



A Remarkable Long-Lasting Response to Short Course Cabozantinib Therapy in a Patient with Metastatic Renal Cell Carcinoma

Bramati Annalisa¹, Moretti Anna¹, Piva Sheila¹, Bocci Barbara¹, Presazzi Arianna², Boido Beatrice¹, Farina Gabriella¹ and Girelli Serena^{1*}

¹Department of Oncology, ASST Fatebenefratelli Sacco, Italy

²Department of Radiology, ASST Fatebenefratelli Sacco, Italy

Abstract

In this paper, we report the case of a patient with metastatic renal cell carcinoma who was treated with cabozantinib in a third line setting for 2 weeks and experienced an asymptomatic but severe cardiac impairment, with a decrease of the cardiac Left Ventricular Ejection Fraction (LVEF). This event caused the discontinuation of cabozantinib but surprisingly, despite the short period on treatment, the first disease evaluation performed 3 months later showed a remarkable partial remission of the disease. Moreover, from June 2017 to January 2019 the patient underwent several follow-up CT scans which confirmed the disease response which lasted over 2 years despite never having resumed treatment with cabozantinib.

Introduction

Renal Cell Carcinoma (RCC) represents 80% to 85% of primary renal neoplasms [1]. In about 30% of patients a stage IV disease is present at the initial diagnosis, and a further 20% to 40% of patients will develop distant metastasis after local treatment [2]. A treatment milestone of metastatic Renal Cell Carcinoma (mRCC) is VEGF-targeted therapy: Sunitinib [3] and Pazopanib [4] are the leading frontline VEGF-Inhibitors (VEGF-I), currently used for mRCC. Usually in the past standard second-line therapies after VEGF-I included both axitinib (a VEGFR tyrosine-kinase inhibitor) and everolimus (a mTOR inhibitor) [5]. In literature, no difference between these two drugs was demonstrated in an indirect comparison [6].

For the first time, in late 2015, two agents demonstrated an overall survival improvement in the second-line setting: Nivolumab (a PD-1 checkpoint inhibitor) and cabozantinib.

Cabozantinib inhibits several types of tyrosine kinase pathways implicated in oncogenesis, tumor pathobiology, tumor angiogenesis, tumor cell survival and tumor invasion or metastasis, including also VEGFR (specifically VEGFR2), MET and AXL [7,8]. Cabozantinib is approved for the treatment of patients with mRCC, progressing after prior anti-angiogenic therapy [9]. It's the first VEGF-I drug that improves Overall Survival (OS), Progression Free Survival (PFS) and Overall Response Rate (ORR) in a phase III trial in this setting. Patients with a long response to prior VEGF-I, are the best candidates for cabozantinib treatment, after a first line of therapy for their mRCC.

The safety profile of cabozantinib is characterized by cardio-vascular Adverse Events (AEs) like hypertension in 37% of patients, but no data about acute coronary syndromes are reported [9]. In the METEOR study, these adverse effects were manageable but 60% of dose reductions for toxicity was recorded [9].

Case Presentation

We report the case of a 73-year-old male, with diabetes, benign prostatic hypertrophy and hyperlipidemia, who underwent a radical left nephrectomy with regional lymph node dissection in October 2008. A histopathological specimen showed the presence of RCC infiltrating the renal parenchyma, with perinephritic fat invasion and peripheral nodules, stage pT3a G2 N0, according to AJCC 2007.

In May 2009 the patient underwent a biopsy of one of multiple lung nodules, diagnosed at a follow-

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*Correspondence:

Girelli Serena, Department of Oncology,
ASST Fatebenefratelli Sacco, P.O.

Fatebenefratelli, Princess Clotilde
Square 3 20121, Milan, Italy,

E-mail: serena.girelli@asst-fbf-sacco.it

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up Computed Tomography (CT) scan, and the histopathological specimen showed the presence of clear cell carcinoma. Soon after, he started treatment with Sunitinib, obtaining a complete radiological response. Treatment with Sunitinib was interrupted after 30 months, due to G2 hand foot syndrome, G2 dysphagia, G2 fatigue and G2 hypertension.

In January 2013, one year after discontinuing treatment, the CT scan revealed disease progression with an increase in the number of lung nodules and the appearance of metastatic mediastinal lymph nodes.

The patient resumed treatment with Sunitinib, obtaining a partial disease response, so the therapy was continued for over 30 months.

In May 2016 the CT scan showed evidence of further disease progression with an increasing number of lung nodules and the appearance of liver metastases.

On June 6th, 2016 the patient began treatment with everolimus, which lead to rapid weight loss, G2 fatigue, and G2 thrombocytopenia. Treatment with everolimus was first suspended for a week and then resumed at the first dose reduction of 5 mg daily and was then continued uninterruptedly. After 3 months on everolimus, the patient developed worsening fatigue and a new CT scan revealed lung and liver progression with the appearance of a pancreatic nodule and a right kidney nodule.

On November 8th, 2016 the patient started treatment with cabozantinib at a dose of 60 mg per day. After 2 weeks of therapy the patient reported only G1 hand-food syndrome, G1 fatigue and G1 hypertension, which required the introduction of anti-hypertensive drugs. Due to G1 hypertension, specific cardiac tests were requested (electrocardiogram, echocardiogram, cardiological examination).

The echocardiogram showed a generalized severe hypokinesia, with a calculated LVEF of 25% to 30%, and akinesia of the inter-ventricular septum was reported. The Electrocardiography showed an ST segment elevation in V1-V2 and a q wave in V1-V2. A normal QT interval was reported.

The patient reported no symptoms of cardiovascular disease. Considering the clinical history of this patient, treatment with cabozantinib was interrupted after only 2 weeks.

The patient was admitted to the Cardiology Department and underwent a coronarography that showed trivascular coronary disease, with the stenosis of the circumflex artery and the obstruction of the proximal anterior descending artery.

On December 30th, 2016 a percutaneous coronary angioplasty was performed and two stents were positioned on the anterior Inter-Ventricular Artery (IVA).

The echocardiogram performed one month after the coronary angioplasty showed an improvement of the LVEF (50%) with an akinetic septum and hypokinesia of the apex. In February 2017, three months after the interruption of cabozantinib, a CT scan was performed and surprisingly it showed a very good partial response, despite the time elapsed from treatment interruption.

In particular the lung and pleural nodules and the mediastinal lymph nodes appeared considerably reduced in size and number. Even the liver and kidney metastasis showed a reduction in size, confirming the great benefit from such a brief period of treatment with cabozantinib (Figures 1-3).



Figure 1A: November 2016 CT scan: Lung nodules before treatment with cabozantinib.



Figure 1B: February 2017 CT scan: Lung nodules three months after the interruption of cabozantinib. The comparison between the two images (red circles) demonstrates a remarkable reduction in the number and size of lung nodules.

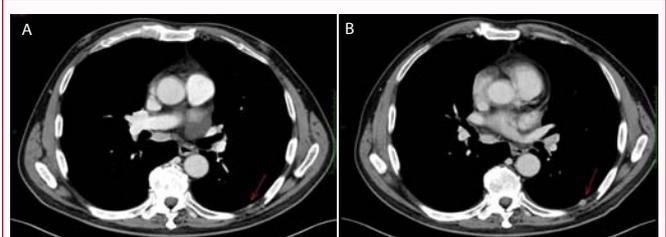


Figure 2: A) November 2016 CT scan: Pleural nodules before starting treatment with cabozantinib. B) February 2017 CT scan: Pleural nodules three months after the interruption of cabozantinib. The comparison between the two images (red arrows) demonstrates a remarkable reduction in the size of pleural nodules.

From June 2017 until January 2019 the patient underwent several follow-up CT scans which confirmed the disease response that lasted for over 2 years without the need to resume cabozantinib.

In January 2019, following disease progression of the preexisting metastases, the patient started a new line of treatment with nivolumab which is currently underway without any significant toxicities.

Discussion

This case report adds evidence about the efficacy of a short course of cabozantinib in subsequent lines of treatment after VEGF-therapy. We couldn't find any other reports dealing with coronary syndrome, which isn't even described in the population treated in clinical trials.

We also carried out a literature search in order to investigate any post-marketing cardiovascular safety data on tyrosine kinase inhibitors [10]. Available reported data suggest that there is only a mild to moderate degree of QTc interval prolongation and an elevated risk of hypertension associated with cabozantinib.



Figure 3: A) November 2016 CT scan: The kidney nodule before starting treatment with cabozantinib. B) February 2017 CT scan: The kidney nodule three months after the interruption of cabozantinib. The comparison between November CT scan images and February CT scan images demonstrates a remarkable reduction in the size of the kidney nodule.

We cannot establish a sure correlation between cabozantinib and this cardiac event.

We point out that the patient who started cabozantinib was a 73-year-old male that had received anti VEGF treatment for many years; besides, he had diabetes and was affected by hyperlipidemia, two major risk factors for cardiovascular disease.

Anyway, because of this cardiovascular event treatment with cabozantinib was immediately interrupted. Since then we observed the patient and noticed the very long duration of disease response, so we decided not to resume treatment with cabozantinib until disease progression.

We point out how the antiangiogenetic effect lasted so long, even after drug discontinuation.

This is the first case report of such a dramatic and durable response to cabozantinib after a short course of treatment, providing further support to the evidence of drug activity, particularly in patients with a previous long-term response to VEGF-I. Since in recent years several agents have been approved and their indication has been extended,

there is a compelling need for an ongoing evaluation of their safety and risk/benefit profile. This information about coronary syndrome could help us in better understanding the safety profile of cabozantinib and may help clinicians to improve their knowledge about AEs in order to prevent them and improve their early management.

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