Original Study

Sequential Targeted Therapy After Pazopanib Therapy in Patients With Metastatic Renal Cell Cancer: Efficacy and Toxicity

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Abstract

Sequential therapy benefits patients with metastatic RCC. However, the best sequence of drugs has not been established. We evaluated the efficacy and toxicity of subsequent therapies in 35 patients after pazopanib progression. On second-line, targeting VEGF was an effective strategy, although OS was not significantly different among patients treated with VEGF targeted therapies or mTOR inhibitors.

Introduction/Background: Patients with metastatic renal cell carcinoma (mRCC) in whom first-line therapies have failed might derive clinical benefit with sequential targeted agents. Limited data are available on the efficacy and toxicity of subsequent therapies after disease progression during pazopanib therapy. **Patients and Methods:** Patients with mRCC who received subsequent systemic treatment after pazopanib treatment failure were identified across 7 institutions. Pazopanib was given as first-line therapy in 28 patients and after cytokines therapy in 7 patients. Clinical outcome and toxicity analyses of 2 sequential treatment options (anti-vascular endothelial growth factor [VEGF] or mammalian target of rapamycin inhibitor [mTORi]) is presented. **Results:** Subsequent therapy was anti-VEGF in 22 patients and mTORi in 13. One patient who received bevacizumab and temsirolimus combination was excluded. VEGF-targeted therapies included sorafenib (n = 10), sunitinib (n = 3), bevacizumab (n = 2), cediranib (n = 4) and cabozantinib (n = 3). Patients treated with mTORi received everolimus. Median progression-free survival was 5.6 months from the start of subsequent therapy with anti-VEGF and 2.4 months with mTORi ($P = .009$). Overall survival (OS) was not significantly different ($P = .68$). Clinical benefit (including partial response and stable disease) on subsequent therapy was observed in 15 patients (64%) and 4 patients (31%) of anti−VEGF- and everolimus-treated patients, respectively ($P = .021$). **Conclusion:** In this retrospective study, targeting VEGF was an effective strategy after disease progression during pazopanib treatment, although OS was not different among patients treated with VEGF or mTORi.

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Introduction

Clear cell renal cell carcinoma (RCC) is the most common subtype of kidney cancer and accounts for approximately 80% of cancers that arise from the renal epithelium.[1] Although surgery is potentially curative at early stages, recurrences will occur in up to 30% of these patients.[2] In the advanced disease, there are now several treatments available that provide a substantial clinical benefit.[3]

Inactivation of von Hippel-Lindau gene in clear cell RCC upregulates hypoxia-inducible factor (HIF) expression.[4] The overexpression of HIFs promotes activation of important pathways

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that regulate angiogenesis such as vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR).[5,6] This rationale has resulted in multiple targets for therapeutic intervention.

Over the past years, several drugs that target angiogenesis have been developed and have improved the clinical outcome of patients with metastatic RCC (mRCC).[3] VEGF-targeted therapies are the standard first-line treatment for most patients with this disease,[7] with sunitinib being the most widely used agent in this setting. A recent large noninferiority study of >1100 patients (COMPARZ)[8] demonstrated that the efficacy of pazopanib was not inferior to sunitinib in the first-line setting. In addition, a patient preference study showed that patients significantly preferred pazopanib over sunitinib.[9] These results added important information in the decision-making process and pazopanib might become widely used in the first-line setting.[10,11] Despite these advances in the RCC therapeutic armamentarium, the vast majority of patients fail to achieve durable responses,[12] and currently, there are no clinical factors or biomarkers that can predict the targeted therapies to which patients will respond.[13,14]

Although targeted therapies became the cornerstone of the treatment of mRCC, the best sequence of drugs has not been established.[15] Currently, 3 phase III randomized trials: RECORD-1,[16] AXIS,[17] and INTORSECT,[18] have addressed this question. However, there is a lack of data on the efficacy and safety profiles of subsequent therapy after pazopanib treatment failure.

In this multicenter retrospective study, we sought to evaluate the outcome of patients whose disease progressed after pazopanib therapy, analyzing the outcome and tolerability of the 2 sequential treatment options: anti-VEGF or mTOR inhibitors.

Patients and Methods

Patients and Characteristics

We retrospectively collected patient data from 35 patients identified in the databases of 7 institutions (Hospital del Mar, Barcelona, Spain; Dana-Farber Cancer Institute, Boston, MA; GU Center of Excellence Texas Oncology, Dallas, TX; St Bartholomew's Hospital, London, UK; San Matteo University Hospital Foundation, Pavia, Italy; Istituto Toscano Tumori, Arezzo, Italy; and San Camillo and Forlanini Hospitals, Rome, Italy) between 2009 and 2012. The characteristics and outcome of these patients were recorded using standard data collection templates. This study was approved by the local institutional review boards.

Inclusion criteria were the following: (1) patients with mRCC in whom pazopanib therapy had failed and subsequently received another targeted therapy; (2) patients in whom previous cytokine therapy had failed (n = 7) but must have received pazopanib as part of first-line VEGF targeted therapy; (3) patients who switched from sunitinib to pazopanib after receiving ≤ 1 cycle during first-line therapy for toxicity reasons (n = 2).

Further therapy included mTOR inhibitor (everolimus)- or further VEGF-targeted therapy (sorafenib, sunitinib, bevacizumab, cediranib, and cabozantinib). One patient who had data collected was not included in this analysis because of subsequent therapy with a combination of VEGF- and mTOR-targeted therapies as part of a clinical trial (bevacizumab with temsirolimus).

Statistical Analysis

The predefined primary end point of this study was to establish the progression-free survival (PFS) for subsequent therapy after exposure to pazopanib. Secondary end points included a comparison of PFS and OS with mTOR- and VEGF-targeted therapies after pazopanib treatment. PFS was defined as the period from targeted therapy initiation to progression, drug cessation, death, or censored at the last follow-up visit. OS was defined as the period between targeted therapy initiation and the date of death, or censored on the last follow-up visit. Toxicities were assessed according to Common Terminology Criteria for Adverse Events version 4.0 criteria.

Analysis was limited to identify factors that were likely to affect PFS, OS, and toxicity. Potential relationships between patient characteristics (Memorial Sloan-Kettering Cancer Center [MSKCC] and Heng risk scores, age, sex, Eastern Cooperative Oncology Group [ECOG] performance status [PS], and histology) and response were explored. Treatment breaks, dose reduction, and pazopanib taken as first- or second-line therapy were also explored.

We used Kaplan-Meier plots to obtain median PFS and OS estimates for pazopanib treatment and subsequent anti-VEGF and mTOR inhibitor therapies. Log rank tests enabled us to check that the results were statistically significant.

Results

Patient Characteristics

Patient characteristics are outlined in Table 1. Twenty-five percent of all patients had received previous systemic therapy before taking pazopanib including cytokines (n = 7) and sunitinib (n = 2). Both patients who took sunitinib as first-line therapy stopped the drug before completing the first cycle because of toxicity. Therefore, pazopanib was considered to be part of the first-line targeted therapy regimen in these 2 patients.

Outcome With First-Line Therapy

Most patients had a good/intermediate MSKCC score (91%) and Heng prognostic score (71%) at the time of starting pazopanib therapy. MSKCC risk score was not available for 2 patients and 1 patient had a poor MSKCC score. Heng score was not available for 8 patients (23%).

The overall PFS was 7.9 months (range, 0.4-34.8 months). The OS from the time of starting pazopanib was 23.1 months (range, 5.4-68.8 months). Median PFS for patients with good MSKCC prognostic score was 8.0 months compared with 7.5 months for patients with intermediate or poor risk scores, as shown in Table 2 and Figure 1A. OS for good MSKCC risk score patients has not yet been reached and for intermediate and poor risk scores the OS was 28.1 months (Figure 1B).

According to Response Evaluation Criteria In Solid Tumors 1.1, overall partial response (PR) to pazopanib was 40% (14/35 patients). Six of 9 patients with previous cytokine or sunitinib intolerance had a PR with the remainder having stable disease (SD). Eight of 26 patients (31%) given pure first-line pazopanib had a PR (Table 2).

Outcome After Failure of Pazopanib Therapy

Reasons for stopping therapy after first-line pazopanib were progressive disease in 29 patients and cumulative toxicity in 6 patients.

Table 1 Patient Characteristics

Characteristic	Anti-VEGF	mTOR Inhibitors	Total
Patient n	22	13	35
Sex			
Male	21 (95.5)	10 (76.9)	31 (88.6)
Female	1 (4.5)	3 (23.1)	4 (11.4)
Histology, Clear Cell Component	22 (100)	13 (100)	35 (100)
Treatment Before Pazopanib			
INFα	4 (18.2)	2 (15.4)	6 (17.1)
IL-2	1 (4.5)	0	1 (2.9)
Sunitinib	1 (4.5)	1 (7.7)	2 (5.7)
Characteristics at Start of Pazopanib Treatment			
Median age, years	61	63	61
MSKCC risk score			
Good	11 (50)	2 (15.4)	13 (37.1)
Intermediate	9 (40.9)	10 (76.9)	19 (54.3)
Poor	1 (4.5)	0	1 (2.9)
Heng risk score			
Good	10 (45.5)	2 (15.4)	12 (34.3)
Intermediate	5 (22.7)	8 (61.5)	13 (37.1)
Poor	2 (9.0)	0	2 (5.7)
Nephrectomy	20 (90.9)	13 (100)	33 (94.3)
Characteristics at Time of Disease Progression During Pazopanib Therapy			
Median age, years	61	63	62
ECOG PS			
0	9 (40.9)	7 (30.4)	16 (45.7)
1	9 (40.9)	5 (21.9)	14 (40)
2	3 (13.6)	0	3 (8.6)
3	1 (4.5)	0	1 (2.9)
Unknown	0	1 (4.3)	1 (2.9)
Nephrectomy	22 (100)	13 (100)	35 (100)

Data are presented as n (%) except where otherwise noted.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; IL = interleukin; INF = interferon; MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin; VEGF = vascular endothelial growth factor.

All patients considered in this analysis had switched to taking either an mTOR inhibitor (n = 13) or further anti-VEGF therapy (n = 22). VEGF-targeted therapies included sorafenib (n = 10), sunitinib (n = 3), bevacizumab (n = 2), cediranib (n = 4), and cabozantinib (n = 3). All 13 patients who received mTOR therapy were treated with everolimus. ECOG PS was recorded at the time at which it was determined that pazopanib therapy had failed and the results are described in Table 1.

Table 2 Pazopanib Treatment

	Good MSKCC	Intermediate/Poor MSKCC
Median Treatment Duration (*P* = .37)	8.0 (5.3-11.0)	7.5 (5.7-13.8)
Overall Survival (*P* = .73)	NYR (15.3-NE)	28.1 (11.2-NE)
Best Response	**Anti-VEGF**	**mTOR Inhibitor**
CR	0	0
PR	8 (36.4)	6 (46.1)
SD	13 (59.1)	4 (30.8)
PD	1 (4.5)	1 (7.7)
Unknown	0	2 (15.4)

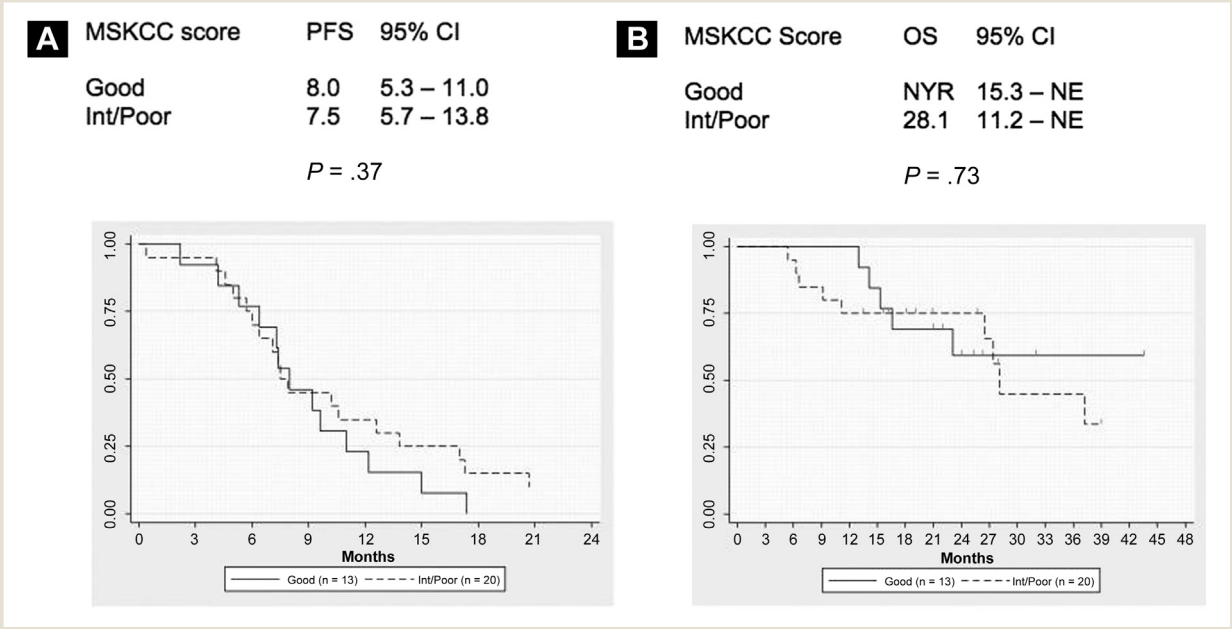
Abbreviations: MSKCC = Memorial Sloan-Kettering Cancer Center; mTOR = mammalian target of rapamycin; NYR = not yet reached; VEGF = vascular endothelial growth factor.

For anti–VEGF-treated patients, the PFS was 5.6 months (range, 0.9-31.4 months) and OS was 17.8 months. With mTOR inhibitor treatment, the PFS was 2.4 months (range, 0.6-12.2 months) and OS was 20.8 months. Only 1 patient (3%) had a PR to therapy, whose subsequent therapy was VEGF-targeted therapy. The patient receiving bevacizumab with temsirolimus was not included in the analysis but achieved a PR to this second-line therapy after has had SD as best response to first-line on pazopanib.

Comparison of VEGF and mTOR Inhibition After Pazopanib Therapy

On univariate analysis, ECOG PS at relapse inicated a significant difference in PFS, but not OS (Fig. 2) in terms of subsequent

Figure 1 (A) Progression-Free Survival and (B) OS With Pazopanib Therapy According to MSKCC Score

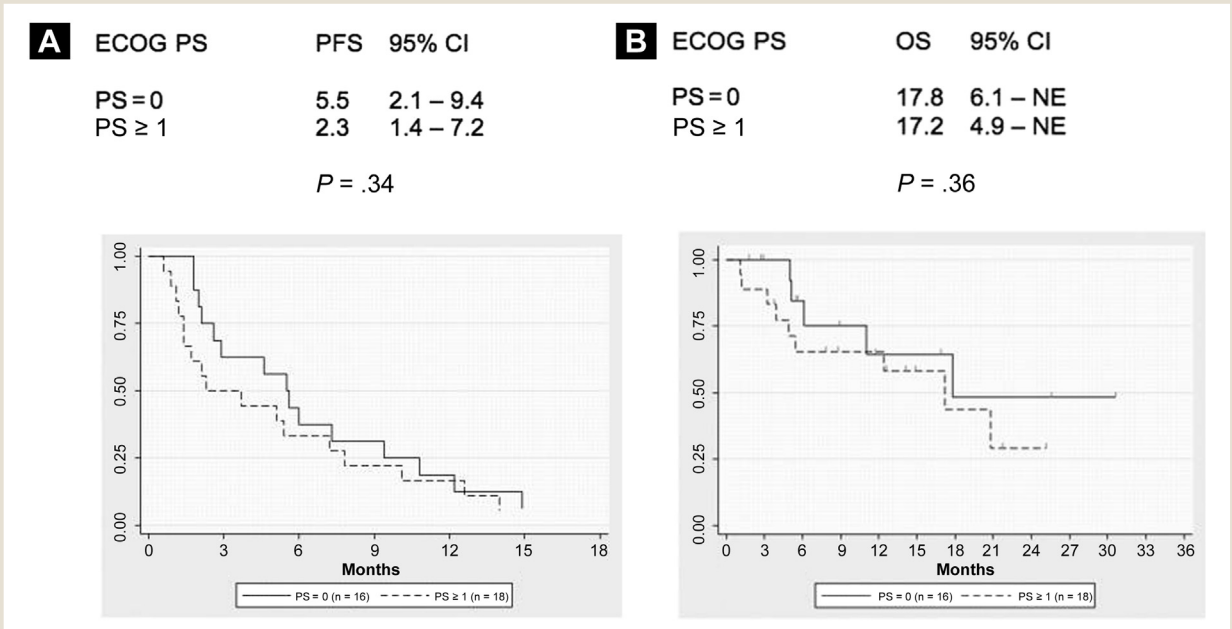


Abbreviations: Int = intermediate; MSKCC = Memorial Sloan-Kettering Cancer Center; NE = non-estimable; NYR = not yet reached; OS = overall survival; PFS = progression-free survival.

therapy. The PFS and OS for the ECOG PS 0 or 1 groups were 5.5 months (range, 1.8-31.4 months) and 2.3 months (range, 0.6-12.6 months), respectively.

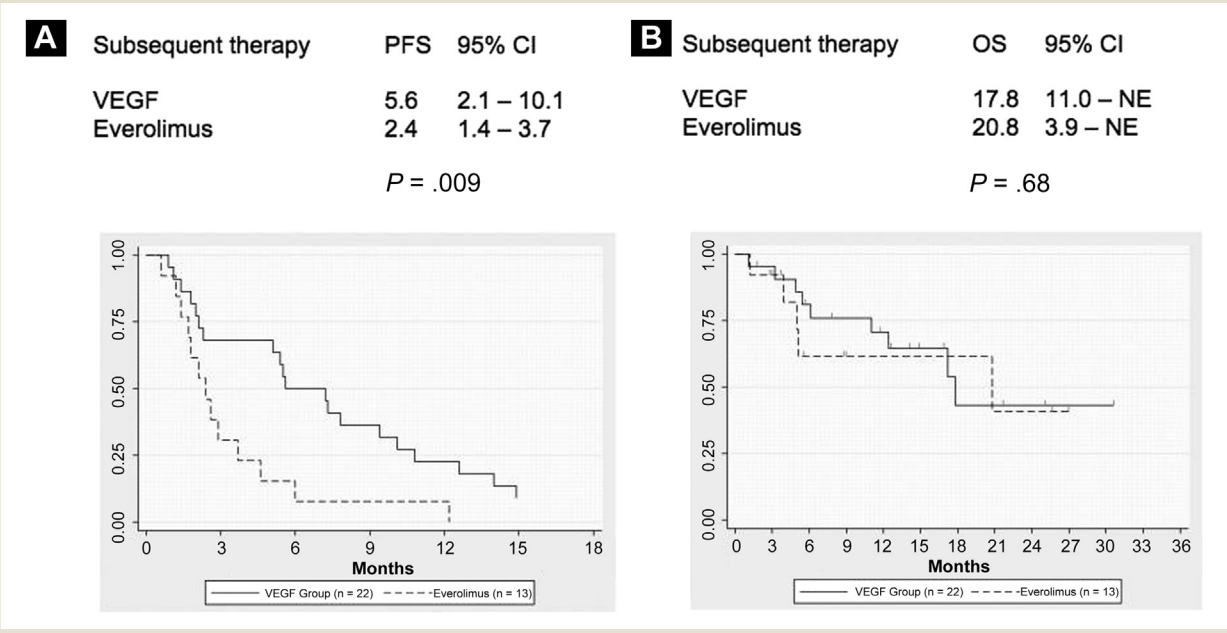
Overall, the median PFS was significantly longer for patients given anti-VEGF than for mTOR inhibitor therapy (5.6 months and 2.4 months, respectively; unadjusted $P = .009$; Fig. 3). There were slightly fewer patients with ECOG PS 0/1 who were given mTOR inhibitors than were given VEGF inhibitors, but also more patients with ECOG PS 2/3 who were given VEGF inhibitors than were given mTOR inhibitor therapy (Table 1).

Figure 2 (A) Progression-Free Survival After Pazopanib Therapy and (B) OS From the Start of Subsequent Therapy According to ECOG PS 0 and ECOG PS ≥1



Abbreviations: ECOG = Eastern Cooperative Oncology Group; NE = non-estimable; OS = overall survival; PFS = progression-free survival; PS = performance status.

Figure 3 (A) Progression-Free Survival After Pazopanib Therapy With VEGF- and mTOR-Targeted Therapies, and (B) OS From the Start of Subsequent Therapy



Abbreviations: mTOR = mammalian target of rapamycin; NE = non-estimable; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor.

Clinical benefit (PR + SD) was observed in 15 patients (64%) and 4 patients (31%) of anti-VEGF and everolimus-treated patients, respectively (unadjusted $P = .021$). The median OS for anti-VEGF and mTOR inhibitors were 17.8 and 20.8 months, respectively, from the starting point of therapies (unadjusted $P = .68$) (Table 3).

Toxicity After Pazopanib Treatment: Anti-VEGF Versus mTOR Inhibitors

Overall, toxicities in both groups are summarized in Table 4. Treatment interruption for more than 7 days occurred in 30.8% of the mTOR group, compared with 21.7% of the VEGF-treated patients.

Discussion

Multiple retrospective analyses provided the first insights on the role of subsequent therapies in mRCC, showing benefits of second-line therapies with an acceptable toxicity profile.[15,19,20]

The sequential administration of sunitinib after sorafenib and vice versa has provided a rationale for the sequential administration of VEGF-targeted therapies. Interestingly, in 3 retrospective studies, PFS was longer in patients who were treated with the sequence sorafenib then sunitinib compared with sunitinib then sorafenib.[20-22] Based on these results, a phase III, randomized trial (SWITCH) was designed to validate these findings (NCT00732914). Another

Table 3 Response to Further Therapy After Pazopanib Therapy

Variable	Anti-VEGF	mTOR Inhibitors	Total
Median Second-Line Treatment Duration ($P = .009$)	5.6 (2.1-10.1)	2.4 (1.4-3.7)	–
Treatment Interruption			
Total	4 (18.2)	4 (30.8)	8 (22.9)
<7 Days	3 (13.6)	4 (30.8)	7 (20)
Dose Reduction	7 (31.8)	3 (23.1)	10 (28.6)
Subsequent Third-Line Treatment	10 (45.5)	9 (69.2)	19 (54.3)
Overall Survival From Second-Line Treatment Start ($P = .68$)	17.8	20.8	17.8
Best Response			
CR	0	0	0
PR	1 (4.5)	0	1 (2.9)
SD	14 (63.6)	4 (30.8)	18 (51.4)
PD	4 (18.2)	8 (61.5)	12 (34.3)

Abbreviations: mTOR = mammalian target of rapamycin; VEGF = vascular endothelial growth factor.

Table 4 Toxicity After Pazopanib Treatment

	Anti-VEGF		mTOR Inhibitors	
	G1-2	G3-4	G1-2	G3-4
Hand-foot Syndrome	6 (27.3)	2 (9.0)	0	0
Rash	5 (22.7)	0	0	0
Asthenia	11 (50)	0	4 (30.8)	0
Diarrhea	7 (31.8)	0	0	0
Hypertension	1 (4.5)	0	0	0
Stomatitis	3 (13.6)	0	0	1 (7.7)
Anemia	1 (4.5)	1 (4.5)	0	1 (7.7)
Nausea	3 (13.6)	0	0	0
Hepatotoxicity	0	0	1 (7.7)	0
Thrombocytopenia	1 (4.5)	0	0	1 (7.7)
Respiratory	2 (9.0)	0	3 (23.1)	0
Edema	1 (4.5)	0	1 (7.7)	0
Metabolic (Hyperglycemia, Hypercholesterolemia, Hypomagnesemia, Hypothyroidism)	5 (22.7)	0	2 (15.4)	0
Leucopenia	1 (4.5)	0	0	0
Fever	0	0	2 (15.4)	0
Other	13 (59.0)	0	3 (23.1)	0
Laboratory Findings (Creatine Kinase Increase, Hyperamylasemia, Creatinine Increase)	3 (13.6)	0	1 (7.7)	0

Abbreviations: G = Grade; mTOR = mammalian target of rapamycin; VEGF = vascular endothelial growth factor.

phase III trial, (SWITCH-II), is designed to evaluate the efficacy and safety of sorafenib followed by pazopanib versus pazopanib followed by sorafenib in the treatment of mRCC (NCT01613846).

Sorafenib was evaluated after bevacizumab or sunitinib progression and there was limited efficacy of this agent in a small number of patients who were refractory to VEGF-targeted therapies.[23] These findings were corroborated by another phase II trial that enrolled 52 patients to receive sorafenib as second-line therapy after disease progression with sunitinib therapy.[24]

Trying to answer the question of anti-VEGF treatment followed by another anti-VEGF treatment versus anti-VEGF followed by mTOR inhibitor treatment, data from the International Metastatic RCC Database Consortium reported the results from a large retrospective analysis of 216 mRCC patients in whom VEGF-targeted therapy had failed and then received second-line therapy. There was no significant difference in OS among patients treated with VEGF-targeted therapies or mTOR inhibitors, and targeting VEGF was an active strategy resulting in a longer time to treatment failure.[15]

Although the best sequence is not yet established, there is a rationale to switch a drug to another with a different mechanism of action.[25,26] To answer this question, the RECORD-1 trial evaluated the role of mTOR inhibitors after disease progression during anti-VEGF therapy. This phase III, randomized study showed a significantly better PFS in patients who received mTOR inhibitors compared with placebo after failure of VEGF-targeted therapy (sunitinib or sorafenib) in the first-line setting.[16] Another study (RECORD-3) compared the sequence, everolimus then sunitinib versus sunitinib then everolimus. Median OS was 22.4 months for everolimus then sunitinib therapy and 32.0 months for sunitinib then everolimus therapy.[27] Although the primary end point of this trial was PFS with sunitinib versus everolimus in the first-line setting, the analysis of the sequential therapy considering PFS on first-line and PFS on second-line (secondary end points) showed a trend for an OS benefit in patients who were treated with the sequence sunitinib then everolimus rather than everolimus then sunitinib. Results from the final OS analysis are awaited to confirm this difference.

Direct comparison between a second-line VEGF-targeted therapy and second-line mTOR inhibitor therapy have been reported in the INTORSECT trial. This trial compared temsirolimus versus sorafenib in patients in whom first-line sunitinib treatment had failed. Results showed no significant difference in PFS, which was defined as the primary end point. However, patients who received sorafenib experienced longer OS (16.6 vs. 12.3 months; $P = .01$).[18] These data raise questions about the role of PFS as a valid surrogate marker to evaluate outcome in this setting and the time required to achieve the best outcome using the same VEGF-targeted therapy.[25] These findings support the hypothesis that continuing blockade of the VEGF pathway might be a better option than mTOR inhibitor therapy and that the biology of mRCC might be altered by first-line therapy.

A phase III, randomized trial (METEOR) will evaluate the effect of cabozantinib, an anti-VEGF therapy, compared with everolimus on PFS and OS in mRCC patients who have progressed after previous VEGF-targeted therapy including pazopanib (NCT01865747). It is important to note that the anti mesenquymal epithelial transition factor activity of cabozantinib might influence the nature of response.

The prospective sequential use of a first-line VEGF-targeted therapy followed by 2 different anti-VEGF therapies has been studied in the AXIS trial. Rini and collegues conducted a trial comparing axitinib versus sorafenib in patients whose disease had

progressed after sunitinib or cytokine therapy. The PFS favored axitinib in both groups, albeit the benefit in patients who were treated with sunitinib in the first-line setting was modest (4.8 vs. 3.4 months; $P = .011$). These results led to approval of this drug by regulatory agencies and support the use of axitinib after disease progression during sunitinib therapy.[17]

An indirect comparison between axitinib and everolimus after sunitinib treatment failure using the results from the phase III trials suggest a similar efficacy (PFS 4.9 months for everolimus and 4.8 months for axitinib)[18,27] of both sequences.[18,26] These results support the hypothesis that the 2 drugs could be part of the sequential treatment in advanced RCC and the decision of which sequence to use needs to be based on other end points.

An important question is how to explain the benefit of sequential use of an anti-VEGF treatment followed by another anti-VEGF treatment. Distinct mechanisms of resistance of these agents have been proposed, based on their individual pharmacokinetics and different affinities for target kinases,[28] supporting the lack of cross-resistance in this class of drugs.[29] As an example, 1 patient who had SD with pazopanib treatment achieved a PR with sorafenib as a subsequent therapy (PFS = 13.8 months). In addition, it is not known if combination therapy targeting multiple pathways could compensate for resistance in 1 of these targets. Although the combination of antiangiogenic drugs did not increase PFS in the first-line setting,[30] the role of this strategy was being evaluated in the second-line setting in a phase III randomized trial which combined everolimus and bevacizumab versus everolimus alone (NCT01198158).[14] Unfortunately, this study closed for poor accrual.

As seen in previous reports,[15,31] our results showed a longer PFS with VEGF-targeted therapy compared with everolimus, with a good safety profile. This is provocative and needs to be interpreted with caution, because results could be explained by a selection bias. Imbalances in MSKCC risk score at pazopanib treatment initiation, differences in ECOG PS, and also specific reasons to receive a second-line mTOR inhibitor like cumulative toxicity to previous anti-VEGF therapy might also explain these different results. It is also noteworthy that OS was not significantly different in a comparison of these 2 groups of agents.

Our study has several limitations. First, the retrospective analysis could result in missing data or patient characteristics that were not collected which might lead to a selection bias. Although we have selected patients across 7 institutions, the sample size was small with only 35 patients included. In addition, the mTOR inhibitor-treated subgroup was significantly smaller than the VEGF inhibitor-treated group and differences for choosing second-line therapy were not controlled. Thus, a comparison between these 2 different cohorts limits the conclusion. Moreover, different types of VEGF-targeted therapies, including some agents that are not yet approved as standard treatment, were used as part of clinical trials and could certainly have an effect on our results.

This is, to our knowledge, the first retrospective analysis to address clinical outcomes of patients who receive therapies after pazopanib therapy. Our results suggest that targeting VEGF after pazopanib treatment is an effective and tolerable strategy. The PFS and OS from the time of starting second-line therapy are what one would expect after treatment failure with sunitinib.

Conclusion

Randomized data support the use of sequential therapy in mRCC, although the best sequence of agents is not well established. Our findings support the use of VEGF-targeted therapy and mTOR inhibitors in patients whose disease has progressed after first-line pazopanib therapy. Additional efforts must be done to identify predictive biomarkers for selected agents and results from ongoing clinical trials are awaited.

Clinical Practice Points

- Sequential therapy may benefit patients with metastatic RCC who failed to first-line. However, the best sequence of drugs has not been established.
- Limited data is available on the efficacy and toxicity of subsequent therapies after progression on pazopanib.
- In this retrospective study, we sought to evaluate subsequent therapies in 35 patients who received pazopanib on first-line.
- Targeting VEGF was an effective and tolerable strategy after pazopanib progression, although OS was not significantly different among patients treated with VEGF targeted therapies or mTOR inhibitors.
- Additional efforts must be done to identify predictive biomarkers for selected agents and to optimize the therapy in patients with metastatic RCC.

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Disclosure

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