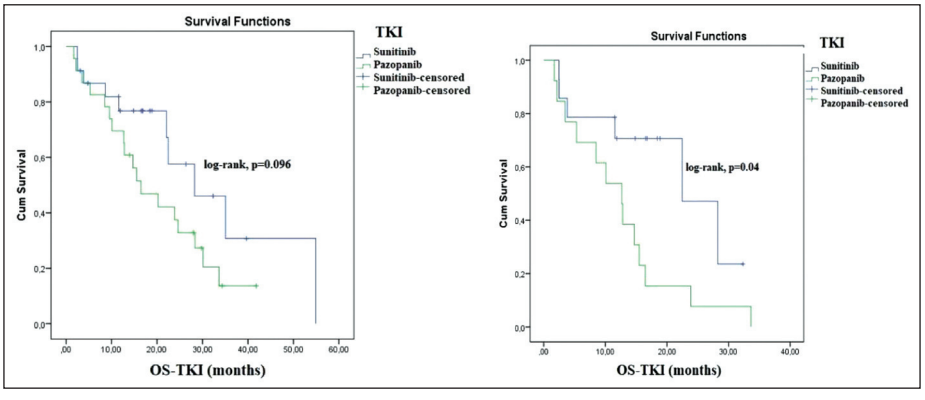

FIGURE 7: a) The OS-TKI according to TKI in the entire study population; **b)** the OS-TKI according to TKI among poor-risk patients only.

patients constitute less than 10% of the patients in these trials.

In a pivotal phase III trial comparing sunitinib with IFN, the PFS was significantly longer in the sunitinib group across all prognostic subgroups; however, only 6.4% of patients had a poor-risk disease in that study.[10] Similarly, in the pivotal phase III trial of pazopanib that demonstrated pazopanib's efficacy over placebo, only 3.2% of the study population had a poor-risk disease.[11] The results of a randomized phase II study comparing the effectiveness of pazopanib and temsirolimus in intermediate- to poor-risk patients were presented recently; pazopanib had higher response rates than temsirolimus (21.2% vs. 5.9) and a longer PFS (2.7 months vs. 5.2 months).[19] In a retrospective study, including 48% of patients with poor-risk features, VEGF-TKIs, which were mostly sunitinib, were reported to have a one-year survival rate of 41%.[20]

The efficacy of pazopanib and sunitinib were previously compared in the randomized COMPARZ non-inferiority trial, a large, retrospective, multi-center trial, and small, retrospective real-world trials.[13,21-23]

In the COMPARZ study, the efficacy and median PFS of sunitinib and pazopanib were similar (9.5 months vs. 8.4 months, respectively); pazopanib was non-inferior to sunitinib in terms of the progression of disease or death from any cause (1.05 hazard ratio [H], non-inferiority margin <1.25); and pazopanib was safer than sunitinib. Additionally, the OS was similar. However, similar to other prospective randomized trials, the COMPARZ study included very few poor-risk patients (only 10.7% according to the MSKCC criteria).[13] An efficacy comparison was not performed according to risk features, probably due to the remarkably small poor-risk population. However, many fragile patients are treated in clinical practice than those included in randomized clinical trials.

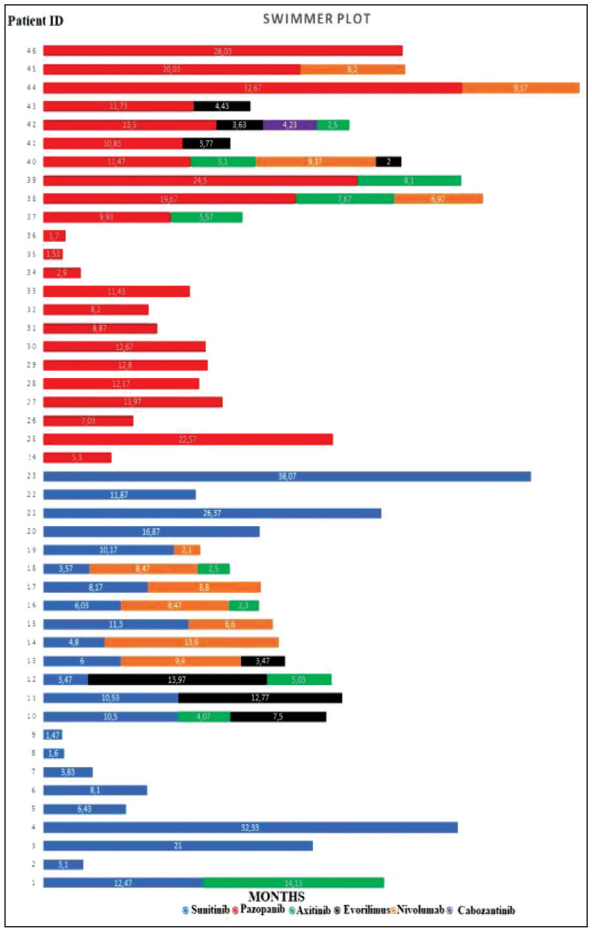

FIGURE 8: Case summary of subsequent therapies.

Ruiz-Morales et al. retrospectively reported the efficacy results of first-line sunitinib vs. pazopanib from the IMDC, including the data of 29 cancer centers and 7438 mRCC patients out of whom approximately 20% had IMDC poor-risk characteristics.[21] The median OS and PFS were similar, and there was no difference in response rates. The hazard ratio for death and PFS for pazopanib vs. sunitinib were 1.03 and 1.08, respectively, when adjusted for IMDC risk criteria. The authors discussed whether an alternative dosage scheme of sunitinib could change these results, as the schedule might be changed as per the recently published studies that support that alternating sunitinib therapy, two weeks on and on week off is safer than and equally effective as standard dosing.[21,24,25] In the present study, more than half of the patients were administered sunitinib according to the standard regimen of four weeks on and two weeks off. However, on observing toxicities before a dosage reduction, most of these patients' treatment schedule was converted to an alternating regimen of two weeks on and one week off.

One report compared pazopanib and sunitinib's efficacy retrospectively in a real-world Canadian patient population in which 20% of the patients had IMDC poor-risk disease.[22] The number of patients treated with sunitinib were significantly greater than those treated with pazopanib (577 vs. 93). The ORRs were not recorded in that report; however, the median time to treatment failure (TTF) was statistically similar, with a tendency of a more prolonged TTF in the sunitinib group.[22] Besides, the OS of patients treated with sunitinib was significantly longer than those

TABLE 5: Toxicity rates of sunitinib versus pazopanib.

Toxicity	Sunitinib group n (%)	Pazopanib group n (%)	p-value
Hand and foot syndrome	2 (8.7%)	3 (13%)	0.61
Hypertension	13 (56.5%)	14 (60.9%)	0.76
Proteinuria	9 (39.1%)	9 (39.1%)	1
Hyponatremia	4 (17.4%)	7 (30.4%)[#]	0.3
Liver dysfunction	2 (8.7%)	5 (21.7%)	0.24
Thyroid dysfunction	12 (52.2%)	11 (47.8%)	0.98
Anemia	15 (65.2%)	17 (73.9%)*	0.52
Leucopenia	9 (39.1%)[†]	4 (17.4%)	0.10
Neutropenia	8 (34.8%)[‖]	2 (8.7%)	0.032
Thrombocytopenia	5 (21.7%)	5 (21.7%)	1

[#]Two patients experienced acute symptomatic hyponatremia and were hospitalized. *Anemia was grade IV in three patients. [†]Leucopenia was grade III in three patients. [‖]Neutropenia was grade IV in three patients.

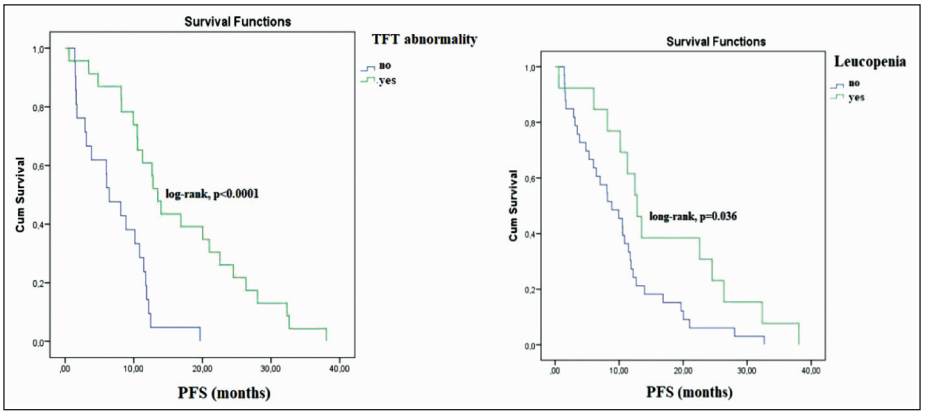

FIGURE 9: a) PFS analysis based on thyroid function test (TFT) abnormality. **b)** PFS analysis based on leucopenia.

treated with pazopanib, and this result was more pronounced in intermediate-risk patients. The authors focused on the fact that pazopanib was administered to more fragile patients with multiple comorbidities.[22] Kim et al. also compared the efficacy of sunitinib and pazopanib in a real-world Korean population in which 15% of the patients had poor-risk mRCC according to the Heng risk criteria.[23] The number of patients in the two groups was almost equal (293 vs. 261). The ORRs, PFS, and OS were comparable. However, the authors did not investigate the efficacy of both drugs in a subgroup of poor-risk patients.[23]

The efficacy of VEGF-TKIs in poor-risk patients has only been investigated in retrospective studies. In one of these studies, the survival of 88 poor-risk patients who were treated either with sunitinib or sorafenib was reported.[26] The majority of patients received sunitinib (86%), and the ORR, the median PFS, and the median OS were 22%, five months, and 9.3 months, respectively.[20] The second study included 172 mRCC patients, of whom 52.9% had poor-risk disease according to the Applied Research in Cancer Control (ARCC) criteria.[26] Seventy-two patients were treated with pazopanib, and 100 were treated with sunitinib. Immunotherapy had previously been administered in 8.1% of patients. The number of patients with poor performance status (Karnofsky Performance Status score <80) was more significant in the pazopanib group than in the sunitinib group (59.7 vs. 45%). The ORR was 36.1% in the pazopanib group and 23% in the sunitinib group. The median OS and PFS were significantly longer in the pazopanib group.[26]

In the present study, the age of sunitinib and pazopanib patients was similar; however, the patients in the pazopanib group had more visceral involvement and higher tumor burden than those in the sunitinib group, and more fragile patients received pazopanib. Despite these facts, the median PFS of the pazopanib group was longer both in the entire study population and specifically in poor-risk patients. Also, the median PFS of poor-risk patients in the pazopanib group was 9.9 months compared to six months in the sunitinib group; the median PFS difference was approximately four months. In contrast, the median PFS of favorable- to intermediate-risk patients was 13.9 and 12.4 months in the pazopanib and sunitinib groups, respectively. This result is relatively similar to that of the CheckMate 218 study in which favorable-risk patients had better results with sunitinib than with ipilimumab and nivolumab combination therapy. Still, the immunotherapy combination resulted in longer OS and PFS and a significantly higher ORR in intermediate- to poor-risk patients.[14] Similarly, in the phase II CABOSUN study, sunitinib was inferior to cabozantinib in terms of PFS and the ORR in intermediate- to poor-risk mRCC patients; the median PFS of sunitinib was 5.3 months in that study.[15] Thus, the literature points out that sunitinib is not an ideal treatment for poor-risk patients.

Additionally, partial response rates were significantly higher in patients treated with pazopanib in the present study. This observation is consistent with the significant response results in the COMPARZ study, in which the ORRs for pazopanib and sunitinib were 31% and 25%, respectively.[13]

Despite the improved ORRs and PFS, the pazopanib group's OS was shorter than that of the sunitinib group in the present study. This finding may be attributed to patient factors and subsequent therapies. When the subsequent therapies in each group were examined, it was observed that more patients in the sunitinib group received subsequent treatments. Furthermore, more patients in the sunitinib group received immunotherapy (i.e., nivolumab) as second-line therapy after TKIs than patients in the pazopanib group (63.6% vs. 22.2%). Many studies demonstrate that checkpoint inhibition prolongs OS independent of ORRs. As the sunitinib group included healthier patients who could receive subsequent therapy, mostly immunotherapy, improved OS in the sunitinib group is a likely result.

In conclusion, pazopanib may be an appropriate first-line therapy in poor-risk mRCC patients because of the improved PFS and ORRs compared to sunitinib. However, extensive, multi-center studies are required (such as comparisons of cabozantinib versus pazopanib or pazopanib versus combination immunotherapy) to standardize the first-line treatment in poor-risk mRCC.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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