Clinics in Oncology

Research Article
Published: 16 Apr, 2019

Efficacy and Safety of First-Line Pazopanib in Patients with Metastatic Renal Cell Carcinoma: Real-Life Multi Institutional Experience

Abeer Hussien Anter[1], Rasha Hamdy Hamed[1] and Amrallah A Mohammed[2]*

[1]Department of Clinical Oncology and Nuclear Medicine, Mansoura University, Egypt

[2]Department of Medical Oncology, Zagazig University, Egypt

Abstract

Background: Pazopanib is an oral multi targeted tyrosine kinase inhibitor that has been approved for first-line treatment of metastatic Renal Cell Carcinoma (mRCC). This trial aimed to investigate the real-life clinical outcomes of the first-line pazopanib in Egyptian patients with mRCC.

Patients and Methods: Data from 30 patients with mRCC, treated with pazopanib at our institutions during the period from January 2016 to December 2018, were analyzed retrospectively. All patients received 800 mg/day pazopanib. The primary end point was Progression-Free Survival (PFS). Secondary end points included overall survival, tumor response rate, and safety.

Results: Thirty patients were included 23 (76.7%) male and 7 (23.3%) female, of median age 53 years (range, 20-76 years). Clear cell pathology was reported in 80%. Lung and Lymph nodes were the most common sites of metastasis 53.3%, 46.7 respectively. Most AEs were grade 1/2, Diarrhea (33.3%), hypertension (26.7%), and stomatitis (23.3%) were the most common AEs reported while thrombocytopenia was the most common hematological toxicities. The median PFS was 9 months (95% CI 7.12-10.87) and the median OS was 28 months. The estimated 2-year survival rate was 57%. The objective response rate was 30%.

Conclusion: This study proved that pazopanib treatment has clinically acceptable efficacy and safety profile in unselected real-world Egyptian patients with mRCC.

Keywords: Metastatic renal cell carcinoma; Pazopanib; First-line; Efficacy

OPEN ACCESS

Correspondence:
Abeer Hussien Anter, Department of Clinical Oncology and Nuclear Medicine, Mansoura University, Egypt, E-mail: abeerantar75@yahoo.com

Received Date: *06 Mar 2019*
Accepted Date: *08 Apr 2019*
Published Date: *16 Apr 2019*

Citation:
Anter AH, Hamed RH, Mohammed AA. Efficacy and Safety of First-Line Pazopanib in Patients with Metastatic Renal Cell Carcinoma: Real-Life Multi Institutional Experience. Clin Oncol. 2019; 4: 1605.

Abbreviations

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease

Introduction

Kidney cancer is the eighth most common cancer in the United States. Renal Cell Carcinoma (RCC) represents the most common type of kidney cancer in adults. The clear cell type represented the main histological subtype accounting approximately 80% of all RCC [1].

In newly diagnosed RCC, a quarter of patients will present with metastatic RCC (mRCC), while an additional 20% to 40% who initially present with localized disease will go on to develop mRCC [2,3]. mRCC portends a poor prognosis with median Overall Survival (OS) less than three years [4].

Localized RCC can be successfully managed with surgery whereas metastatic RCC is refractory to conventional chemotherapy. However, over the past decade, marked advances in the treatment of mRCC have been made with targeted agents work by targeting angiogenesis and inhibit Vascular Endothelial Growth Factor (VEGF) and its receptors (VEGFRs) [5]. Pazopanib is an oral Tyrosine Kinase Inhibitor (TKI) that inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR-1, -2, and -3), platelet-derived growth- factor receptors, (PDGFR α/β), and stem cell factor receptor (c-Kit) and proliferation and is approved as first-line treatment for mRCC [6].

The Progression-Free Survival (PFS) was significantly improved with pazopanib vs. placebo in patients with mRCC [7]. In the large non-inferiority COMPARZ trial, a head to head trial comparing the safety and efficacy of sunitinib and pazopanib in naïve patients with mRCC. The reported results showed comparable efficacy profile but the safety and quality-of-life profiles favor pazopanib [8].

Table 1: Baseline patient characteristics.

	No. of patients (N=30)	
	No. of patients	**Percent**
Age (years)		
Median (range)	53 (20-76)	
Sex		
Male	23	76.70%
Female	7	23.30%
ECOG performance status		
1	21	70%
2	9	30%
Comorbid illness		
Diabetes	8	26.7
Hypertension	3	10
IHD	1	3.3
Histology		
Clear cell	24	80%
Non-clear cell	6	20%
Time from diagnosis to treatment		
<1 year	17	56.7
≥ 1 year	13	43.3
Prior nephrectomy	22	73.3
Prior systemic treatment	0	0
Treatment naïve	30	100
No. of organs involved		
1	4	13.3
2	19	63.3
≥ 3	7	23.4
Sites of metastases		
Lung	16	53.3
Lymph nodes	14	46.7
Bone	11	36.7
Liver	7	23.3
Local recurrence	5	16.7
MSKCC risk category		
Favorable (0)	9	30
Intermediate (1-2)	14	46.7
Poor ≥ 3	2	6.7
Unknown*	5	16.7

ECOG, Eastern Cooperative Oncology Group
*Patients with an unknown MSKCC risk category were missing results for one or more of the five risk criteria

The aim of our study was to investigate the real-world clinical outcomes of the first-line pazopanib in Egyptian patients with mRCC.

Patients and Methods

A retrospective collection of clinical data of patients with mRCC from January 2016 to December 2018 treated at Clinical Oncology & Nuclear Medicine Department, Mansoura University and EL-Mabra Hospital Zagazig. Inclusion criteria were as follow: age ≥ 18 years, histologically confirmed RCC; measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [9]; performance status evaluation by an Eastern Cooperative Oncology Group score (ECOG) of at least 2; adequate organ function and receiving first-line treatment with pazopanib.

Table 2: Pazopanib - related toxicities in overall population.

	Grade 1/2		Grade 3/4	
	N	%	N	%
Hematological				
Leukopenia	0	0	0	0
Anemia	2	6.7	0	0
Thrombocytopenia	3	10	0	0
Diarrhea	10	33.3	3	10
Nausea	4	13.3	0	0
Anorexia	3	10	0	0
Vomiting	2	6.7	0	0
Stomatitis	7	23.3	1	3.3
Fatigue	6	20	0	0
Hand–foot syndrome	5	16.7	0	0
Changes in hair color	9	30	0	0
Hepatic	3	10	1	3.3
Hypertension	8	26.7	0	0

Exclusion criteria were patients with other malignancies, poor performance status (ECOG ≥ 3), end-stage renal disease, Child-Pugh C liver cirrhosis, or poor heart or lung function, and patients who received prior chemotherapy or cytokines.

Baseline demographics and clinical data collected. The response was measured using RECIST guidelines [9]. Adverse Events (AEs) were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) [10].

The primary endpoint of this study was Progression-Free Survival (PFS), which was defined as the time from the initiation of pazopanib to the date of progressive disease or death. Secondary endpoints included the objective Response Rate (RR), safety and Overall Survival (OS), which was defined as the time from the initiation of pazopanib to date of death or last follow up. As this study is a retrospective study, the requirement of informed consent was waived. The study was approved by the Institutional Review Board (IRB) at the faculty of medicine, Mansoura University.

Statistics

Descriptive analysis was performed to clinical data of patients by reporting them as frequencies and proportions. We estimated the survival rates during the entire follow-up period by the Kaplan–Meier method. For all tests, significance was defined at $p<0.05$. The statistics were accomplished through Statistical Package Version 23 (SPSS, INC., Chicago, IL, USA).

Results

Patients' characteristics

Medical records were collected from 30 consecutive patients who were treated with the first-line pazopanib at two hospitals between January 2016 and December 2018. The baseline demographic and clinical characteristics, tumor features and risk group stratification as per Memorial Sloan-Kettering Cancer Center risk model (MSKCC)

Table 3: Summary of tumor response.

Response	N	%
CR	0	0
PR	9	30
SD	13	43
PD	6	20
Response rate CR+ PR)	9	30
Unknown	2	7

[11] are listed in Table 1.

Median age was 53 years with male predominance (76.7%) and 70% of patients were of ECOG PS 1. Clear cell pathology was reported in 80%.

Lung, Lymph nodes and bone were the most common sites of metastasis 53.3%, 46.7% and 36.7% respectively. Nineteen patients (63.3%) presented with two sites of metastasis. Twenty-one patients (70%) in this study were initially diagnosed with localized disease and had radical nephrectomy. Approximately 24% of those who had metastatic disease at presentation underwent cyto reductive nephrectomy before pazopanib treatment. Five patients did not have baseline LDH level or serum calcium before starting pazopanib; therefore, only 25 patients could be evaluated for MSKCC risk stratification.

Safety and toxicity

Tolerance to pazopanib was good with very few Grade III-IV toxicities. Only 2 patients (6.7%) needed dose modifications and no patient required discontinuation due to AEs. The toxicity profile in our study is illustrated in Table 2. Most AEs were grade 1/2. Diarrhea (33.3%), hair color changes (30%), hypertension (26.7%), and stomatitis (23.3%) were the most common AEs reported while thrombocytopenia followed by anemia were the most common hematological toxicities. The most common grade 3/4 AEs was diarrhea occurring in three patients (10%), which recovered after withholding pazopanib for 1-2 weeks and conservative management.

Efficacy

The efficacy analysis is documented in Table 3. The best ORR could not be evaluated for 2 patients as they lost the follow up after a description of treatment. At the time of analysis, 17 out 28 patients were alive-five patients continuing pazopanib, ten patients on the second line and two patients shifted to palliative care.

There were no patients with Complete Response (CR). Only nine patients (30%) had a Partial Response (PR) while thirteen patients (43%) had Stable Disease (SD). three patients (10%) failed on pazopanib therapy with primary progression. The RR for pazopanib-treated patients in the overall study population was 30%.

Median PFS and OS were 9 (95% CI 7.12-10.87) and 28 (95% CI 3.78-52.12) months, respectively. The 2-year survival rate was 57%. The survival data were assessed in the Kaplan–Meier analysis shown in Figures 1 and 2.

Discussion

In our country, we have recently used the pazopanib in the management of mRCC, may be due to financial issues. In this retrospective observational study, we tried to address its efficacy and safety when used in naive cases in our populations.

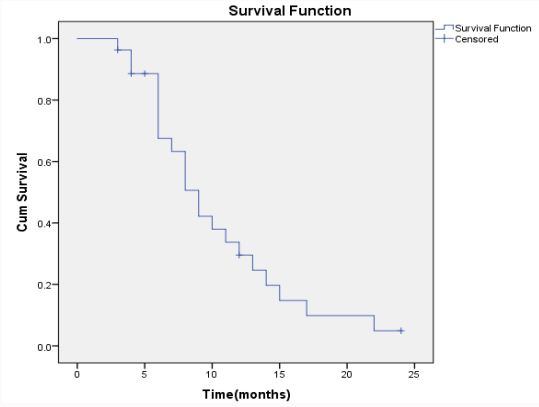

Figure 1: Kaplan–Meier estimates of progression free survival among metastatic renal cell carcinoma patients treated with first-line pazopanib.

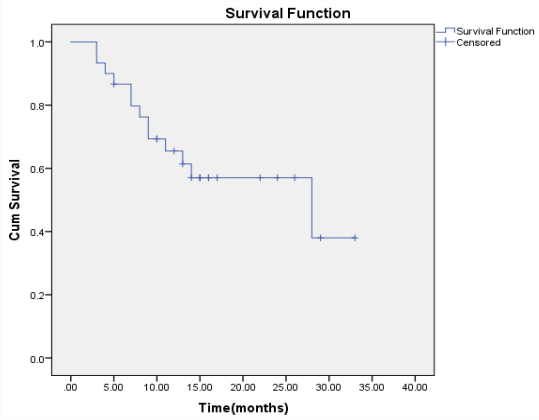

Figure 2: Kaplan–Meier estimates of overall survival among metastatic renal cell carcinoma patients treated with first-line pazopanib.

Our patients experienced acceptable tolerance and self-limiting. While there were no patients discontinued the treatment due to AEs, only two patients needed dose reduction. Diarrhea (33.3%), hair color changes (30%), and hypertension (26.7%) was the most common side effects. Referring to the efficacy, RR and SD were 30% and 43% respectively. The median PFS and OS were 9 months (95% CI, 7.12-10.87) and 28 months (95% CI, CI 3.78-52.12), respectively with estimated 2-year survival was 57%. Our results are comparable with many previous studies [8,12,13] and although it is small sample size and retrospectives, it denotes the good tolerability response of our patients to pazopanib.

Although mRCC is treatable, still incurable so, the rationale of treatment is to get the best response with the least toxic modalities. Target therapy using anti-angiogenesis, and or TKIs represented the backbone of treatment in both first and second-line. Pazopanib inhibits Vascular Endothelial Growth Factor (VEGF) receptors (VEGFR-1, -2, and -3), platelet-derived growth- factor receptors, (PDGFR α/β), and stem cell factor receptor (c-Kit) in the tumor cells with subsequent inhibition of cellular growth and proliferation. Worldwide, it has been used for the management of mRCC [14].

The approval in the first line- treatment was based on randomized prospective, multicenter, placebo-controlled double-blind phase III trial in treatment-naive and cytokine-pre-treated mRCC patients. The PFS was significantly improved with pazopanib *vs.* placebo in whole study population, treatment naïve subgroup, and the pre-

treated subgroup (PFS 9.2 *vs* 4.2 months; HR, 0.46; 95% CI, 0.34 to 0.62; P<0.0001; PFS 11.1 *vs* 2.8 months; HR, 0.40; 95% CI, 0.27 to 0.60; P<0.0001, and PFS, 7.4 *vs* 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; P<0.001), respectively. The ORR was 30% and 3% for pazopanib and placebo, respectively. Diarrhea, hypertension, and hair color changes were the most common AEs. There was no statistically significant difference in the quality of life in both groups [15].

Although there was no statistically significant difference in OS between the two groups, the results were confounded not only due to the extensive and early crossover to pazopanib group but also the prolonged crossover treatment. In an extension of the previous study; in the placebo group, all the patients who had DP shifted to receive pazopanib. At the interim analysis, all patients stopped pazopanib due to DP and did not link to side effects [16].

The PISCES is a phase IIIb trial supported the results of COMPARZ trial, designed to evaluate the patients' preference for pazopanib or sunitinib at 22 weeks of treatment. About 70% of enrolled patients preferred pazopanib due to better QOL, while 22% of patients had selected sunitinib.

Referring to the non-inferiority COMPARZ trial, a head to head trial comparing the safety and efficacy of sunitinib and pazopanib in naïve patients with mRCC. While, the reported results showed comparable efficacy profile, the safety, and quality of life were different.

The alanine aminotransferase level was more elevated in patients treated with pazopanib (60% *vs* 43%), while thrombocytopenia (78% *vs* 41%), fatigue (63% *vs* 55%), and hand-foot syndrome (50% *vs* 29%), were more common in sunitinib- treated patients [8].

As we know COMPARZ trial included 1110 candidate patients were enrolled at sites in 14 countries in Europe, North America, Asia, and Australia. In sub-analysis of the patients revealed that ethnic and geographic differences in efficacy and toxicity profiles. For example, pazopanib demonstrated better median PFS compared with sunitinib (11.1 *vs* 8.4 months) respectively. The explanation for this phenomenon is not clear, however, the effect of ethnicity may be accused; through differences in drug exposure with subsequently change in both the pharmaco dynamics and Pharmacogenetics. The treatment discontinuation related to AEs was 24% for pazopanib compared with 20% for sunitinib [14].

Although this sub-analysis results, up till now there no ethnic-based therapy selection in MRCC. Both pazopanib and sunitinib are category 1 recommendation as per NCCN guidelines. The selection of therapy should be individually based on clinical and laboratory data as the severity of symptoms, patient preference, and QOL [18].

The results of our study report that pazopanib demonstrated an acceptable safety and efficacy in our patients corresponding to the international data.

To our knowledge, this is the first study in Egypt to evaluate the safety and efficacy of pazopanib on our patients. The included patients were treated with pazopanib in two separate academic oncology departments to decrease selection bias.

Limitations

The retrospective studies are usually accused as the data most always incomplete and depending mainly on medical documentation which may lead to selection bias. Although the utility of different imaging techniques with different intervals evaluation considered a drawback, it is considered a reflection of real-life oncologists' experience. The small sample size and absence of a comparative group are another important limitation.

Conclusion & Recommendations

Our results reported that pazopanib is well tolerable and active in our patients with mRCC in the first-line setting. We need further studies to clarify the possible genetic variations or molecular markers in various ethnicities which may be related to tumor responsiveness or resistance to TKIs.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.
2. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. N Engl J Med. 1996;335(12):865-75.
3. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am. 2003;30:843-52.
4. Ko JJ, Xie W, Kroeger N, Lee JL, Rini BI, Knox JJ, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: Apopulation-based study. Lancet Oncol. 2015;16(3):293-300.
5. Figlin R, Sternberg C, Wood CG. Novel agents and approaches for advanced renal cell carcinoma. J Urol. 2012;188(3):707-15.
6. Poprach A, Fiala O, Chloupkova R, Melichar B, Lakomy R, Petrakova K, et al. Pazopanib for Metastatic Renal Cell Carcinoma: A Registry-based Analysis of 426 Patients. Anticancer Res. 2018;38(1):449-56.
7. Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH, et al. A randomized, double-blind, phase 3 study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: Final overall survival results and safety update. Eur J Cancer. 2013;49(6):1287-96.
8. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib vs. sunitinib in metastatic renal cell carcinoma. N Engl J Med. 2013;369:722-31.
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
10. The NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE) March 31, 2003. 2006.
11. Mekhail TM, Abou-Jawde RM, Boumerhi G, Malhi S, Wood L, Elson P, et al. Validation and Extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol. 2005;23(4):832-41.
12. Méndez-Vidal MJ, Molina Á, Anido U, Chirivella I, Etxaniz O, Fernández-Parra E, et al. Pazopanib: Evidence review and clinical practice in the management of advanced renal cell carcinoma. BMC Pharmacol Toxicol. 2018;26;19(1):77.
13. Kim MJ, Park SH, Lee JL, Lee SH, Lee SJ, Lim HY. A Korean multi-center, real world, retrospective study of firstline pazopanibin unselected patients with metastatic renal clear-cell carcinoma. BMC Urol. 2016;16(1):46.
14. Pick A, Nystrom K. Pazopanib for the treatment of metastatic renal cell carcinoma. Clin Ther. 2012;34(3):511-20.
15. Sternberg C, Davis I, Mardiak J, Szczylik C, Lee E, Wagstaff 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):1061-8.
16. Sternberg C, Davis I, Deen K, Sigal E, Hawkins R. An open-label extension

study to evaluate safety and efficacy of pazopanib in patients with advanced renal cell carcinoma. Oncology. 2014;87(6):342-50.

17. Escudier B, Porta C, Bono P, Powles T, Eisen T, Sternberg CN, 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):1412-8.

18. National Comprehensive Cancer Network In: NCCN clinical practice guidelines in oncology (NCCN Guidelines®) Kidney Cancer. 2019.