Survival Outcomes of Patients in Advanced Non-Clear Renal Cell Carcinoma Treated with Pazopanib: A Retrospective Single Institution Experience

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ABSTRACT

The precise benefit and safety of pazopanib in non-clear cell renal cell carcinoma (nccRCC) has not yet been elucidated. Therefore, the aim of the present study was to investigate the role and safety profile of pazopanib in nccRCC. A total of 40 nccRCC patients treated with pazopanib were enrolled. Progression-free survival (PFS), and overall survival (OS) times were analyzed with Kaplan-Meier method. Univariable and multivariable Cox regression models were used to identify the predictive factors for PFS, and OS. The primary endpoint was the response assessment of pazopanib according to Response Evaluation Criteria in Solid Tumors in non-ccRCC patients. The median age of patients was 62 (range: 45-78). Considering histologic subtypes, the numbers of papillary, chromophobe, sarcomatoid differentiation and unclassified type were 21 (52.5%), 6 (15%), 5 (12.5%), and 8 (20%), respectively. The median PFS, and OS in all cohort were 13.8 (95% CI: 0-30.7), and 45.6 months (95% CI: 24.3-66.9), respectively. The overall response rate (complete response+partial response), and disease control rate (complete response+partial response+stabil disease) were 45%, and 77.5%, respectively. Grade 3 or more adverse effects that were managed with dose reduction, and treatment delay effectively were observed in 16 (40%) patients. The independent determinants that were associated with PFS and OS in the multivariate analyses were IMDC scoring system (p= 0.001), lactate dehydrogenase (LDH) level (p= 0.015) for PFS, and only IMDC scoring system (p< 0.001) for OS. Pazopanib can be used as an effective agent with tolerable safety profile for the treatment of advanced nccRCC patients.

Keywords: Chromophobe RCC, Non-clear cell renal cell carcinoma, Papillary RCC, Pazopanib

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 3% and 5% of all cancer cases in women and in man, respectively.[1] Clear cell renal cell carcinoma (ccRCC) is the predominant histologic subtype, accounting for approximately 80% of renal epithelial tumors. All of the remaining tumors are classified as non-clear cell renal cell renal carcinoma (nccRCC). Papillary (type I/II), and chromophobe subtypes are most commonly seen nccRCC, constituting of 80% of all nccRCC cases.[2] The other subtypes are carcinoma associated with neuroblastoma, renal medullary collecting duct, renal medullary, spindle cell, mucinous tubular, Xp11 translocation, and unclassified carcinomas.[2] The sarcomatoid variant is associated with aggressive clinical presentation at diagnosis and survival outcomes in patients with nccRCC. However, it is not included as a distinct histologic subtype. The exact benefit of approved targeted therapeutic options in patients with metastatic nccRCC remains unclear. Since there are a variety of treatment options with clear evidence for metastatic ccRCC, the treatment choices and sequencing of nccRCC remain controversial according to available data.

Currently, 2 well-defined scoring systems, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), and The Memorial Sloan-Kettering Cancer Center (MSKCC) Criteria are used for the estimation of the prognosis of RCC patients with advanced disease.[3,4] According to these scoring systems, patients are classified into favorable, intermediate, and poor-risk groups depending on the variables including particular laboratory and clinical factors. Immunotherapy, anti-vascular endothelial growth factor (VEGF) agents (sunitinib, pazopanib), or both of them can be given to the patients with advanced disease for first line treatment according to risk groups. The recommendation of sunitinib followed by everolimus for advanced nccRCC is based on 3 phase II prospective trials.[5-7] While pazopanib is a safe, and efficient alternative to sunitinib for treatment of nccRCC, the efficacy of pazopanib has not been prospectively evaluated in randomized clinical trials. However, pazopanib gained approval from the United States Food and Drug Administration in October 2009 for treatment of metastatic RCC for all histologies. Therefore, the present study was aimed to investigate the efficacy, and safety profile of pazopanib in metastatic nccRCC treated with pazopanib.

PATIENTS and METHODS

Patients and Study Design

The present retrospective study included 40 patients treated with pazopanib from October 2009 to October 2020 at Hacettepe University Cancer Institute, a tertiary referral medical Center in Turkey. The following inclusion criteria were used for the present study; age ≥ 18 years old, treatment with pazopanib for advanced nccRCC, no previous history of treatment with any targeted therapy (sunitinib, sorafenib), and immune-checkpoint inhibitors, and those with normal liver, and kidney function tests. However, all the patients had a previous history of immune therapy (interferon). All the patients had Eastern Cooperative Oncology Group performance status of 0 or 1, and pathologically confirmed nccRCC subtype, including papillary, chromophobe, and unclassified tumors. Additionally, patients with mixed histology who had sarcomatoid differentiation were included if the sarcomatoid component constituted less than 5% of the entire tumor. Patient risk stratification was evaluated according to the IMDC scoring system, which is the most commonly used prognostification system currently.[4] The prognostic determinants included in this system are Karnofsky Performance Status < 80, time from diagnosis to initiation of therapy < 1 year, serum calcium higher than the upper limit of normal (ULN), hemoglobin count less than the lower limit of normal, neutrophil count higher than the ULN, platelet count greater than ULN. The whole cohort was classified into three risk groups as favorable (no risk factor), intermediate (1-2 risk factors), and poor-risk group (3 or more risk factors). Patients were treated with pazopanib at a dose of 800 mg/day until progression or unacceptable adverse events and lower doses (600 mg/day or 400 mg/day) were used because of toxicity and intolerance to the drug. Adverse events were graded in accordance with the National Cancer Institute's Common Toxicity Criteria version 3.0. All the performed procedures in the present study complied with the 1964 Helsinki declaration and its later amendments. Hacettepe University's Ethics Committee (15.12.2020, GO 20/1143) approved the study, and all of the study subjects or their relatives gave written informed consent.

Statistical Analysis

Descriptive statistics were measured as the median and interquartile range (IQR; 25th-75th percentile) for continuous parameters and frequency and percentage for categorical parameters.

Mann-Whitney U and Chi-square tests for categorical, and continuous variables were done to compare independent groups. The progression-free survival (PFS) was described as the time from initiation of pazopanib to the progression (by Response Evaluation Criteria in Solid Tumors) and/ or death, whichever occurred first. The overall survival (OS) was described as the time from initiation of pazopanib to the last follow-up and/or death. Kaplan-Meier analyses were performed for the estimation of PFS, and OS. One-sided Fisher exact test was used to investigate the relationship between the tumor response, and treatment with pazopanib.

The Cox proportional hazards regression models were performed for the identification of predictive indicators of PFS, and OS. Disease-free survival of patients with no metastasis at presentation was described as the time from diagnosis to the documentation of locoregional or distant metastasis. All the analyses were performed in SPSS 25 (IBM Inc., Armonk, NY, USA) software. P value less than 0.05 was the threshold limit for statistical significance.

RESULTS

Patient Characteristics

Baseline patient clinical, and pathological characteristics were shown in Table 1. A total of 40 consecutive patients with nccRCC treated with pazopanib were included. The number of male and female patients were 31 (77.5%), and 9 (22.5%). The mean age at diagnosis was 58 (Standart Deviation ± 11.6). Papillary histology was the most common subtype (n= 21). Tumors with sarcomatoid differentiation were observed in five patients (papillary, n= 3; chromophobe n= 2). During the median follow-up time of 21 months, 19 (47%) patients died, and disease progression with pazopanib was determined in 28 (70%) patients (papillary: 14/21; chromophobe: 3/6; sarcomatoid variant: 4/5; unclassified: 3/8). Thirty-two patients had previous surgery (17 for early-stage disease, and 15 for advanced disease). The median time from diagnosis to recurrence in 17 (42.5%) patients with early-stage disease were 54.4 months (SD ± 25). According to IMDC scoring system, 27.5%, 37.5%, and 35% of patients were evaluated in favorable, intermadiate, and poor-risk groups, respectively. Lung was the most common metastatic region site (65%). Taking patients' later line treatment lines into consideration, 23 (57.5%), and 12 (30%) of patients were treated with second-line, and third-line therapy, respectively (axitinib n= 12, everolimus n= 8, nivolumab n= 3 for second-line therapy; axitinib n= 6, everolimus n= 3, nivolumab n= 3 for forth-line therapy). Only three patients (7.5%) received fourth-line therapy (axitinib n= 1, nivolumab n= 2).

Tablo 1. Baseline clinical and histopathological charecteristics of nccRCC patients

Clinical and pathological charecteristics		Value
Median age (range)	62 (45-78)	
Gender	Male	31 (77.5%)
	Female	9 (22.5%)
Surgery	Yes	32 (80%)
	No	8 (20%)
Stage at diagnosis	Stage I, II, III	17 (42.5%)
	Stage IV	23 (57.5%)
Histologic subtypes	Papillary	21 (52.5%)
	Chromophobe	6 (15%)
	Sarcomatoid differentiation	5 (12.5%)
	Unclassified	8 (20%)
Tumor grade	Grade I-II	7 (21.2%)
	Grade III-IV	26 (78.8%)
Metastatic region	1-2	35 (87.5%)
	3	5 (12.5%)
IMDC subgroups	Favorable	11 (27.5%)
	Intermediate	15 (37.5%)
	Poor	14 (35%)

IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

The Efficacy and Survival Outcomes

In the whole population, considering response to pazopanib, one patient (2.5%) had a complete response (CR). The number of patients who achieved partial response (PR), stable disease (SD), and progressive disease (PD) were 17 (42.5%), 13 (32.5%), and 9 (22.5%). Overall response rate (ORR), disease control rate (DCR) were 45%, and 77.5%, respectively. Response rates to pazopanib in patients stratified according to histologic subtypes were shown in Table 2. The median PFS (mPFS), and the median OS (mOS) of all patients were 13.8 (95% CI: 0-30.7), and 45.6 months (95% CI: 24.3-66.9), respectively. Considering IMDC prognostic risk groups; the mPFS times for favorable, intermediate, and poor-risk groups were 29 months (95% CI: 24.8-33.3), 22 months (95% CI: 5-38.9), and 4 months (95% CI: 2.9-6.7), respectively. While the mOS was not reached for intermediate group, thus the mean OS was 56+

Table 2. Response evaluation to pazopanib in patients with nccRCC stratified according to histologic subtypes

Histologic subtype	Papillary (n= 21)	Chromophobe (n= 6)	Sarcomatoid differantiation (n= 5)	Unclassified (n= 8)
Response				
CR	–	1 (16.7%)	–	–
PR	11 (52.4%)	1 (16.7%)	1 (20%)	4 (50%)
SD	7 (33.3%)	2 (33.3%)	2 (40%)	2 (25%)
PD	3 (14.3%)	2 (33.3%)	2 (40%)	2 (25%)
ORR	11 (52.4%)	2 (33.3%)	1 (20%)	4 (50%)
DCR	18 (85.7%)	4 (66.7%)	3 (60%)	6 (75%)

CR: Complete Remission; PR: Partial Remission; SD: Stabile Disease; PD: Progressive Disease; ORR: Overall Response Rate; DCR: Disease Control Rate

months (Standard error: 8 months) during ongoing follow-ups, the mOS times for favorable, and poor risk groups were 47.7 (95% CI: 0-30.7), and 10.6 (95% CI: 5.4-15.8) months, respectively. As shown in Table 3, univariate Cox analyses demonstrated that metastasis at presentation, and IMDC scoring system were associated with PFS (p= 0.001 for metastasis at presentation; p< 0.001 for IMDC scoring system) However, multivariate analyses demonstrated that high lactate dehydrogenase (LDH) and IMDC scoring system were determined as independent indicators for PFS (p= 0.015 for LDH; p= 0.001 for IMDC scoring system). While the IMDC scoring system and the presence of bone metastasis were associated with OS in univariate analyses (IMDC, p= 0.001; presence of bone metastasis, p= 0.02), only independent determinant in predicting OS was the IMDC scoring system (p< 0.001) (Table 4).

Adverse Event Profile of Pazopanib

Adverse events regarding all grades were observed in 95% of patients (n= 38) (Table 5). Hair color

Table 3. Univariate Cox regression model determining the potential variables for the estimation of PFS and OS times

	PFS		OS	
Charecteristic	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Age	1 (0.97-1.03)	0.858	0.99 (0.95-1.03)	0.725
Surgery (yes vs no)	0.82 (0.33-2.04)	0.675	0.5 (0.2-1.5)	0.242
Fuhrman grade (Grade III-IV vs Grade I-II)	1.64 (0.48-5.56)	0.425	0.5 (0.1-2)	0.378
Stage at diagnosis (Stage IV vs Stage I-II-III)	4.42 (1.8-10.4)	0.001	2.8 (1-7.5)	0.042
Lung metastasis (Yes vs No)	0.97 (0.45-2.12)	0.958	2.4 (0.8-7.3)	0.121
Bone metastasis (Yes vs No)	1.88 (0.81-4.35)	0.137	3.3 (1.2-8.8)	0.02
Liver metastasis (Yes vs No)	1.02 (0.37-2.80)	0.964	0.84 (0.27-2.64)	0.778
Adrenal metastasis (Yes vs No)	0.84 (0.32-2.22)	0.730	0.2 (0-1.5)	0.116
LDH (> ULN vs ≤ ULN)	1.99 (0.87-4.56)	0.101	1.4 (0.5-3.7)	0.410
IMDC risk groups		< 0.001		0.001
Favorable	1 (ref)	1	1 (ref)	
Intermediate	1.32 (0.47-3.75)	0.591	0.9 (0.3-3.5)	0.926
Poor	15.64 (4.52-54.04)	< 0.001	10.2 (2.4-42.6)	0.001

PFS: Progression free survival; OS: Overall survival; LDH: Lactate dehydrogenase; ULN: Upper limit of Normal; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

Table 4. Multivariate Cox regression model determining the independent variables for the estimation of PFS and OS times

Survival outcomes	HR	95% CI for HR		P value
		Lower	Upper	
PFS				
LDH (> ULN vs ≤ ULN)	2.96	1.23	7.12	0.015
IMDC risk groups				0.001
Favorable	1 (reference)			
Intermediate	0.72	0.17	2.95	0.653
Poor	6.97	1.14	42.4	0.035
OS				
IMDC risk groups				< 0.001
Favourable	1 (reference)			
Intermediate	1.29	0.31	5.35	0.719
Poor	15.4	3.186	19.945	0.001

HR: Hazard ratio; PFS: Progression free survival; LDH: Lactate dehydrogenase; ULN: Upper limit of normal; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; OS: Overall survival

Table 5. Adverse events in nccRCC patients treated with pazopanib

Toxicity event	All grades	Grade ≥ 3
Clinical sign and symptom		
Anorexia	18 (45%)	3 (7.5%)
Fatigue	17 (42.5%)	1 (2.5%)
Myalgia	12 (30%)	-
Nausea/vomitting	23 (57.5%)	1 (2.5%)
Hypertension	20 (50%)	1 (2.5%)
Headache	7 (17.5%)	-
Diarrhea	19 (47.5%)	1 (2.5%)
Constipation	3 (7.5%)	-
Hair color change	27 (67.5%)	-
Alopecia	8 (20%)	
Hand-foot syndrome	10 (25%)	-
Mucositis	15 (37.5%)	-
Labaratory values		
LFT abnormalities	17 (42.5%)	5 (12.5%)
Hypothroidism	4 (10%)	1 (2.5%)
Anemia	6 (15%)	1 (2.5%)
Leukopenia	3 (7.5%)	-
Trombocytopenia	6 (15%)	2 (5%)
Hyperkalemia	2 (5%)	-
Hypokalemia	2 (5%)	-
Hyponatremia	4 (10%)	-

LFT: Liver functiton tests

change, hypertension, nausea/vomiting, anorexia, and fatigue were most commonly observed adverse clinical events. Liver function test abnormality, thrombocytopenia, and anemia were most commonly detected laboratory parameters. Grade≥ 3 adverse events were evaluated in 16 (40%) of the patients. Most of the adverse events were managed with dose reduction (n= 21, 55%), and or treatment delay (n= 19, 50%). However, treatment cessation were observed in only one patient because of thrombocytopenia with grade 4 toxicity. There was no treatment-related deaths with pazopanib.

DISCUSSION

nccRCCs are rare kidney cancers that have different histological, and genetic alterations from ccRCC. Genetic alterations in VHL a tumor suppressor gene, have been observed approximately in 90% of patients with ccRCC.[8] However, Moore et al. reported that fewer VHL gene alterations were detected in the patients with nccRCC in comparison to those with ccRCC (16% vs 87%). Additionally, it was reported that papillary RCCs had lower VEGF mRNA levels than ccRCC.[9] Patients with nccRCC have a worse prognosis than patients with ccRCC.[10]

The optimal treatment type and sequencing remain unclear, and also the response rates of cytokine or cytotoxic therapy in the treatment of both ccRCC,

and nccRCC remain limited. Anti-VEGF directed drugs, sunitinib, and pazopanib are approved therapies in the treatment of nccRCC. Regarding the studies conducted with sunitinib in the treatment of nccRCC, in the phase II ASPEN trial (Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma), patients with sunitinib arm had significantly higher mPFS compared with everolimus for first-line treatment of nccRCC patients (Hazard ratio: 1.41; 8.3 months vs 5.6 months; p= 0.16).[5] In another phase II tiral, ESPN (Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma), the patients with nccRCC were randomized to sunitinib or everolimus as a first-line treatment, and crossover at disease progression was permitted. Median OS was found similar between sunitinib, and everolimus arm (p= 0.18).[6] Additionally, in the RECORD (Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma) trial, patients treated with first-line sunitinib had numerically but not significantly higher PFS compared to those treated with first line everolimus in 66 nccRCC population.[7,11] According to these trials, first-line treatment with sunitinib followed by second-line everolimus is the rational treatment sequencing in nccRCC patients.[5,6,11] However, there are very little current data about the efficacy of pazopanib in the treatment of nccRCC patients. Buti et al. reported that ORR and DCR were 27%, and 81%, respectively in 37 nccRCC patients treated with pazopanib, including papillary (51%), chromophobe (24%), unclassified (22%), and Xp11.2 translocation (3%), the mPFS, and mOS times were 15.9 and 17.3 months, respectively.[12] In phase II Korean study, ORR, and DCR were 28%, and 89% respectively in 29 nccRCC patients treated with pazopanib, and while the mPFS was 16.5 months (95% CI: 10.9-22.1), the mOS was not reached during the follow-up time of 21.3 months.[13] Matrana et al. analyzed the efficacy, and safety of pazopanib in 20 nccRCC patients treated with pazopanib in front-line or salvage settings. mPFS, and mOS were 8.1 months, and 31 months, respectively for front-line group, and 4 months, and 13.6 months, respectively for the salvage group.[14] A systematic review including a total of 318 nccRCC patients in 15 trials which investigated the effect and safety profile of pazopanib showed that pazopanib treatment in the front-line setting resulted in ORR varied from 27% to 33%, DCR of 81% - 89%, mPFS of 8.1-16.5, and mOS of 17.3-31 months.[15] Our study showed that ORR, and DCR were 45%, and 77.5%, respectively. Additionally, mPFS, and mOS of the entire population were 13.8 months, and 45.6 months, respectively. The different response rates and survival outcomes in these studies that investigated the efficacy of pazopanib in nccRCC patients may have resulted from non-standardized experimental designs according to IMDC risk scoring system, nccRCC histologies.

Grade ≥ 3 adverse events related to pazopanib in the treatment of nccRCC varied from 21% to 55% in previous trials.[12-14,16] Similar to the relevant literature, our study showed that during the follow-up time, most of the patients (95%) had any grade adverse events due to pazopanib treatment. Grade ≥ 3 adverse events were detected in half of the patients in the present study. Adverse events related to pazopanib were effectively managed by adjustment of dose, and treatment delay. No pazopanib-associated death was observed, and treatment was stopped only in one patient because of grade 4 thrombocytopenia. The safety profile of pazopanib in our study was not worse than pivotal phase III trials of pazopanib, which investigated the efficacy, and safety of pazopanib in ccRCC.[17,18]

Several promising treatment alternatives, targeted therapies, and immune check-point inhibitors have been evaluated in the treatment of nccRCC. Foretinib targeting MET in addition to VEGF receptor, and other kinases were evaluated in the treatment of 65 papillary RCC patients in a prospective phase II trial, ORR was 50% among patient subgroup with germline mutations of MET (n= 10).[19] The activity of cabozantinib in the 112 patients with advanced nccRCC who received cabozantinib during any treatment line was investigated in a retrospective, multicentre, cohort study, and mPFS, and mOS were 7 months, and 12 months, respectively during the median follow-up time of 11 months.[20] Crizotinib was found as an active and well-tolerating drug achieving ORRs of 50% in four type I papillary nccRCC patients with

MET mutation or amplification in phase II CREATE trial.[21] In a study with retrospective nature, the efficacy of nivolumab was evaluated in the 41 patients with advanced nccRCC, the mPFS, and ORR were 3.5 months, and 20%, respectively.[22]

In summary, to our best knowledge, we investigated the safety and efficacy of pazopanib in the largest nccRCC cohort compared to the current literature. We demonstrated that pazopanib was a safety and efficient alternative therapy to sunitinib in the treatment of nccRCC. However, prospective studies are needed to investigate the exact roles of pazopanib, immune check-point inhibitors, and other targeted therapies in particular histologies, and genotypes of advanced nccRCC patients.

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