Patients with metastatic renal cell carcinoma treated with cabozantinib in the Czech Republic: analysis of four cancer centers

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Aim. The aim of this study was to retrospectively analyze treatment outcomes and tolerance in patients in whom cabozantinib was used after previous targeted therapy.

Patients and Methods. Cabozantinib was administered in dose 60 mg/day, a subset of patients received initial dose of 40 mg/day. The treatment was administered until to progression or unacceptable toxicity. CT scans were assessed according to the RECIST 1.1 and toxicity of treatment was assessed based on the CTCAE (version 4). Kaplan-Meier analysis was used to calculate progression free survival (PFS) and overall survival (OS). We performed a multivariate analysis of risk factors for treatment outcomes (PFS, OS) by Cox regression analysis. All statistics were evaluated at the significance level $\alpha = 0.05$.

Results. 54 patients with metastatic renal cell carcinoma (mRCC) were evaluated. Median PFS in all patients treated with cabozantinib was 9.3 months (95% CI 5.3 – 13.3). One-year survival was 85.2% (95% CI 72.9 – 93.4%). Treatment response was observed in 45.9% of cases, including one complete remission. Cox regression analysis demonstrated that presence of subsequent treatment was the only factor with a significant effect on OS ($P=0.008$). Adverse events occurred in 88.9% of patients, grade 3 – 4 in 46.3%.

Conclusion. The analysis of our cohort of patients treated with cabozantinib in the second or higher lines of treatment showed that cabozantinib represents an effective and safe therapy and contributes to longer survival of our mRCC patients

Key words: cabozantinib, metastases, renal cell carcinoma, toxicity

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INTRODUCTION

The incidence of renal cell carcinoma (RCC) in the Czech Republic is among the highest in the world¹. Recently, a wide array of new options in systemic treatment of metastatic RCC (mRCC) has become available². Targeted therapy aiming at inhibition of vascular endothelial growth factor receptors (rVEGF) has gained particular importance including tyrosine-kinase inhibitors (TKI) sunitinib, pazopanib, axitinib and sorafenib or anti-VEGF monoclonal antibody bevacizumab³⁻⁹. In the Czech Republic, pazopanib and sunitinib are most frequently used in the first-line treatment of mRCC patients^{10,11}. However, an overwhelming majority of patients gradually develop resistance to their targeted therapy¹². PD1/PD-L1 interaction inhibiting immunotherapy had

been shown in recent studies to prolong long-term survival and is now also available as a treatment option¹³. Other options, such as combined immunotherapy (nivolumab + ipilimumab), or a combination of immunotherapy with a TKI (pembrolizumab + axitinib, avelumab + axitinib) also showed significant efficacy even in mRCC treatment-naïve patients¹⁴⁻¹⁶.

Cabozantinib represents another innovative approach to mRCC treatment. This is an orally administered TKI that, in addition to rVEGF, also inhibits other kinases, such as MET, AXL, RET, KIT and FLT3 (ref.^{17,18}). Preclinical studies have shown that the resistance to rVEGF inhibitors is associated with increased MET and AXL gene expression. Upregulated expression of MET and AXL is then associated with a more aggressive course of the disease and worsened prognosis¹⁹. Blocking the

MET and AXL pathways may, therefore, overcome this resistance. METEOR was a pivotal prospective phase III clinical trial that compared cabozantinib to everolimus in patients previously treated with an rVEGF TKI. Cabozantinib was shown to increase progression-free survival, overall survival and response rate compared to everolimus²⁰. In the Czech Republic cabozantinib has been in clinical use since 2018.

The aim of this study was to retrospectively analyze treatment outcomes and tolerance in a cohort of patients from four cancer care centers in the Czech Republic, in whom cabozantinib was used after previous targeted therapy.

Fig. 1. Progression-free survival - all patients treated with cabozantinib.

Fig. 2. Progression-free survival - second line only.

Fig. 3. Progression-free survival of patients with and without (w/o) bone metastases.

PATIENTS AND METHODS

The study included all patients who began their treatment with cabozantinib between May 2018 and December 2019. Data cut off was 31st March 2020. The patients were taking cabozantinib orally once daily. Initial dose of cabozantinib was 60 mg/day, a subset of patients received initial dose of 40 mg/day. The treatment continued until progression of the disease or signs of unacceptable toxicity. Progression was defined as treatment discontinuation due to disease progression or due to death from any cause. Following withdrawal of cabozantinib treatment, some patients continued on subsequent treatment, as defined by the treating physician.

To evaluate treatment efficacy, CT scans were assessed according to the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors, version 1.1). Toxicity of treatment was assessed based on the CTCAE (Common Terminology Criteria for Adverse Events), version 4.

For statistical purposes, we defined progression-free survival (PFS) as the time interval between the initiation of therapy with cabozantinib and the date disease progression was identified, or the date of the last follow-up visit in patients without progression (censored data). Overall survival (OS) was defined as the time interval between the initiation of cabozantinib therapy and the date of death by any cause or the date of the last follow-up visit in living patients (censored data). Kaplan-Meier analysis was used to calculate PFS and OS. Log-rank test was used to evaluate the difference between groups of patients with metastatic process. We performed a multivariate analysis of risk factors for treatment outcomes (PFS, OS), using the Cox regression analysis. Hazard ratio (HR) was calculated with 95% confidence interval (CI). Values of HR

smaller than 1 represent a reduction of risk (favorable prognostic factor), whereas values greater than 1 represent an unfavorable prognostic factor. All statistics were evaluated at the significance level $\alpha = 0.05$.

RESULTS

Patient characteristics

We evaluated 54 patients, 44 (81.5%) were men. Median age was 65.5 years. Nephrectomy was performed in 41 (75.9%). Metastases were most commonly located in the lungs (81.5%). Bone metastatic process was identified in 22 patients (40.7%). The majority of patients (77.8%) had two or more systems affected with metastases. Cabozantinib was most frequently indicated for second line treatment (92.6%). Patients were mostly pre-treated with sunitinib (50%) or pazopanib (43%). The treatment was initiated with 60 mg/day in 47 patients and 40 mg/day in 7 patients. Table 1 summarizes patients characteristics.

Results

Median follow-up was 10.6 months. A total of 25 patients discontinued cabozantinib due to disease progression; therapy was discontinued due to adverse events in two cases. At the time of analysis, 27 patients continued their treatment with cabozantinib. Median PFS in all patients treated with cabozantinib was 9.3 months (95% CI 5.3 - 13.3) (Fig. 1). Median PFS in patients treated with second line cabozantinib only (excluding higher lines; 50 patients) was 10.0 months (95% CI 5.1-14.9) (Fig. 2). Median PFS was 12.7 (95% CI 8.0 - 14.5) months

in patients with bone metastases, and it was 9.1 (95% CI 6.6 - 11.7) months in patients without bone metastases. We applied the log-rank test and found no significant difference in PFS between the groups ($P=0.824$) (Fig. 3). Following discontinuation of cabozantinib, 14 patients were further treated, 13 with nivolumab.

At the time of data analysis, 13 patients had died (24.1%) and 41 patients were alive. One-year survival was 85.2% (95% CI 72.9 - 93.4%). Treatment response was assessed in 48 patients. Six patients were excluded from the analysis due to short cabozantinib treatment duration. Treatment response was observed in 22 patients (45.9%), including one case of complete remission. Clinical benefit was found in 79.2% of patients. Cox regression analysis did not identify any factors with significant effect on PFS (Table 2). The presence of subsequent treatment was the only factor with a significant effect on OS ($P=0.008$). A trend towards significance was also observed in patients with better ECOG performance status ($P=0.101$) and with the first line treatment duration of ≥ 6 months ($P=0.095$) (Table 3).

Tolerance

Adverse events occurred in 48 patients (88.9%). Grade 3 or 4 toxicity was observed in 25 patients (46.3%). The most common adverse events were diarrhea, weight loss, fatigue, loss of appetite, nausea and hand-foot syndrome. The treatment was discontinued due to toxicity in two patients. The dose of cabozantinib was reduced to 40 mg in 24 patients (44.4%). Further reduction to 20 mg was reported in 7 patients. The median time to the dose reduction was 68 days. No death related to adverse events of cabozantinib was reported. Adverse events are summarized in Table 4.

DISCUSSION

Results of randomized clinical studies often cannot be extrapolated to treatment outcomes in routine clinical practice. This may also be because we indicate treatments for a more diverse range of patients, often with additional comorbidities or other factors that would not satisfy the strict eligibility criteria of randomized studies. For example, 69% of the METEOR study patients had the ECOG performance status of 0, while this was 45% in our cohort²⁰. In the Czech Republic, treatment with cabozantinib is a newer therapeutic approach as it has only been available since 2018. Therefore, evaluation of treatment outcomes and tolerance in an initial group of treated patients provides an important evidence that might inform future treatment decisions. The present data analysis is the first cabozantinib-treated patient analysis in the Czech Republic. The median PFS in our cohort was 9.3 months. This is a longer median PFS than that reported in the METEOR study (7.4 months) (ref.²⁰). The longer median PFS in our cohort may be due to a longer duration of time between follow-ups (median 16 weeks in our cohort) and/or more individualized dosing adjustments to manage adverse events. Furthermore, the response rate was twofold

Table 1. Patients characteristics.

Patient characteristic	n (%)
Age	
median (years)	65.5
range (years)	41–79
Gender	
male	44 (81.5)
female	10 (18.5)
Nephrectomy	41 (75.9)
Primarily metastatic disease	21 (38.9)
Metastases location	
lungs	44 (81.5)
lymphatic nodes	34 (63)
bones	22 (40.7)
liver	7 (13)
other location	23 (43)
Number of metastatic locations	
1	12 (22.2)
2	16 (29.6)
3	19 (35.2)
4 and more	7 (13)
Overall performance status by ECOG	
0	24 (44.4)
1	30 (55.6)
Cabozantinib – line of treatment	
2	50 (92.6)
3	2 (3.7)
4	2 (3.7)
Previous targeted treatment	
sunitinib	27 (50)
pazopanib	23 (43)
other	8 (7)

higher in our cohort compared to the METEOR study (46 vs. 17%). In the METEOR study, grade 3–4 adverse events were observed in 68% of patients and it was 46% in our cohort. Similarly, smaller proportion of patients in our cohort had their cabozantinib dose reduced (44 vs. 60%) and fewer patients had their therapy discontinued due to adverse events (4 vs. 9%). This may also be due to a stricter adverse event recording and reporting rules in prospective randomized studies compared to retrospective data analyses. Several retrospective studies assessing treatment with cabozantinib in second or higher lines have been published. An analysis from four centers in Poland evaluated a total of 115 patients, half of whom had bone metastases. Median PFS was 12.5 months (95% CI 9.2 - 14.2). Treatment response was observed in 19% of patients, 56% patients achieved stable disease. The most common grade 3 or 4 adverse events were fatigue (23%), hand-foot syndrome (12%) and diarrhea (10%). Only 4% of patients discontinued their treatment due to toxicity²¹. A retrospective analysis published by Italian authors presented data from a set of 94 patients from 24 centers. The authors described treatment response in 36% of patients and

Table 2. Factor impact on progression-free survival.

Factor	HR (95% CI)	<i>P</i>
Age (<65 vs ≥ 65 year)	0.810 (0.356-1.841)	0.616
Gender (female vs. male)	0.435 (0.128-1.470)	0.181
Nephrectomy (yes vs. no)	0.905 (0.338-2.421)	0.842
Primary localized disease (yes vs. no)	0.715 (0.323-1.582)	0.408
Lung metastases (yes vs. no)	1.186 (0.406-3.466)	0.755
Metastases in LN (yes vs. no)	0.810 (0.363-1.809)	0.608
Bone metastases (yes vs. no)	0.913 (0.409-2.038)	0.824
Prior TKI (pazopanib vs. sunitinib)	1.089 (0.461-2.572)	0.846
PS (0 vs. 1)	0.828 (0.373-1.842)	0.645
First line duration (≥ 12 vs. < 12 months)	0.532 (0.203-1.393)	0.199
First line duration (≥ 6 vs. < 6 months)	0.564 (0.234-1.356)	0.200
Grade 3-4 toxicity (yes vs. no)	0.862 (0.392-1.895)	0.711

Table 3. Factor impact on overall survival.

Factor	HR (95% CI)	<i>P</i>
Age (<65 vs ≥ 65 year)	0.952 (0.309-2.923)	0.933
Gender (female vs. male)	0.289 (0.037-2.237)	0.235
Nephrectomy (yes vs. no)	0.892 (0.243-3.269)	0.863
Primary localized disease (yes vs. no)	0.487 (0.163-1.450)	0.196
Lung metastases (yes vs. no)	0.773 (0.166-3.607)	0.743
Metastases in LN (yes vs. no)	0.598 (0.199-1.799)	0.360
Bone metastases (yes vs. no)	1.905 (0.579-6.269)	0.289
Prior TKI (pazopanib vs. sunitinib)	0.732 (0.205-2.609)	0.631
PS (0 vs. 1)	0.277 (0.059-1.258)	0.101
First line duration (≥ 12 vs. < 12 months)	0.298 (0.062-1.429)	0.130
First line duration (≥ 6 vs. < 6 months)	0.336 (0.093-1.210)	0.095
Grade 3-4 toxicity (yes vs. no)	0.544 (0.171-1.732)	0.303
Subsequent treatment (yes vs. no)	0.110 (0.021-0.561)	0.008

Table 4. Summary of adverse events.

Adverse event	Total n (%)	Grade 3-4 n (%)
Diarrhea	27 (50.0)	15 (27.8)
Loss of weight	20 (37.0)	3 (5.6)
Fatigue	19 (35.2)	3 (5.6)
Hand-foot syndrome	15 (27.8)	2 (3.7)
Nausea	12 (22.2)	3 (5.6)
Loss of appetite	9 (16.7)	3 (5.6)
Stomatitis	8 (14.8)	1 (1.9)
Arterial hypertension	6 (11.1)	1 (1.9)
ALT/AST elevation	6 (11.1)	1 (1.9)
Anemia	4 (7.4)	1 (1.9)
Pyrosis	4 (7.4)	1 (1.9)
Hypothyroidism	3 (5.6)	0
Acneiform exanthema	3 (5.6)	0
Leukopenia	3 (5.6)	0
Thrombocytopenia	2 (3.7)	1 (1.9)
Hypokalemia	2 (3.7)	1 (1.9)
Pulmonary embolism	1 (1.9)	1 (1.9)
Stroke	1 (1.9)	1 (1.9)

stable disease in 34% of patients. Median PFS was 8.0 months, i.e. shorter than in our cohort. This may be because nearly one third of patients had lower performance status and started their treatment on a reduced dose. In addition, only 29% of patients received cabozantinib as the second line of their treatment, up to 52% were treated in fourth or higher lines. The cause of the difference in median PFS may be the bias in patient selection. Grade 3-4 adverse events were described in 36% of patients²². Both above mentioned studies, together with results of our observations, confirm acceptable tolerance of treatment. This may also be because treatment with cabozantinib is indicated by clinicians, who are familiar with adverse effects normally associated with TKIs and with their management. In the Czech Republic, rVEGF TKIs have been used in clinical practice for more than 10 years. The majority of adverse effects observed with TKIs are predictable and patients can be educated on what adverse effects they might experience and how to respond. Benefits of cabozantinib in patients with bone metastases associated with poor prognosis in mRCC are frequently discussed^{23,24}. Preclinical studies on prostate cancer cells demonstrated that cabozantinib affects bone remodeling, with biphasic impact on osteoblasts and inhibition of osteoclasts²⁵. The METEOR study has shown a more pronounced effect of cabozantinib in patients with bone metastases compared to everolimus. Median PFS was significantly longer (7.4 vs. 2.7 months; HR 0.33, 95% CI 0.21 - 0.51), as was median OS (20.1 vs. 12.1 months; HR 0.54, 95% CI 0.34 - 0.84). Response rate was 17% in patients treated with cabozantinib and 0% in patients on everolimus. Patients with bone metastases represented 23% of all patients treated with cabozantinib²⁶. In our cohort, 40.7% of patients had bone metastases and this is, once again, because cabozantinib is being considered as the treatment of choice in patients who failed on the first line of treatment and have bone metastases. Similarly, half of the patients evaluated in a study by Polish authors had bone metastases²¹. In our cohort, we observed longer median PFS in patients with bone metastatic processes compared to patients without bone injury by 3.6 months, although this result was not statistically significant ($P=0.824$). On the other hand the response rate was higher in patients without bone metastases compared with patients with bone metastases (53.3 vs. 38.3%) in our cohort. The phase II CABOSUN study provided further evidence of the less favorable prognostic outcome in patients with bone metastases. The study evaluated targeted treatment-naïve mRCC patients with intermediate and poor prognosis. The study showed longer PFS on cabozantinib compared to sunitinib^{27,28}. A subgroup analysis showed that treatment with cabozantinib provided greater benefit in patients with bone metastases than in patients without them in terms of median PFS (5.5 versus 3.3 months; HR 0.51, 95% CI 0.16 - 0.63) (ref.²⁹). We also used the Cox analysis to evaluate the effect of other factors on treatment results. We did not identify any factor that significantly affected PFS. OS was significantly impacted by whether or not a subsequent line of treatment

was used. Nivolumab was the most frequently used subsequent treatment in our cohort (93% of cases, $P=0.008$). A trend towards positive effect on OS was observed in patients with better performance status ($P=0.101$). Previous therapy (sunitinib or pazopanib) did not have any significant effect on the efficacy of cabozantinib. This finding is in line with the conclusions of the METEOR study³⁰. Similarly, treatment duration did not have any significant impact on cabozantinib efficacy, even though a trend was observed towards longer OS in patients treated ≥ 6 months ($P=0.095$). When deciding about the second line treatment after TKI therapy in clinical practice, we most frequently consider cabozantinib and nivolumab since, similarly to cabozantinib, nivolumab showed improvement of overall survival and higher treatment response in comparison to everolimus¹³. However, nivolumab did not significantly prolong median PFS. Direct comparison of cabozantinib and nivolumab treatment efficacy is not available. Indirect statistical comparison did not confirm any significant difference between cabozantinib and nivolumab in terms of OS, while cabozantinib significantly prolonged PFS (HR 0.58, 95% CI 0.34 - 0.98) (ref.³¹). The significant impact of nivolumab on OS but not PFS is associated with the specifics of how immunotherapy exerts its effect. Cabozantinib has fast onset of therapeutic response with a median of 1.9 months⁶. Therefore, in summary, we consider cabozantinib in patients rapidly progressing on a previous TKI in order to achieve fast treatment response, in case of bone metastases and in patients who tolerated their previous TKI treatment well. However, no clear predictive factors for cabozantinib treatment have been identified so far. The number of treatment options, particularly in the first line of mRCC treatment, is continuously growing and, in specific groups of patients, we might be deciding between combined immunotherapy with nivolumab and ipilimumab, monotherapy with cabozantinib, or a combination of pembrolizumab with axitinib or avelumab with axitinib^{14-16,27}. The results of the CheckMate-9ER study assessing first line mRCC treatment with a combination of nivolumab and cabozantinib are also to be soon published. Despite these advanced treatment options, we will still have mRCC patients treated with first line TKIs (sunitinib, pazopanib) in whom, upon progression, second line treatment with cabozantinib might be an appropriate treatment option. Further prognostic and predictive factors are also being sought in RCC. Similar to other types of cancer, we have already conducted an analysis of primary cilia in RCC patients^{32,33}. Overall survival according to the frequency of primary cilia was significantly shorter in patients with higher frequency than in patients with lower frequency. Median OS was also significantly shorter in patients with higher CD8+ TIL and higher (>25%) PD1+ expression than in patients with lower (<25%) expression. The study provides the first data on the potential association and combined prognostic significance of frequency of primary cilia, PD1+ cells and CD8+ TIL in patients with clear cell renal cancer.

CONCLUSION

The analysis of our cohort of patients treated with cabozantinib in the second or higher lines of treatment showed that cabozantinib is an effective and safe therapy and contributes to longer survival of our mRCC patients.

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