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Journal of Oncology Research and Therapy

Research Article

Rouvinov K, et al. J Oncol Res Ther 6: 10109.

DOI: 10.29011/2574-710X.010109

Cabozantinib as Advanced Treatment Line for Metastatic Renal Cell Carcinoma: Real World Outcomes and Associated Factors

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Citation: Rouvinov K, Neiman V, Shrem NS, Peer A, Sarid D, et al. (2021) Cabozantinib as Advanced Treatment Line for Metastatic Renal Cell Carcinoma: Real World Outcomes and Associated Factors. J Oncol Res Ther 6: 10109. DOI: 10.29011/2574-710X.010109

Received Date: 02 August, 2021; **Accepted Date:** 10 August, 2021; **Published Date**: 14 August, 2021

Abstract

Background: The Phase III METEOR trial showed a survival benefit of cabozantinib over everolimus in patients with metastatic renal cell carcinoma who progressed after a VEGF targeted therapy. However, there is limited data about the real world activity of cabozantinib after present standard of care as immunotherapy. Herein we report real world national multicenter experience with cabozantinib therapy as advance treatment line.

Methods: Records from metastatic renal cell carcinoma patients treated with cabozantinib as advanced treatment line, in 6 medical centers, were reviewed. Outcomes and associated clinico-pathologic factors were analyzed.

Results: Sixty patients were included in the study. Median age was 64 years, 80% (n=48) were male, and 83% (n=50) had a prior nephrectomy. Heng score at metastases diagnosis was favorable in 8% (n=5), intermediate in 68% (n=41), and poor in 23% (n=14). Sixteen patients were treated as second line, 29 as third line, and 15 as ≥4th line. 50 patients were treated with immunotherapy before cabozantinib (30 with nivolumab, 18 with ipilimumab plus nivolumab, and 2 with avelumab plus axininib). 68% had a clinical benefit (partial response 28%, stable disease 40%) while 30% were refractory to therapy. Median duration of treatment was 8.6 months. Median overall survival was 17.6 months. Analyzed factors that may be associated with survival were a prior nephrectomy, bulky disease, and the Heng risk.

Conclusions: The present study real world multicenter analysis revealed the activity of cabozantinib as advanced treatment line of metastatic renal cell carcinoma. Outcome associated factors may aid in treatment selection.

Keywords: Cabozantinib; Renal cell cancer; Metastatic disease; Outcome; Real world

Introduction

Treatment options for patients with Metastatic Renal Cell Carcinoma (mRCC) include targeted therapy, immunotherapy or combinations of both. A decade ago, the first line standard of care therapy for mRCC were Vascular Endothelial Growth Factor (VEGF) targeted drugs as sunitinib or pazopanib [1,2]. Later, immunotherapy combinations, as ipilimumab and nivolumab, as first line therapy, were associated with a survival benefit in most mRCC patients (i.e, with intermediate and poor risk) [3]. More recently, the combination of pembrolizumab and axitinib became a first line standard of care with associated with improved response rate (RR), Progression Free Survival (PFS) and Overall Survival (OS) [4].

Cabozantinib is an oral Tyrosine Kinase Inhibitor (TKI) of MET, RET, AXL, VEGFR2, FLT3, and c-KIT [5]. It is a first and advanced line standard of care. As first line therapy, the phase 2 CABOSUN trial [6] revealed a better RR and PFS versus sunitinib in patients with intermediate and poor risk mRCC.

As advanced treatment line, the METEOR phase III trial revealed improvement of OS (21.4 months versus 16.5 months, p=0.00026), PFS (7.4 months versus 3.9 months, p<0.0001), and RR (17% versus 3%, p<0.0001) in patients with clear cell mRCC, after previous VEGFR targeted therapy [7]. Grade 3-4 serious adverse events occurred in 39% of patients treated with cabozantinib, most commonly hypertension, diarrhea, fatigue and palmar-plantar erythrodysaesthesia.

There is limited data about the real world activity of cabozantinib after present standard of care as immunotherapy. Thus, in the present study we sought to retrospectively evaluate the outcome of cabozantinib as advanced treatment line, and to analyze outcome associated clinico-pathologic factors.

Patients and methods

Study group

The study multicenter cohort included patients with metastatic RCC that were treated with advanced line cabozantinib between May 2017 and October 2019 in six Israeli medical centers including Soroka Medical Center, Rabin Medical Center, Rambam Medical Center, Tel-Aviv Sourasky Medical Center, Sheba Medical Center, and Lin Medical Center. Patient data were retrospectively collected from electronic medical records and paper charts, including the following clinico-pathologic information: age, gender, line of treatment, histology (clear cell versus non-clear cell), the HENG risk at metastases diagnosis, the ECOG performance status, pre-cabozantinib status of smoking (active, past, never), BMI, hypertension, diabetes, past nephrectomy, metastatic sites, medical cannabis use, pretreatment levels of hemoglobin, corrected calcium , white blood cells, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, platelets, and LDH. Outcome data were last updated on May 30, 2020.

Cabozantinib treatment

All patients had disease progression on computed tomography before starting cabozantinib treatment. Cabozantinib was administered orally, using usually a starting dose of 60 mg once daily. In patients with significant comorbidities or poor performance status, treatment was initiated at a reduced dose, with following dose escalation if feasible. Dose reduction or treatment interruption were done upon the occurrence of adverse events according to standard guidelines recommendations. Treatment was continued until disease progression, unacceptable adverse events, or death. Patient follow-up consisted of regular physical examinations, laboratory assessments, every 4-6 weeks, and imaging every 12-16 weeks.

Treatment outcomes

Follow-up time was defined as the time from cabozantinib treatment initiation to May 30 2020. For the evaluation of response, the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was applied [8]. The response was assessed by independent radiologists and treating physicians. Duration of treatment was defined as the time from cabozantinib treatment initiation until treatment termination, including treatment beyond progression. Overall survival was defined as the time from the initiation of treatment to death of any cause.

Statistical analysis

Patients who did not progress or die by May 30 2020 were censored in analysis of treatment duration and overall survival. We analyzed by univariate analysis (unadjusted) the association between outcomes and pre-cabozantinib treatment clinico-pathologic factors, using logistic regression for response rate and Cox regression model for survival outcome. Survival probabilities and median survival times were estimated from Kaplan–Meier curves. Clinico-pathologic factors included in the analysis were age, gender, histology, past nephrectomy, previous systemic therapies (no immunotherapy versus nivolumab monotherapy versus combination nivolumab and ipilimumab), number of metastases sites, presence of lung, liver, bone metastases, pre-treatment blood counts, and the HENG risk, . Data were analyzed using the SPSS software (SPSS for Windows, USA).

Results

Patient characteristics

The medical records of 60 patients with mRCC treated with advanced line cabozantinib were identified and reviewed. Cabozantinib was given as second line in 16/60 patients, third line in 29/60 patients and forth line or beyond in 15/60 patients. The median age was 64 years, 80% were male. 88% (n=53) had a clear cell histology, and 83% (n=50) had a prior nephrectomy. Patient characteristics are presented in table 1.

Factors	Distribution	Univariate analysis for OS p-value
Age (yr), median (range)	64 (35-88)	0.7
Gender		0.52
Female	20%(n=12)	
Male	80%(n=48)	
Heng risk stratification		0.04
Favorable	8.3%(n=5)	
Intermediate	68.3%(n=41)	
Poor	23.3%(n=14)	
Number of prior lines		0.109
1	26.6%(n=16)	
2	48.3%(n=29)	
3	16.7%(n=10)	
4	8.3%(n=5)	
Histology		0.44
Clear cell	88.3%(n=53)	
Non-clear cell	11.7%(n=7)	
Past Nephrectomy	83.3%(n=50)	0.003
Bulky disease	60%(n=36)	0.029
Cannabis use	38.3%(n=23)	0.249
Obesity	8%(n=5)	0.253
Smoking history	36.7%(n=22)	0.473
DM	18.3%(n=11)	0.701
Previous immunotherapy		0.7
Nivolumab	50%(n=30)	
Ipilimumab/Nivolumab	28%(n=18)	
Avelumab/Axitinib	3.3%(n=2)	
Metastatic site		0.718
Lung	75%(n=45)	
Bone	30%(n=18)	
Liver	15%(n=9)	
Lymph node	25%(n=15)	
Brain	3.3%(n=2)	
Other	18.8%(n=11)	

Table 1: Distribution of clinico-pathologic and prognostic factors.

60% of patients had a bulky disease. As first line therapy, 55% were treated with sunitinib, 13% with pazopanib, 7% with ipilimumab and nivolumab, and 3% with avelumab and axitinib. 15% of the patients did not received prior immunotherapy, 30% received prior ipilimumab and nivolumab combination, 50% were previously treated by single agent nivolumab, 2% by avelumab and axitinib.

70% of the patient initiated therapy with full dose. The reasons for dose reduction at treatment initiation were grade 3-4 side effects during previous treatment (26%), poor performance status (18%), and low ejection fraction (3%). Dose reduction after treatment initiation was done in 53% of the patients, while treatment interruption due to side effects was done in 48% of the patients.

Cabozantinib Treatment outcomes

Median follow-up time was 16 months (range 4-37 months). Best response to therapy was partial response in 28% (n=17), stable disease in 40% (n=24), while 30% (n=18) were refractory to treatment (Table 2).

Median duration of treatment was 8.64 months (range 7.67-9.08). Median OS was 17.6 months (range14.9-20) (Figure 1).

Type of response	Value n(%)
Best overall response	
Complete response	0(0)
Partial response	17(28)
Stable disease	24(40)
Progressive disease	18(30)

Table 2: Response to cabozantinib in patients with mRCC.

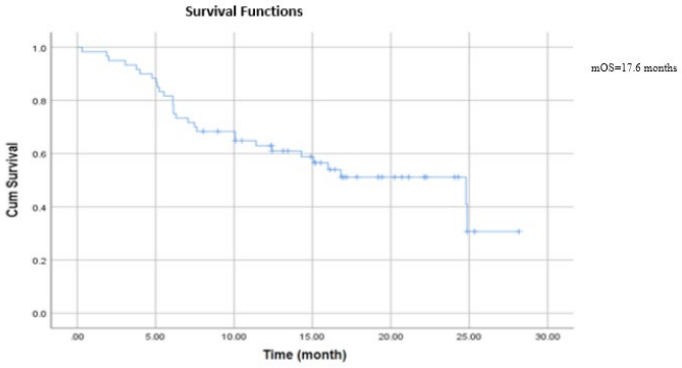

Figure 1: Median Overall Survival (mOS).

The median overall survival of patients that achieved a partial response was 20.9 months, while it was 19.3 months in patients with a stable disease, and 9.1 months in patients refractory to therapy ($p<0.0001$) (Figure 2).

10% of the patients were treated with cabozantinib beyond progression, with a median treatment beyond progression time of 2 months (range 1-3 months).

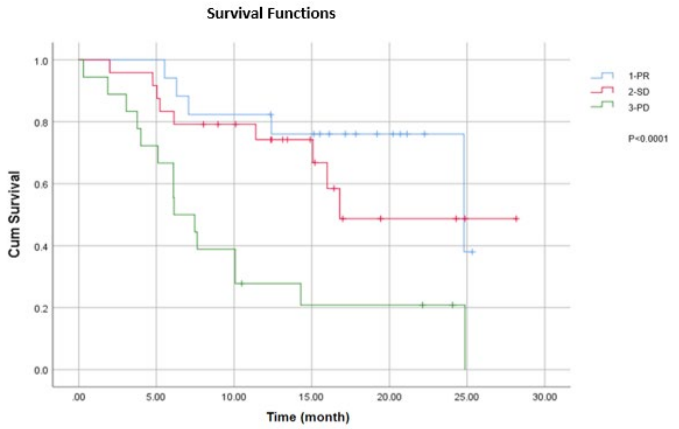

Figure 2: Median Overall Survival based on response.

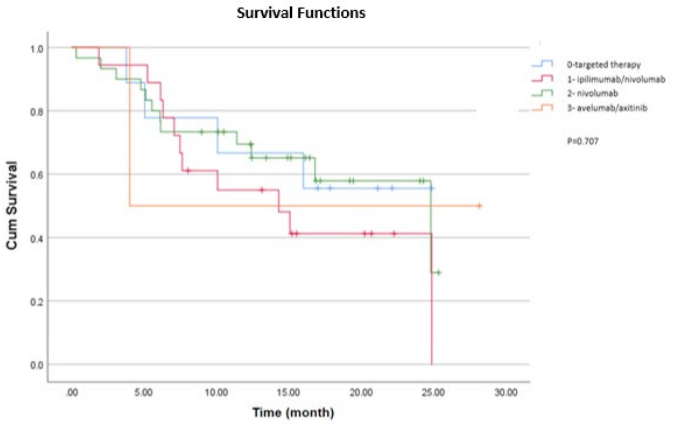

Figure 3: Median Overall Survival based on pre-cabozantinib treatment.

Factors associated with OS

In univariate analysis, the Heng risk (favorable and intermediate versus poor; p=0.04), bulky disease (non-bulky vs bulky, OS 21.7 months vs 14.1 months; p=0.029), and past nephrectomy (yes vs no, OS 19.2 months vs 8.8 months; p=0.003) were individually associated with overall survival. Furthermore, the response to cabozantinib was associated with overall survival (<0.0001).

None of the following factors were associated with overall survival: gender (male vs female, p=0.5); number of previous treatment line(1,2,3, 4 or more, p=0.109); histology type (clear vs non-clear, p=0.44); metastases sites (p=0.708); smoking status (p=0.473); pre-treatment diabetes (p=0.701); obesity (p=0.253); medical cannabis during treatment (p=0.249); pre-cabozantinib levels of hemoglobin (p=0.708), corrected calcium(p=0.787), white blood cells (p=0.657), absolute neutrophils(p=0.383); absolute lymphocytes (p=0.444), absolute monocytes(p=0.493); platelets (p=0.188); and LDH(p=0.608).

The pre-cabozantinib therapies did not influence overall survival. The OS of patients previously treated by targeted therapy as a single agent was 17.6 months versus 15.2 months after ipilimumab/nivolumab, 17.8 months after single agent nivolumab, and 17.8 months after avelumab/axitinib (p=0.707) (Figure 3). Finally, the initial dose of cabozantinib did not influence the OS (p=0.35).

Importantly, patients treated with cabozantinib beyond progression (n=6) had a shorter survival compared to patients that switched to the next treatment line (9.5 months vs 18.2 months, p=0.043).

Toxicity

Reported adverse events are shown in table 3. The most common were fatigue in 31.6%, diarrhea in 16.7%, palmar-plantar erythrodysaesthesia syndrome in 13.3%, and mucositis in 11.6%. The most common grade 3 or 4 toxicities were fatigue in 6.6%, diarrhea in 8.3%, and mucositis in 8.3%. One patient died due to toxicity (gastrointestinal perforation after one month of treatment). One patient permanently discontinued cabozantinib after three weeks because of Stevens-Johnson syndrome.

Adverse event	All grade, n(%)	Grade 3 or 4, n(%)
Fatigue	19(31.6)	4(6.6)
Diarrhea	10(16.7)	5(8.3)
Palmar-plantar erythrodysaeshtesia syndrome	8(13.3)	2(3.3)
Mucositis	7(11.6)	5(8.3)
Rash	5(8.4)	1(1.7)
AST ALT increased	3(5)	0(0)
LVEF decreased	2(3.3)	0(0)
Vaginal bleeding	2(3.3)	0(0)
Hypertension	1(1.7)	0(0)
Rectal bleeding	1(1.7)	0(0)
Abdominal pain	1(1.7)	0(0)
Stevens-Johnson syndrome	1(1.7)	1(1.7)

Table 3: Treatment-related adverse events.

Discussion

The present study retrospective real word multicenter analysis revealed similar efficacy and safety of cabozantinib as advanced treatment line, to what was reported in clinical trials [7]. The disease control rate in our cohort was 68%, and the median overall survival was 17.6 months. In the present study, the incidence of adverse events was reduced versus the one reported in clinical trials [7]. This could be secondary to the retrospective data collection and grading of adverse events.

Univariate analysis of our data showed that the Heng risk (p=0.04), bulky disease (p=0.029), and past nephrectomy (p=0.003) were associated with OS. 30% of our patients (18/60) initiated cabozantinib treatment at a reduced dose. The main reasons for initial dose reduction were serious adverse events on prior therapy and poor performance status. At univariate analysis, initial dose reduction was not associated with OS.

Data on the activity of cabozantinib therapy in patients previously treated by immunotherapy are limited. Breakpoint trial is the first prospective phase 2 study evaluated efficacy and safety of cabozantinib after first line treatment including an immune-checkpoint combination [9]. 22 pts were enrolled to this trial, 27.2% achieved partial response and median PFS was 7.2 months. Additional published data include relatively small and retrospective studies [10-12]. Bodnar et al reported data from Polish access program. 115 pts were enrolled in this analysis, and were treated with at least one VEGF TKI. No information was provided about the percentage of patients treated by immune checkpoint inhibitors before cabozantinib [10]. Safety and efficacy analysis of 96 patients treated with cabozantinib from Italian managed access program were reported by Procopio et al. Only 21% of them were treated by checkpoint inhibitors [11]. A recent retrospective study included 84 pts who received cabozantinib immediately after nivolumab. The overall RR was 52% and median PFS was 11.5 months [12]. 50 pts in our study were treated by checkpoint inhibitors, 18 pts with the combination of ipilimumab and nivolumab, 30 pts with nivolumab as single agent, and 2 pts with avelumab and axitinib. In subgroup analysis, pre-cabozantinib treatment (no imunotherapy vs ipilimumab/nivolumab vs nivolumab vs avelumab/axitinib) was not associated with overall survival (p=0.7).

The results from the CheckMate-9ER were recently presented. This trial showed that combination with cabozantinib and nivolumab significantly improved response rate (55.7% vs 27.1%, p<.0001), progression free survival (16.6 months vs 8.3 months, p<.0001) and overall survival (p .0010) versus sunitinib in first line treatment [13]. Cabozantinib is also under investigation in combination with nivolumab and ipilimumab as a first line treatment in advanced RCC patients in the COSMIC-313 trial. The concept of this trial is to examine doublet versus triplet in intermediate and poor risk mRCC patients [14].

Our study has some limitations. First, this is a multicenter retrospective study. This trial represent an unselected cohort of patients that were treated by cabozantinib in 6 different institutions. We cannot exclude that unequal distribution of unidentified clinic-pathologic parameters may have biased the observed results. Second, the total number of pts (60 pts) is relatively small. Moreover, AE were collected and graded retrospectively.

Despite these limitations, our clinical data of unselected cohort of pts confirm the activity of safety results of cabozantinib treatment in metastatic renal cell carcinoma.

Conflict of interests: Conflict of interest relevant to this article was not reported.

Acknowledgement: The authors received no financial support for the research, authorship, and/or publication of this article.

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