

Clinical outcomes of the sequential use of pazopanib followed by everolimus for the treatment of metastatic renal cell carcinoma: A multicentre study in Korea

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Abstract

Introduction: The aim of this study was to investigate the real-world clinical outcomes of first-line pazopanib and second-line everolimus in Korean patients with metastatic renal cell carcinoma (mRCC).

Methods: Data of patients who had mRCC with clear-cell component between 2001 and 2015 at multiple institutions were collected retrospectively. To be included in the analysis, patients had to meet the following criteria: age ≥ 18 years; received first-line targeted therapy with pazopanib; and received second-line targeted therapy with everolimus. The primary outcomes included overall survival (OS), progression-free survival (PFS), and adverse events (AEs).

Result: A total of 36 patients were included in the analysis. The median followup period was 33.5 months (range 17–49.5). The median PFS was eight months (95% confidence interval [CI] 6.4–9.6) after treatment with pazopanib and three months (95% CI 1.9–4.1) with everolimus. The median OS was 27 months (95% CI 16.6–37.4). The median treatment duration was seven months (range 4.3–10.8) after treatment with pazopanib and 3.5 months (range 3–4) with everolimus. Multivariate analysis revealed that the Heng risk criteria were independently associated with OS ($p < 0.001$). Almost every patient experienced some form of AE, the majority of which were mostly mild or moderate in severity. The most common AEs were diarrhea (50%), hypertension (44.4%), and fatigue (41.7%) after treatment with pazopanib, and anemia (47.2%), stomatitis (41.7%), and fatigue (38.9%) with everolimus.

Conclusions: The outcomes for the patients treated with pazopanib followed by everolimus in Korea as observed by us were consistent with those reported by previous studies. The Heng risk criteria were significantly associated with the prognosis of patients with mRCC. AEs were mainly mild to moderate and readily managed.

Introduction

During the last decade, a number of novel agents that have markedly improved the prognosis of patients with metastatic

renal cell carcinoma (mRCC) have been introduced in clinical practice.^{1,2} These agents work by targeting angiogenesis through pathways involving the vascular endothelial growth factor (VEGF) receptor and mammalian target of rapamycin (mTOR). One of these agents, pazopanib, is an oral tyrosine kinase inhibitor (TKI) that targets the VEGF receptor, platelet-derived growth factor (PDGF) receptor, and c-kit, and is approved as first-line treatment for mRCC.³ Pazopanib has been shown to prolong progression-free survival (PFS) compared to placebo in patients with mRCC.⁴ In the large phase 3 COMPARZ (comparing the efficacy, safety, and tolerability of pazopanib vs. sunitinib) trial, pazopanib showed similar efficacy to sunitinib, which is currently the most widely used first-line drug for the treatment of mRCC.⁵ The present guidelines recommend the use of pazopanib as first-line treatment for favourable- or intermediate- risk patients with clear-cell mRCC.

The phase 3 study of everolimus in patients with mRCC whose disease had progressed despite receiving VEGF-targeted therapy demonstrated that patients treated with everolimus had a better PFS compared with those treated with placebo.^{6,7} Adverse events (AEs) were more frequent in the everolimus group, but were mostly of mild or moderate severity.^{6,7} Everolimus was the first mTOR inhibitor to be approved for sequential use after a prior targeted therapy, and it is one of the most commonly used treatments in this setting.^{8–10} For the second-line treatment of mRCC, several targeted agents have been introduced, including TKIs and mTOR inhibitors; however, in Korea, everolimus is the only available drug for VEGF-refractory patients with mRCC. Although several studies have proposed an optimal sequence of targeted therapy, no firm recommendations are currently available.¹¹

The pivotal trial for these two agents has provided clinicians and patients with promising results, but few studies have examined the efficacy and tolerability of these drugs in Asian patients.^{3,6} Therefore, this study aimed to assess the efficacy and safety of pazopanib and everolimus in Korean patients with mRCC.

Methods

Patients and methods

Clinical data of patients treated with pazopanib and everolimus for mRCC were retrospectively collected between 2001 and 2015 at four different institutions (Dongnam Institute of Radiological & Medical Sciences Cancer Centre, Dong-A University Hospital, Pusan National University Hospital, Pusan National University Yangsan Hospital) from the medical record system. The inclusion criteria were as follows: age ≥ 18 years; histologically confirmed clear-cell RCC; metastases measurable on computed tomography (CT) or magnetic resonance imaging (MRI); a performance status of 0–2 based on Eastern Cooperative Oncology Group (ECOG) criteria; and receiving first-line treatment with pazopanib and second-line treatment with everolimus. After excluding patients aged < 18 years and those who received prior chemotherapy or cytokines, 36 patients were enrolled. Baseline demographics and clinicopathological data were collected. The treatment continued until disease progression or unacceptable toxicity. The response was measured using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0. AEs were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The primary endpoint of this study was PFS. PFS was defined as the time from the initiation of treatment to the date of progressive disease or death. Overall survival (OS) was defined as the time from the initiation of treatment to all-cause death.

This study was approved by the Institutional Review Board of Dongnam Institute of Radiological & Medical Sciences Cancer Centre and performed according to the ethical standard laid down by the 1964 declaration of Helsinki and its later amendments. As this was a retrospective study, the requirement of informed consent was waived.

Statistical analysis

OS and PFS were calculated using the Kaplan-Meier method, and 95% confidence interval (CI) was considered statistical significant. All statistical analyses were performed using IBM SPSS v.20 software (SPSS, Inc., Chicago, IL), with a two-sided p value < 0.05 indicating statistical significance.

Results

The clinicopathological characteristics of the 36 patients included in this study are summarized in Table 1. Of these patients, six (16.7%) had favourable-risk disease, 26 (72.2%) had intermediate-risk disease, and four (11.1%) had poor-risk disease according to the Heng risk criteria.¹² Nephrectomy was performed in 21 patients (58.3%). The rest of the patients

underwent ultrasound-guided percutaneous renal biopsy and were diagnosed with RCC.

First-line pazopanib

The median PFS with first-line pazopanib was eight months (95% CI 6.64–9.36). Of the 36 patients, 12 (33.3%) achieved a partial response, 11 (30.6%) had stable disease, and 13 (36.1%) had progressive disease, as the best response (Table 2). The median treatment duration was seven months (95% CI 6.37–10.98). The primary reason for treatment discontinuation was disease progression (88.9%), followed by AEs (11.1%). Most patients (77.8%) experienced AEs of any grade (Table 3). The most common AEs were diarrhea (50%), hypertension (44.4%), fatigue (41.7%), nausea (33.3%), and vomiting (33.3%). The proportion of patients experiencing an AE with maximum Grade of 3/4 was 50%. The most common laboratory abnormalities were serum creatinine elevation (19.4%), aspartate aminotransferase elevation (16.7%), and anemia (13.9%).

Second-line everolimus

The median PFS with second-line everolimus was three months (95% CI 2.08–3.92). Of the 36 patients, three (8.3%)

Table 1. Patients characteristics

Variables, n	36
Age (years) mean \pm SD	65.9 \pm 9.9
Sex	
Male (%)	28 (77.8)
Female (%)	8 (22.2)
BMI (kg/m ²), mean \pm SD	22.76 \pm 3.59
Followup period (months), median (range)	33.5 (17–49.5)
DM (%)	8 (22.2)
Hypertension (%)	18 (50)
CKD (%)	2 (5.6)
Cardiovascular disease (%)	2 (5.6)
Symptoms (%)	13 (36.1)
Heng risk criteria	
Favourable (%)	6 (16.7)
Intermediate (%)	26 (72.2)
Poor (%)	4 (11.1)
Diagnostic methods	
Nephrectomy	21 (58.3)
Sites of metastatic disease	
Lung	27 (75)
Liver	6 (16.7)
Bone	15 (41.7)
Brain	2 (5.6)

BMI: body mass index; CKD: chronic kidney disease; DM: diabetes mellitus; SD: standard deviation.

Table 2. Summary of efficacy

Variables, n	36
Pazopanib	
Best response (%)	
Complete response	0 (0)
Partial response	12 (33.3)
Stable disease	11 (30.6)
Progressive disease	13 (36.1)
Overall progression-free survival, months (95% CI)	8 (6.4–9.6)
Everolimus	
Best response (%)	
Complete response	0 (0)
Partial response	3 (8.3)
Stable disease	17 (47.2)
Progressive disease	13 (36.1)
Unknown	3 (8.3)
Overall progression-free survival, months (95% CI)	3 (1.9–4.1)
Overall survival, months (95% CI)	27 (16.6–37.4)

CI: confidence interval.

achieved a partial response, 17 (47.2%) had stable disease, and 13 (36.1%) had progressive disease, as best response (Table 2). The median treatment duration was 3.5 months (95% CI 3.14–4.86). The primary reason for treatment discontinuation was disease progression (66.7%), followed by AEs (22.2%). Most patients (94.8%) experienced AEs of any grade (Table 3). The most common AEs were stomatitis (41.7%), fatigue (38.9%), rash (36.1%), asthenia (27.8%), and anorexia (25%). The most common laboratory abnormalities were anemia (47.2%), serum cholesterol elevation (38.9%), and serum glucose elevation (30.1%). No statistical association was found between the therapeutic effects of pazopanib in the first-line therapy and those of everolimus.

Overall survival

The median OS of the 36 patients analyzed in the study was 27 months (95% CI 16.6–37.4) (Fig. 1). Multivariate analysis revealed that the Heng risk criteria were independently associated with OS ($p < 0.001$) (Table 4).

Table 3. Treatment-related adverse events

	Pazopanib (n=36)		Everolimus (n=36)	
	Any	Grade ≥3	Any	Grade ≥3
Non-hematological			Non-hematological	
Diarrhea	18 (50)	1 (2.8)	Stomatitis	15 (41.7) 1 (2.8)
Hypertension	16 (44.4)	0 (0)	Fatigue	14 (38.9) 1 (2.8)
Fatigue	15 (41.7)	1 (2.8)	Rash	13 (36.1) 0 (0)
Vomiting	12 (33.3)	1 (2.8)	Asthenia	10 (27.8) 0 (0)
Nausea	12 (33.3)	2 (5.6)	Anorexia	9 (25) 0 (0)
Asthenia	11 (30.1)	0 (0)	Nausea	8 (22.2) 0 (0)
Hair color change	11 (30.1)	0 (0)	Diarrhea	7 (19.4) 1 (2.8)
Anorexia	10 (27.8)	0 (0)	Pneumonitis	4 (11.1) 2 (5.6)
Headache	3 (8.3)	0 (0)	Infection (Pneumonia)	3 (8.3) 0 (0)
Peripheral edema	2 (5.6)	0 (0)	Vomiting	2 (5.6) 0 (0)
Stomatitis	1 (2.8)	0 (0)	Peripheral edema	2 (5.6) 0 (0)
Infection (pneumonia)	1 (2.8)	0 (0)	Epistaxis	2 (5.6) 0 (0)
Hematological			Hematological	
Decreased hemoglobin	5 (13.9)	1 (0)	Decreased hemoglobin	17 (47.2) 2 (2.8)
Decreased neutrophil	5 (13.9)	0 (0)	Decreased leukocyte	10 (27.8) 0 (0)
Decreased leukocyte	3 (8.3)	0 (0)	Thrombocytopenia	9 (25) 0 (0)
Thrombocytopenia	2 (5.6)	0 (0)	Lymphocytopenia	7 (19.4) 0 (0)
Clinical chemistry			Clinical chemistry	
Increased creatinine	7 (19.4)	0 (0)	Increased cholesterol	14 (38.9) 0 (0)
Increased AST	6 (16.7)	1 (2.8)	Increased glucose	11 (30.1) 0 (0)
Hypocalcemia	3 (8.3)	0 (0)	Increased creatinine	9 (25) 0 (0)
Hyponatremia	3 (8.3)	0 (0)	Increased AST	7 (19.4) 1 (2.8)
Increased glucose	2 (5.6)	0 (0)	Hypophosphatemia	6 (16.7) 0 (0)
Hypoglycemia	2 (5.6)	0 (0)	Increased ALT	5 (13.9) 1 (2.8)
Increased cholesterol	2 (5.6)	1 (2.8)	Hyponatremia	3 (8.3) 0 (0)

AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Discussion

In the phase 3 pivotal trial, pazopanib showed promising anti-tumour activity in patients with mRCC. Pazopanib significantly prolonged PFS compared with placebo in the treatment-naïve subpopulation (11.1 months in the pivotal trial and 8.4 months in the COMPARZ trial).^{3,5} Several retrospective studies reported similar efficacy. For example, Matrana et al investigated the efficacy of pazopanib as a first-line setting for mRCC and reported a median OS of 29.1 months and a median PFS of 13.7 months.¹³ In another study on the efficacy of pazopanib, Vogelzang et al reported that the median OS and PFS were 22 months and 8.5 months, respectively.¹⁴ In a study of Asian patients, Kim et al reported that the median OS and PFS were 21.9 months and 12.2 months, respectively.¹⁵ In our study, the median PFS for patients treated with first-line pazopanib was eight months, which was slightly shorter compared to the studies mentioned above.

The efficacy of everolimus in mRCC is well-known, but there are subtle differences in PFS. Several studies on everolimus in patients with VEGF-refractory mRCC reported a median PFS ranging from 3.8–6.9 months.^{6,16–20} Almost all of these studies have demonstrated a slightly better outcome than that obtained in this study. There are several reasons for these differences in outcome. First, the proportion of patients with favourable risk in this study was relatively low compared with other studies. The importance of prognostic models was well-defined and widely used to predict the results of VEGF-targeted therapy.^{12,21} According to the above-mentioned

reports, the hazards ratio for OS increased from favourable-risk criteria to poor-risk criteria. Second, the number of patients who had undergone nephrectomy was low in this study. The nephrectomy rate was 58.3% in the present study, and this is relatively low compared to that in other studies in which the nephrectomy rate was 80–96%.^{3,6,15–20} The benefit of cytoreductive nephrectomy is not well-defined in the era of targeted therapy; however, many studies showed improved OS in patients treated with cytoreductive surgery.^{22–24} In the present study, nephrectomy was not universally performed because this decision was left to the discretion of the surgeon. Third, this study included Asian patients and, therefore, it is possible that outcomes were affected by ethnic differences between study populations. Although the COMPARZ trial reported no significant differences across ethnic groups in the results of pazopanib's clinical activity and tolerability profile, reliable data on ethnic differences in the efficacy of everolimus are not yet available.⁵ Therefore, we think that these discrepancies in patient characteristics may have adversely affected outcomes in our patients compared to those reported in other studies. The patients included in this study slightly differ from those enrolled in clinical trials, and may be more similar to the patient group observed by clinicians in daily practice. Because of this, we believe our results are more representative of real-world outcomes.

The multivariate analysis of PFS revealed that the Heng risk criteria were significantly related with prognosis. Currently, the most widely used prognostic models for mRCC are the Memorial Sloan-Kettering Cancer Centre (MSKCC) and the Heng model. According to Kwon et al, the Heng model had

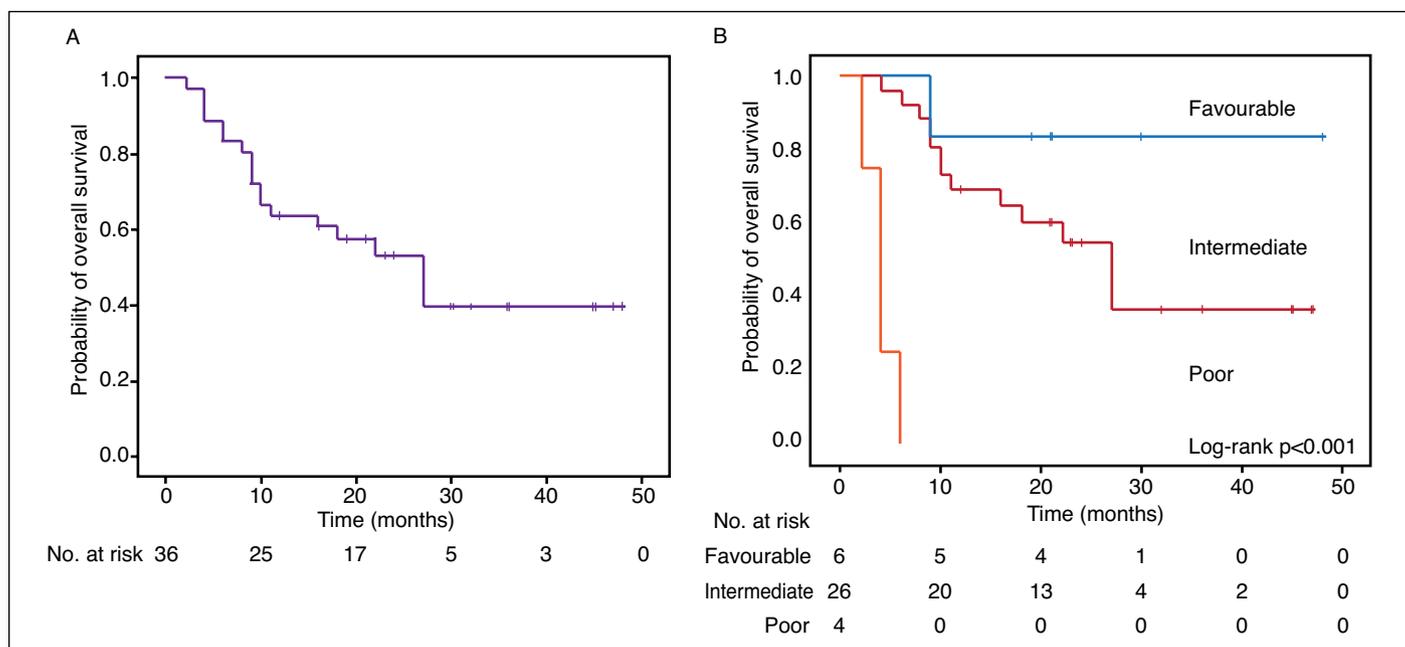


Fig. 1. Kaplan-Meier survival curve of overall survival. **(A)** Median overall survival: 27 months (95% confidence interval 16.6–37.4); **(B)** overall survival stratified by Heng risk criteria.

Table 4. Univariate and multivariate Cox regression analyses of overall survival

Variable	Univariate analysis	Multivariate analysis	
	p	p	Adjusted HR (95% CI)
Heng risk criteria	<0.001	<0.001	
Intermediate	0.229	0.229	3.49 (0.46–26.69)
High	0.001	0.001	91.39 (6.83–1223.14)
Nephrectomy	0.237	0.485	0.679 (0.23–2.01)
No. of metastasis	0.857	0.752	0.89 (0.44–1.8)
Synchronous metastasis	0.388	0.399	1.57 (0.55–4.44)
Site of metastasis	0.424	0.494	
With bone metastasis	0.247	0.278	1.87 (0.6–5.78)
With brain metastasis	0.756	0.99	0.98 (0.08–12.76)

CI: confidence interval; HR: hazard ratio.

slightly better discriminatory ability than the MSKCC model for Korean patients.²¹ Therefore, the present study applied the Heng model to classify each patient.

There is no consensus regarding the best sequential use of targeted therapies.^{8,25,26} Although guidelines recommend initial treatment with VEGF-targeted therapy for most patients with mRCC, subsequent treatment options have not been clearly defined. Everolimus has been widely accepted as the most appropriate second-line treatment for mRCC to date, and it is the only available second-line agent in Korea; however, nivolumab and cabozantinib showed superior efficacy compared with everolimus in recent studies and, therefore, guidelines have recommended these agents for VEGF-refractory mRCC.^{16,20,27} Given the ongoing research and clinical updates, it is likely that the treatment paradigms are going to change in the near future.

This study has some limitations. First, this is a retrospective study; therefore, we could not exclude possible selection bias. Second, because of the small sample size, caution is needed when generalizing the study results. Third, there was no common followup protocol between the institutions included in this study, and this could have affected the study results. Fourth, the goal of this study was to observe the response of patients following drug administration in a real clinical setting. It was not to compare the therapeutic effects of different drugs. Thus, it must be noted during the interpretation of our study results that the therapeutic effects of the drugs discussed in this study cannot be objectively compared to those of other drugs.

Conclusion

Although this study showed slightly different results compared with the previously cited clinical trials, we found that pazopanib and everolimus were efficacious in the treatment of mRCC and were well-tolerated in Korean patients. The prognosis of mRCC was significantly associated with the Heng

risk criteria. Further investigations determining the optimal treatment algorithm should be conducted to ensure patients obtain the maximum possible benefit from their treatment.

Competing interests: The authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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