VIA MEDICA

ORIGINAL ARTICLE

Senar Ebinç, Ziya Kalkan, Zeynep Oruç, Zuhat Urakçı, Mehmet Küçüköner, Muhammet Ali Kaplan, Abdurrahman Işıkdoğan

Dicle University Faculty of Medicine, Department of Medical Oncology, Diyarbakır, Turkey

Evaluation of the effectiveness and tolerability of sunitinib and pazopanib in the first line treatment of metastatic renal cell carcinoma

Address for correspondence:
Senar Ebinç, MD
Dicle University Faculty of Medicine, Department of Medical Oncology, Diyarbakır, Billstreet Sur, 21280 Diyarbakır; Turkey
e-mail: senarebinc@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/OCP.2021.0033

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. It is known that sunitinib and pazopanib are effective in the first-line and subsequent treatment of metastatic renal cell carcinoma (mRCC). This study aims to investigate the effectiveness and tolerability of sunitinib and pazopanib in the first-line treatment of mRCC.

Material and methods. This study included 78 patients followed up in our clinic due to a diagnosis of mRCC, who received pazopanib or sunitinib treatment between 2006 and 2020. Along with clinical and laboratory findings, survival times obtained with each treatment and medication side effects were assessed. Sunitinib and pazopanib were compared in terms of effectiveness (ORR, PFS and OS) and tolerability.

Results. The patients' median age at diagnosis was 55 years (25–81). In the first-line treatment, 54 patients (69.2%) received sunitinib and 24 (30.8%) received pazopanib. The comparison of sunitinib and pazopanib yielded an ORR of 66.7% *vs.* 45.8% ($p = 0.08$), PFS of 24 months *vs.* 19 months ($p = 0.66$) and OS of 27 months *vs.* 30 months ($p = 0.73$), respectively. The most common side effect was hypothyroidism in those on sunitinib (25.9%) and nausea-vomiting in those on pazopanib (41.7%). In our study, hemoglobin ≥ 13 g/dL, an ECOG PS of 0–1 and the occurrence of hypothyroidism as a medication side effect were found to be predictive factors of PFS for both agents. An International Metastatic RCC Database Consortium score corresponding to the poor risk group was associated with a poor PFS.

Conclusions. This study, which provides current real-world data, confirms that sunitinib and pazopanib have similar effectiveness and side-effect profiles in the first-line treatment of mRCC.

Key words: renal cell carcinoma, sunitinib, pazopanib, VEGFR inhibitors

Oncol Clin Pract 2022; 18, 4: 226–234

Introduction

Although the prevalence of renal cell carcinoma varies across regions, it is estimated to have a worldwide annual incidence of 403,000 and 175,000 patients lose their lives due to renal cancer every year [1]. Renal cancers are more common in males and in the 6th–8th decade [2]. Surgery constitutes a curative treatment approach in early-stage renal cell carcinomas, while systemic treatment options take precedence in advanced-stage disease. However, the excision of the primary tumor can sometimes result in the spontaneous regression of metastases [3].

Systemic treatment approaches include programmed cell death 1 protein (PD-1), programmed cell death

Received: 23.04.2021 Accepted: 13.08.2021 Early publication date: 10.11.2021

ligand 1 (PD-L1), vascular endothelial growth factor receptor (VEGFR) inhibitors and anti-cytotoxic T-lymphocyte-associated protein (CTLA-4) antibodies [4]. The core treatment of intermediate and poor prognostic groups of metastatic renal cell carcinoma consists of an immunotherapy combination or a combination of VEGFR inhibitors with immunotherapy. This would also remain a treatment option for the favorable prognostic group. On the other hand, VEGFR inhibitors can be used alone in situations where immunotherapy is not appropriate or accessible in later lines of treatment. The effect mechanisms of these medications rely on the interruption of the VEGF signaling pathway, which causes physiological escape [5, 6]. Sunitinib is an oral tyrosine kinase inhibitor (TKI) that inhibits the endothelial growth factor receptor (VEGFR) and the platelet derived growth factor receptor (PDGFR) [7]. Similarly, pazopanib is an oral angiogenesis inhibitor that targets the VEGFR, PDGFR and c-kit [8]. Both agents have been used as single agents in the treatment of renal cell carcinoma for many years. In the recent years, immunotherapy and immunotherapy-TKI combinations have been introduced to the treatment algorithm. However, particularly in places where immunotherapy is not accessible as first-line treatment, single use of TKIs is still among the treatment options. In this study, we investigated the effectiveness and tolerability of pazopanib and sunitinib in the first-line treatment of metastatic renal cell carcinoma. Our study evaluated the response rates, PFS and OS times obtained with pazopanib and sunitinib in the first-line treatment of mRCC. It was investigated whether or not the two agents were different in terms of response rates, survival times or side effects.

Material and methods

In this study, the files of patients who presented to the Medical Oncology Clinic of Dicle University, Faculty of Medicine between 2006 and 2020 and received pazopanib or sunitinib as first-line treatment for a diagnosis of metastatic renal cell cancer were retrospectively reviewed. Data of a total of 78 patients who received pazopanib [24 (30.8%)] or sunitinib [54 (69.2%)] in the first-line treatment could be retrieved. Data concerning age, gender, smoking, ECOG PS (Eastern Cooperative Oncology Group performance status), IMDC (International Metastatic RCC Database Consortium) score, comorbidities, previous nephrectomy, tumor histology, primary tumor localization (right/left), metastatic sites (liver, lung, bone), hemoglobin levels, albumin levels, treatment agent used in the first-line treatment (pazopanib/sunitinib), and drug-induced side effects were obtained from the patient files. The effects of tumor characteristics and clinical parameters on the clinical outcomes and the effectiveness and tolerability of the first-line agent were evaluated. Treatment response was assessed at 3-month intervals based on clinical and radiological data. Radiological response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

The administered treatment included the use of 50 mg daily sunitinib (without regard to meals) for four weeks followed by two-week off or drug use for two weeks followed by one-week off (in case of adverse effects) in the sunitinib arm. In the pazopanib arm, 800 mg pazopanib (1 hour before or 2 hours after meals) was administered daily. Drug toxicity was assessed according to the Common Terminology Criteria for Adverse Events.

Statistics

Statistical analysis of the data used the SPSS 18.0 program package. Descriptive statistics were used to evaluate patient characteristics and the frequencies of parameters, Student's t-test was used for normally distributed numeric variables and the Mann-Whitney U test was used for the analysis of non-normally distributed or non-parametric variables. For univariate analyses, the t-test, chi-square test, Fisher's exact test and Mann-Whitney U test were used. A confidence interval of 95% and a p significance level < 0.05 were adopted. For survival analysis and subgroup analyses, the Kaplan-Meier method (log-rank, Breslow, Tarone-Ware tests) and Cox regression analysis were used. The parameters evaluated in subgroup analyses {gender, ECOG PS [≥ 2 *vs.* 0–1], smoking, tumor laterality [left/right], nephrectomy [yes/no], metastatic sites [liver, lung, bone), presence of comorbidity, histological subtype [clear-cell *vs.* non-clear-cell], albumin g/dL level [< 3.6 *vs.* ≥ 3.6], hemoglobin g/dL level [≥ 13 *vs.* < 13] [in ROC analysis, the cut-off value for albumin was determined as 3.6 g/dL (AUC = 0.735, p = 0.002) at 85% sensitivity and 53% specificity, the cut-off value for hemoglobin was determined as 13 g/dL (AUC = 0.667, p = 0.025) at 70% sensitivity and 50% specificity], drug-induced hypothyroidism, palmar-plantar erythrodysesthesia, hypertension and fatigue}, the first-line agent (pazopanib/sunitinib) were assessed with respect to the prediction of PFS.

Terminology

Overall survival (OS) was computed as the length of time from the occurrence of metastasis to death, progression-free survival (PFS) was computed as the duration of time from the initiation of first-line treatment to progression on this treatment or death from any cause. Objective response (OR) was accepted as the sum of complete responses and partial responses obtained

at the third month of treatment. The IMDC scoring system included risk factors such as a duration of time from diagnosis to systemic therapy < 1 year, Karnofsky performance status < 80%, hemoglobin level < 12 g/dL, corrected serum calcium level > 10.2 mg/dL, platelet count > 400 × 10^9/L and neutrophil count > 7 × 10^9/L. Patients with no risk factors were accepted as the favorable risk group, patients with 1–2 risk factors as the intermediate risk group, and patients with risk factors ≥ 3 as the poor risk group.

Results

Our study included a total of 78 patients with metastatic renal cell carcinoma, comprising 61 (78.2%) males and 17 (21.8%) females. The patients' median age at diagnosis was 55 years (25–81). ECOG PS at diagnosis was 0–1 in 66 (84.6%) patients, ≥ 2 in 12 (15.4%) patients. There were 60 (76.9%) patients who smoked and 37 (47.4%) patients who had at least one comorbidity. The primary tumor was localized in the right kidney in 39 (50%) patients and in the left kidney in 39 (50%) patients. Fifty-nine (75.6%) patients had undergone nephrectomy at any stage of the disease. As to the metastatic localizations, metastases were found in the liver in 9 (11.6%) patients, in the lung in 52 (66.7%) patients, in the bone in 36 (46.2%) and in other localizations in 13 (16.7%) patients. Of our patients, 63 (80.8%) had clear-cell histology, while 15 (19.2%) had non-clear cell histology. In our study, 54 patients (69.2%) received sunitinib and 24 (30.8%) received pazopanib. When grouped with respect to the IMDC score, 3.8% patients (n = 3) were in the favorable risk group [1 (4.2%) on pazopanib, 2 (3.7%) on sunitinib], 57.7% patients (n = 45) were in the intermediate risk group [17 (70.8%) on pazopanib, 28 (51.9%) on sunitinib] and 38.5% patients (n = 30) were in the poor risk group [6 (25%) on pazopanib, 24 (44%) on sunitinib] (Tab. 1).

With regard to the three-month treatment response rates, partial response was obtained in 11 (45.8%) patients and stable disease was observed in 13 (54.2%) patients on pazopanib, with no cases of complete response or progressive disease. In the sunitinib arm, complete response was obtained in 2 (3.7%) patients, partial response was obtained in 34 (63%) patients, and stable disease was observed in 18 (33.3%) patients. Progressive disease was also not encountered in this arm. With regard to the objective response rates (ORR), an ORR of 45.8% (n = 11) was obtained in the pazopanib arm and an ORR of 66.7% (n = 36) was obtained in the and sunitinib arm, with no statistically significant difference between the two arms (p = 0.08). When evaluated with regard to survival, PFS was 19 months [95% CI: (8.4–29.5)] in the pazopanib arm and 24 months [95% CI: (16.1–31.9)] in the sunitinib arm and there was no statistically significant difference between the two groups in terms of PFS [HR, 0.88; 95% CI, 0.50–1.55], (p = 0.66), (Fig. 1). OS was 30 months [95% CI: (24.5–35.4)] in the pazopanib arm as opposed to 27 months [95% CI: (15.9–38)] in the sunitinib arm [HR, 1.10; 95% CI, 0.61–1.97], (p = 0.73) (Fig. 2). For the entire study group, the first-line treatment was associated with a PFS of 22 months [95% CI (15.2–28.7)] and an OS of 30 months [95% CI (21.6–38.3)] (Tab. 2).

It was found that ECOG PS, hemoglobin levels, IMDC scores (intermediate/poor) and the occurrence of drug-induced hypothyroidism predicted PFS for both drugs. Median PFS was 5 months (2.0–8.0) in patients with an ECOG PS ≥ 2, as opposed to 24 months (18.1–29.8) in patients with an ECOG PS 0–1 (Log-rank p = 0.001). Median PFS was 25 months (14.1–35.8) in patients with a hemoglobin level ≥ 13 g/dL, while it was 22 months in those with a hemoglobin level < 13 g/dL (14.9–29) (Log-rank p = 0.030). Median PFS was 24 months in patients with an intermediate IMDC score as opposed to 12 months in patients with a poor IMDC score (Log Rank p = 0.045). The majority of our patients were categorized in the intermediate or poor IMDC risk group. PFS was 30 months (27.3–32.7) in patients who developed hypothyroidism as a side effect, as opposed to 15 months (7.8–22.1) in others (Log-Rank p = 0.016). Other parameters listed above (gender, smoking, tumor laterality (right/left), nephrectomy (yes/no), metastatic sites (liver, lung, bone), presence of comorbidity, histological subtype (clear-cell *vs.* non-clear-cell), albumin g/dL level (< 3.6 *vs.* ≥ 3.6), drug-induced palmar-plantar erythrodysesthesia, hypertension and fatigue) were not found to predict PFS with statistical significance. Univariate and multivariate analysis results are specified in Table 3.

When the two agents, sunitinib and pazopanib, were compared with regard to PFS, [HR = 0.88, 95% CI (0.50–1.55), p = 0.66] no statistically significant difference was found in terms of PFS. When the parameters that influenced the PFS times obtained with pazopanib and sunitinib were inspected in subgroups, no statistically significant difference was found between the two agents in terms of gender, smoking, nephrectomy (yes/no), metastatic sites (liver, lung, bone), histological subtype (clear-cell *vs.* non-clear-cell), drug-induced hypothyroidism, hypertension, palmar-plantar erythrodysesthesia, albumin g/dL level (< 3.6) hemoglobin g/dL level (< 13) and IMDC score (intermediate/poor) (Tab. 4, Fig. 3).

When evaluated with regard to medication side effects, the most common side effects of any grade were nausea-vomiting, hypothyroidism, hyperten-

Table 1. General characteristics of patients

	All patients	Pazopanib	Sunitinib
N (%)	78	24 (30.8)	54 (69.2)
Age, yrs (median, range)	55 (25–81)	57 (28-81)	55 (25–78)
ECOG PS			
0–1	66 (84.6)	19 (79.2)	47 (87)
≥ 2	12 (15.4)	5 (20.8)	7 (13)
Gender			
Male	61 (78.2)	14 (58.3)	47 (87)
Female	17 (21.8)	10 (41.7)	7 (13)
Comorbidities			
Yes	37 (47.4)	15 (62.5)	22 (40.7)
No	41 (52.6)	9 (37.5)	32 (59.3)
Smoking			
Yes	60 (76.9)	14 (58.39	46 (85.2)
No	18 (23.1)	10 (41.7)	8 (14.8)
Nephrectomy			
Yes	59 (75.6)	18 (75)	41 (75.9)
No	19 (24.4)	6 (25)	13 (24.1)
Metastasis site			
Liver	9 (11.6)	2 (2.6)	7 (9)
Lung	52 (66.7)	18 (23.1)	34 (43.6)
Bone	36 (46.2)	11 (14.1)	25 (32.1)
Others	13 (16.7)	5 (6.4)	8 (10.3)
Histological type			
Clear cell	63 (80.8)	20 (83.3)	43 (79.6)
Non-Clear cell	15 (19.2)	4 (16.7)	11 (20.4)
Tumor location			
Left	39 (50)	15 (62.5)	24 (44.4)
Right	39 (50)	9 (37.5)	30 (55.6)
IMDC score			
Favorable	3 (3.8)	1 (4.2)	2 (3.7)
İntermediate	45 (57.7)	17 (70.8)	28 (51.9)
Poor	30 (38.5)	6 (25)	24 (44.4)

ECOG — Eastern Cooperative Oncology Group performans status; IMDC — International Metastatic RCC Database Consortium

sion and skin reactions in the pazopanib arm and hypothyroidism, nausea-vomiting, palmar-plantar erythrodysesthesia and hypertension in the sunitinib arm. Although the side effects associated with the two agents were similar, nausea-vomiting was encountered at a higher rate in the pazopanib arm when compared with sunitinib [respectively 41.7% *vs.* 14.8%, (p = 0.01)]. Medication side effects are specified in detail in Table 5.

Discussion

This study compared the effectiveness and tolerability of pazopanib and sunitinib in the first-line treatment of metastatic renal cell carcinoma. In a study that compared sunitinib with interferon alpha in the treatment of treatment-naive metastatic renal cell carcinoma, it was shown to be superior to interferon alfa in terms of both PFS (11 months *vs.* 5 months) and the objective response

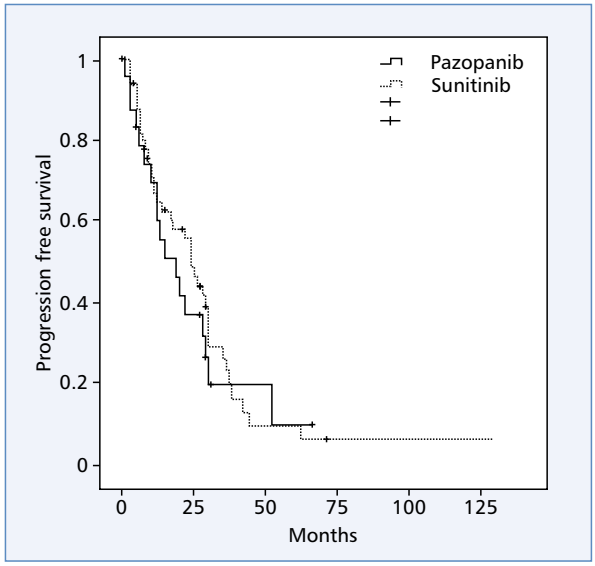

Figure 1. Progression-free survival for sunitinib and pazopanib

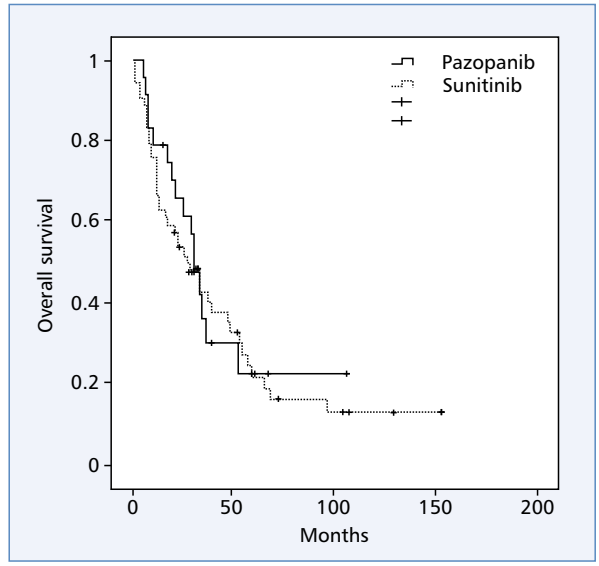

Figure 2. Overall survival for sunitinib and pazopanib

Table 2. Response rates and survivall for pazopanib and sunitinib

	All patients	Pazopanib	Sunitinib	P value
Responses				0.17
CR no. (%)	2 (2.6%)	0 (0%)	2 (3.7%)	
PR no. (%)	45 (57.7%)	11 (45.8%)	34 (63%)	
SD no. (%)	31 (39.7%)	13 (54.2%)	18 (33.3%)	
PD no. (%)	0 (0%)	0 (0%)	0 (0%)	
ORR no. (%)	47 (60.3%)	11 (45.8%)	36 (66.7%)	0.08
PFS (mo) median (95% CI)	22 (15.2–28.7)	19 (8.4–29.5)	24 (19–28.9)	0.58
OS (mo) median (95% CI)	30 (21.6–38.3)	30 (24.5–35.4)	27 (15.9–38)	0.73

CR — complete remission; ORR — objective response rate; OS — overall survival; PD — progressive disease; PFS — progression-free survival; PR — partial response; SD — stable disease

rate (31% *vs.* 6%) [9]. When considered with regard to OS, the overall survival achieved in the sunitinib arm was 26.4 months, while the OS obtained in the interferon alpha arm was 21.8 months [10]. In our study, an OS of 27 months, PFS of 24 months and ORR of 66.7 were obtained with sunitinib as the first-line treatment of metastatic renal cell carcinoma. Both the response rates and the PFS values showed better outcomes in our study when compared with the literature.

In a controlled phase-III study, in which pazopanib was given as first line therapy or subsequent to cytokine therapy in locally advanced or metastatic renal cell carcinoma, it was shown to be superior to placebo in terms of both PFS (11.1 months *vs.* 2.8 months, respectively) and the ORR (30% *vs.* 3%, respectively). In our study, PFS was 19 months and the ORR was 45.8% in the pazopanib arm [11]. The PFS and ORR values obtained in our study were more favorable compared with the literature.

In the prospective COMPARZ study, which included 1100 patients and compared pazopanib and sunitinib in the first-line treatment of mRCC (clear-cell histology), a PFS of 10.5 months was obtained with pazopanib and a PFS of 10.2 months was obtained with sunitinib, and the two groups were evaluated to be similar with respect to PFS (HR, 1.00; 95% CI, 0.86–1.15). However, this study reported pazopanib to be more tolerable according to the side effect profiles [12]. On the other hand, OS data from another study that compared pazopanib and sunitinib in the first-line treatment of mRCC showed pazopanib to be non-inferior to sunitinib, with median OS times for pazopanib and sunitinib reported as 26.9 months (95% CI, 23.1–35.6) and 26.1 months (95% CI, 20.7–31.6), respectively [13]. Considering the real-life data, in the study of Isik U. et al. [14], sunitinib and pazopanib data were evaluated in first-line treatment in meta-

Table 3. Univariate and multivariate analysis results of factors affecting progression-free survival in first line therapy

	Univariate Analysis			Multivariate Analysis		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age	0.99	0.97–1.02	0.96			
ECOG PS (0–1/≥ 2)	4.77	2.10–10.83	**< 0.001**	9.86	3.01–32.2	**< 0.001**
Gender (male/female)	0.72	0.38–1.34	0.30			
Hemoglobin (< 13/≥ 13 g/dL)	0.52	0.29–0.95	**0.03**	0.51	0.26–0.99	**0.05**
Albumin (< 3.6/≥ 3.6 g/dL)	0.78	0.45–1.34	0.37	1.35	0.69–1.74	0.38
Palmar-plantar erythrodysesthesa	0.78	0.35–1.7	0.55			
Hypothyroidism	0.48	0.26–0.89	**0.02**	0.46	0.24–0.89	**0.02**
Fatigue	1.33	0.62–2.84	0.45			
Hypertension	0.67	0.30–1.49	0.32			
Comorbidities (no/yes)	0.82	0.48–1.39	0.46			
Smoking (no/yes)	0.97	0.52–1.82	0.94			
Nefrektomi (no/yes)	0.67	0.34–1.33	0.25			
Metastasis site						
Liver (no/yes)	1.64	0.73–3.66	0.22			
Lung (no/yes)	1.09	0.60–1.95	0.77			
Bone (no/yes)	1.21	0.70–2.07	0.48			
Histological type (clear cell/non-clear cell)	0.86	0.42–1.78	0.69	0.77	0.34–1.74	0.54
Tumor location (left/right)	1.09	0.64–1.84	0.75			
IMDC score (poor/intermediate)			0.09			0.06
Favorable	1.49	0.34–6.50	0.58	0.22	0.36–1.40	0.10
Intermediate	0.56	0.32–0.99	**0.049**	0.46	0.22–0.92	**0.03**
Poor		Reference			Reference	

CI — confidence interval; ECOG — Eastern Cooperative Oncology Group performans status; HR — hazard ratio; IMDC — International Metastatic RCC Database Consortium

static clear cell renal cell carcinoma. A median PFS of 24.3 months was observed in the sunitinib arm, while a median PFS of 34.2 months was observed in the pazopanib arm. There was no statistically significant difference between the two drugs in terms of PFS [14]. In our study, the sunitinib and pazopanib arms were associated with a PFS of 24 months and 19 months, (p = 0.66) and an OS of 27 months and 30 months, (p = 0.73), respectively. The results of our study were consistent with real-life data. The present study confirms that these two agents have comparable effectiveness in terms of PFS and OS.

Previously, prognostic models such as the Memorial Sloan-Kettering Cancer Center (MSKCC) and IMDC risk scores have been used in metastatic RCC. Such models have used hemogram parameters (hemoglobin, platelet count, neutrophil count), lactate dehydrogenase and calcium levels, performance status and the duration of the disease-free interval. Prognostic value was shown by scoring systems [15, 16]. In another study, parameters such as nephrectomy, albumin levels, hemoglobin levels and presence of bone metastasis were investigated as prognostic factors associated with the effectiveness of sunitinib [17]. In the literature, side effects such as hypertension and hypothyroidism were reported to be linked to the survival associated with pazopanib [18, 19]. Again, there exist studies reporting that fatigue and palmar-plantar erythrodysesthesia are related to the effectiveness of TKIs [20, 21]. In the present study, we compared the PFS outcomes of pazopanib and sunitinib in terms of gender, IMDC score (intermediate/poor), smoking, metastatic sites (liver, lung, bone), history of nephrectomy (yes/no), histological subtype (clear-cell *vs.* non-clear-cell), albumin g/dL level (< 3.6) hemoglobin g/dL level (< 13) drug-induced palmar-plantar erythrodysesthesia, hypertension, and hypothyroidism. Subgroup analyses showed that these parameters did not cause a significant difference between the

Table 4. Results of pazopanib *vs.* Sunitinib comparison subgroup analysis

	Pazopanib *vs.* Sunitinib		
	HR	95% CI	P value
All patient	0.88	0.50–1.55	0.66
Gender			
Male	0.94	0.46–1.93	0.88
Female	0.77	0.25–2.39	0.66
Smoking (yes)	0.99	0.49–1.98	0.98
Nephrectomy (yes)	1.06	0.55–2.03	0.84
Albumin (< 3.6 g/dL)	0.63	0.24–1.63	0.34
Hemoglobin (< 13 g/dL)	1.14	0.43–3.00	0.77
Metastasis site			
Liver	0.27	0.03–1.96	0.19
Lung	0.71	0.21–2.32	0.57
Bone	0.85	0.36–1.97	0.70
Hypothyroidism	0.57	0.19–1.69	0.31
Hypertension	0.73	0.12–4.31	0.73
Palmar-plantar erythrodysesthesa	1.55	0.17–13.7	0.69
Histological type			
Clear cell	0.96	0.52–1.78	0.90
Non-clear cell	0.52	0.12–2.22	0.38
IMDC score (poor/intermediate)			
Intermediate	0.70	0.35–1.41	0.32
Poor	1.31	0.44–4.11	0.60

CI — confidence interval; HR — hazard ratio; IMDC — International Metastatic RCC Database Consortium

two agents (Tab. 4, Fig. 3). However, a hemoglobin level ≥ 13 g/dL, an ECOG PS of 0–1 and the occurrence of hypothyroidism induced by pazopanib or sunitinib were found to be factors predicting a longer PFS for both agents. Also, PFS times of the patients in the poor IMDC risk group were shorter compared with those in the intermediate risk group. Diverging from the studies in the literature, the present study did not observe a relationship between the occurrence of hypertension and drug effectiveness. Our study had fewer patients in the favorable risk group when compared with the literature. We reasoned that this might be attributable to the late attendance of the patients due to the region our center is located in.

The effect of nephrectomy in mRCC was investigated in the CARMENA and SURTIME studies. In the CARMENA study, sunitinib alone was compared with the nephrectomy + sunitinib arm in the first-line treatment of intermediate- or poor-risk mRCC. This study obtained an OS of 18.4 months with sunitinib alone, as opposed to 13.9 months in the nephrectomy + sunitinib arm (HR: 0.89, 95% CI: 0.71–1.10) [22]. In the SURTIME study, upfront nephrectomy and deferred nephrectomy (after 3 cycles of sunitinib) were compared in mRCC patients with intermediate MSKCC risk, and deferred nephrectomy was determined to be associated with better survival outcomes in terms of OS (32 months *vs.* 15 months) [23]. In our study, most of the patients with a history of nephrectomy had undergone nephrectomy in a localized disease stage. However, the comparison of the nephrectomy subgroups revealed that the history of nephrectomy did not predict PFS in patients on TKI.

In the PISCES study with a prospective, cross-over design, which compared pazopanib and sunitinib with regard to their side effect profiles, sunitinib mostly resulted in diarrhea, vomiting, hypertension, and palmar-plantar erythrodysesthesia and patients on pazopanib demonstrated similar side-effects, except for lower rates of palmar-plantar erythrodysesthesia than sunitinib. In this study, pazopanib was reported to be more preferable by patients in terms of the side effect profile and its side effects were reported to be more tolerable compared with sunitinib [24]. In the comparison of pazopanib and sunitinib in our study with respect to their side effect profiles, the most common side effects were nausea-vomiting (41.7%), hypothyroidism (20.8%) and hypertension (8.3%) in the pazopanib arm, as opposed to hypothyroidism (25.9%), nausea-vomiting (14.8%) and palmar-plantar erythrodysesthesia (13%) in the sunitinib arm. When the two groups were compared with regard to side effects, nausea-vomiting was more frequent in the pazopanib arm ($p = 0.01$), while the other side effects were comparable (Tab. 5). In our study, a significant difference was not determined between the two groups in terms of the side effects.

Previous studies have shown that the mode of sunitinib administration influenced its side effect profile. Daily use of the drug for two weeks followed by one week off was reported to reduce the rate of grade-3 and higher side effects from 45.7% to 8.2% when compared with a four-week-on/two-week-off scheme [25]. In our study, the treatment scheme of some patients (in case of adverse effects) in the sunitinib arm included drug use for two weeks, followed by one week off. Medication side effects could not be evaluated in detail for either of the agents due to the retrospective nature of our study and the lack of details in the patient files.

The single-center, retrospective design of our study and the low number of patients constituted the limitations of our study.

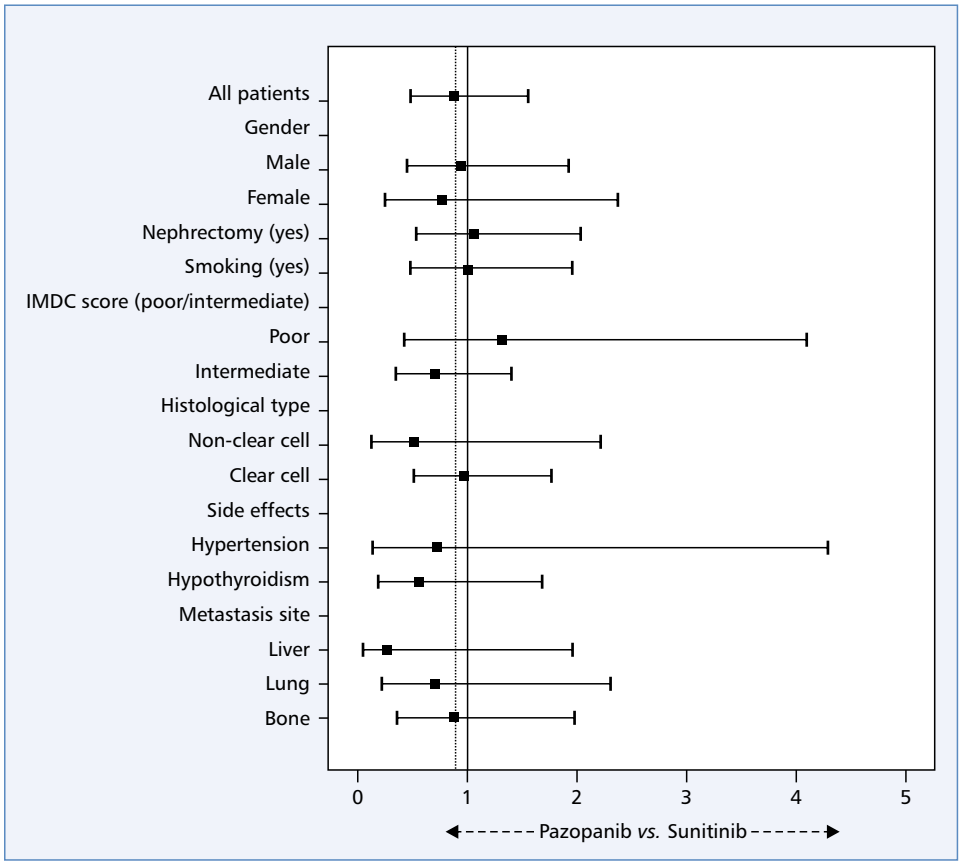

Figure 3. Subgroup analysis of factors affecting progression-free survival for sunitinib and pazopanib

Table 5. Treatment-related side effects

Any grade n(%)	All patients	Pazopanib	Sunitinib	P value
Hypothyroidism	19 (24.4)	5 (20.8)	14 (25.9)	0.62
Hyperthyroidism	1 (1.3)	0 (0)	1 (1.9)	0.69
Pruritus	1. (1.3)	1 (4.2)	0 (0)	0.30
Palmar-plantar erythrodysesthesa	8 (10.3)	1 (4.2)	7 (13)	0.23
Nausea/vomiting	18 (23.1)	10 (41.7)	8 (14.8)	**0.01**
Diarrhea	5 (6.4)	1 (4.2)	4 (7.4)	0.50
Hypertension	8 (10.3)	2 (8.3)	6 (11.1)	0.71
Neutropenia	2 (2.6)	0 (0)	2 (3.7)	0.47
Anemia	0 (0)	0 (0)	0 (0)	
Thrombocytopenia	4 (5.1)	0 (0)	4 (7.4)	0.22
Mucositis	5 (6.4)	1 (4.2)	4 (7.4)	0.59
Fatigue	9 (11.5)	2 (8.3)	7(13)	0.55
Skin reaction	3 (3.8)	2 (8.3)	1 (1.9)	0.22

Conclusions

In conclusion, the use of pazopanib and sunitinib in the first-line treatment of patients diagnosed with mRCC yielded a better PFS outcome in our study when compared with the previous studies. No difference was found between the two agents in terms of PFS, OS and ORR. The side effect profiles were comparable. Pazopanib and sunitinib had similar effectiveness in terms of PFS in the investigated subgroups. In agreement

with the literature, both agents obtained longer PFS times in patients with a hemoglobin level ≥ 13 g/dL, an ECOG PS of 0–1, an intermediate IMDC score and drug-induced hypothyroidism.

Ethics approval

All analyses were performed in accordance with the principles of the Declaration of Helsinki.

Conflict of interest

Authors declare that they have no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
2. Thompson RH, Ordonez MA, Iasonos A, et al. Renal cell carcinoma in young and old patients--is there a difference? J Urol. 2008; 180(4): 1262–6; discussion 1266, doi: 10.1016/j.juro.2008.06.037, indexed in Pubmed: 18707708.
3. Vogelzang NJ, Priest ER, Borden L. Spontaneous regression of histologically proved pulmonary metastases from renal cell carcinoma: a case with 5-year followup. J Urol. 1992; 148(4): 1247–1248, doi: 10.1016/s0022-5347(17)36874-x, indexed in Pubmed: 1404646.
4. Hofmann F, Hwang EuC, Lam TBl, et al. Targeted therapy for metastatic renal cell carcinoma. Cochrane Database Syst Rev. 2020; 10: CD012796, doi: 10.1002/14651858.CD012796.pub2, indexed in Pubmed: 33058158.
5. Zama IN, Hutson TE, Elson P, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer. 2010; 116(23): 5400–5406, doi: 10.1002/cncr.25583, indexed in Pubmed: 21105118.
6. Bracarda S, Bellmunt J, Melichar B, et al. Overall survival in patients with metastatic renal cell carcinoma initially treated with bevacizumab plus interferon-ζ2a and subsequent therapy with tyrosine kinase inhibitors: a retrospective analysis of the phase III AVOREN trial. BJU Int. 2011; 107(2): 214–219, doi: 10.1111/j.1464-410X.2010.09707.x, indexed in Pubmed: 20942831.
7. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res. 2003; 9(1): 327–337, indexed in Pubmed: 12538485.
8. Hutson T, Davis I, Machiels J, et al. Predictive and prognostic factors in phase II renal cell carcinoma trial with pazopanib (GW786034), a multi-kinase angiogenesis inhibitor. Ann Oncol. 2008(suppl 8): abstr 5780.
9. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007; 356(2): 115–124, doi: 10.1056/NEJMoa065044, indexed in Pubmed: 17215529.
10. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27(22): 3584–3590, doi: 10.1200/JCO.2008.20.1293, indexed in Pubmed: 19487381.
11. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010; 28(6): 1061–1068, doi: 10.1200/JCO.2009.23.9764, indexed in Pubmed: 20100962.
12. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013; 369(8): 722–731, doi: 10.1056/NEJMoa1303989, indexed in Pubmed: 23964934.
13. Motzer R, Hutson T, McCann L, et al. Overall Survival in Renal-Cell Carcinoma with Pazopanib versus Sunitinib. N Engl J Med. 2014; 370(18): 1769–1770, doi: 10.1056/nejmc1400731.
14. Isik U, Kostek O, Demiray G, et al. Real life data from Turkey regarding the impact of first-line sunitinib and pazopanib in metastatic renal cell cancer. J Clin Oncol. 2019; 37(15_suppl): e16075–e16075, doi: 10.1200/jco.2019.37.15_suppl.e16075.
15. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002; 20(1): 289–296, doi: 10.1200/JCO.2002.20.1.289, indexed in Pubmed: 11773181.
16. Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009; 27(34): 5794–5799, doi: 10.1200/JCO.2008.21.4809, indexed in Pubmed: 19826129.
17. Patil S, Figlin RA, Hutson TE, et al. Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. Ann Oncol. 2011; 22(2): 295–300, doi: 10.1093/annonc/mdq342, indexed in Pubmed: 20657034.
18. Cecere SC, Rossetti S, Cavaliere C, et al. Pazopanib in Metastatic Renal Cancer: A "Real-World" Experience at National Cancer Institute "Fondazione G. Pascale". Front Pharmacol. 2016; 7: 287, doi: 10.3389/fphar.2016.00287, indexed in Pubmed: 27630568.
19. Wolter P, Stefan C, Decallonne B, et al. Evaluation of thyroid dysfunction as a candidate surrogate marker for efficacy of sunitinib in patients (pts) with advanced renal cell cancer (RCC). J Clin Oncol. 2008; 26(15_suppl): 5126–5126, doi: 10.1200/jco.2008.26.15_suppl.5126.
20. Puzanov I, Michaelson MD, Cohen DP, et al. Evaluation of hand-foot syndrome (HFS) as a potential biomarker of sunitinib (SU) efficacy in patients (pts) with metastatic renal cell carcinoma (mRCC) and gastrointestinal stromal tumor (GIST). J Clin Oncol. 2011; 29(15_suppl): e21113–e21113, doi: 10.1200/jco.2011.29.15_suppl.e21113.
21. Larkin JMG, Pyle LM, Gore ME. Fatigue in renal cell carcinoma: the hidden burden of current targeted therapies. Oncologist. 2010; 15(11): 1135–1146, doi: 10.1634/theoncologist.2010-0078, indexed in Pubmed: 21051659.
22. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2018; 379(5): 417–427, doi: 10.1056/NEJMoa1803675, indexed in Pubmed: 29860937.
23. Bex A, Mulders P, Jewett M, et al. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncol. 2019; 5(2): 164–170, doi: 10.1001/jamaoncol.2018.5543, indexed in Pubmed: 30543350.
24. Trump D, Escudier B, Porta C, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES Study. J Clin Oncol. 2014; 32(14): 1412–1418, doi: 10.1200/JCO.2013.50.8267, indexed in Pubmed: 24687826.
25. Bracarda S, Iacovelli R, Boni L, et al. Rainbow Group. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: the RAINBOW analysis. Ann Oncol. 2015; 26(10): 2107–2113, doi: 10.1093/annonc/mdv315, indexed in Pubmed: 26216384.