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Case Report

Reversible Cabozantinib-Induced Cardiomyopathy

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ABSTRACT

Cabozantinib is a multitargeted tyrosine kinase inhibitor, with activity against vascular endothelial growth factor receptor, as well as MET, RET, and AXL. It is currently approved for treating advanced thyroid and kidney cancers, and is being investigated in other cancers. We present a case of reversible heart failure due to cabozantinib use in a 70-year-old man with metastatic renal cell carcinoma. This is, to our knowledge, one of the first reported cases of cardiomyopathy associated with cabozantinib use.

RÉSUMÉ

Le cabozantinib est un inhibiteur de tyrosine à cibles multiples, qui exerce une activité contre les récepteurs du facteur de croissance de l'endothélium vasculaire, comme le MET, le RET et l'AXL. Il est actuellement approuvé pour le traitement des cancers de la thyroïde et du rein de stade avancé, et fait l'objet d'études pour d'autres cancers. Nous présentons un cas d'insuffisance cardiaque réversible due à l'utilisation du cabozantinib chez un homme de 70 ans souffrant d'un carcinome métastatique à cellules rénales. À notre connaissance, c'est l'un des premiers cas rapportés de cardiomyopathie associée à l'utilisation du cabozantinib.

Case Presentation

A 70-year-old man was diagnosed with stage IIIa, N1 renal cell carcinoma in 2013. He had a past medical history of hypertension, dyslipidemia, atrial fibrillation, and coronary bypass grafting 22 years previously. He underwent left radical nephrectomy and para-aortic lymphadenectomy. In 2014, he was started on pazopanib for metastatic disease to the lungs. An echocardiogram performed in 2016 for the workup of atypical chest pain showed normal left ventricular ejection fraction (LVEF) of 60%, and a concurrent exercise stress test revealed no evidence of myocardial ischemia. On disease progression in 2017, he started cabozantinib 60 mg daily instead of pazopanib. The blood pressure (BP) and heart rate (HR) were recorded twice daily at home during cabozantinib therapy. The mean ± standard deviation (SD) systolic BP was 119 ± 21 mm Hg (range: 79-174 mm Hg), and the mean ± SD HR was 65 ± 12 beats per minute (bpm) (range: 37-126 bpm). Electrocardiograms at every clinical encounter demonstrated atrial fibrillation with controlled ventricular response, and no ischemic changes.

Four months after commencing cabozantinib therapy, he attended the cardio-oncology service with progressive dyspnea, weight gain, and leg swelling. Physical examination demonstrated jugular venous pressure 5-6 cm above the sternal angle, respiratory crepitations, and peripheral oedema, and chest radiograph findings consistent with heart failure. Clinical features were indicative of New York Heart Association functional class III heart failure. Transthoracic echocardiography revealed moderate global hypokinesis of the left ventricle with LVEF of 39% (Video 1, view video online). Treatment with diuretics and β-blocker, and withholding cabozantinib resulted in clinical improvement. The patient was compliant with his cardiac medications. His mean ± SD systolic BP was 105 ± 9 mm Hg (range: 78-135 mm Hg), and mean ± SD HR was 70 ± 10 bpm. One month after holding cabozantinib it was resumed at reduced doses of 20 mg, then 40 mg, while continuing on β-blocker with good HR and BP control. However, 2 months later, heart failure recurred. A repeat echocardiogram revealed severe LV dysfunction with EF 20% to 25 % (Video 2, view video online). A nuclear perfusion scan demonstrated no evidence of myocardial ischemia. An angiotensin-converting enzyme inhibitor was added. Cabozantinib was permanently discontinued despite an ongoing disease response. Subsequent echocardiograms 6 and 14 weeks

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later revealed improved LV function with LVEF of 34% and 50% to 55%, respectively.

Discussion

Cabozantinib is an oral small-molecule tyrosine kinase inhibitor that targets multiple kinases including vascular endothelial growth factor (VEGF) receptor 2, MET, RET, and AXL. Given its efficacy in prolonging progression-free survival, and overall survival, it has been approved for the treatment of progressive metastatic medullary thyroid cancer and advanced clear-cell renal carcinoma. It is currently being tested in a variety of other cancers including prostate, lung, cholangiocarcinoma, hepatocellular, neuroendocrine, colorectal, breast, multiple myeloma, and acute lymphoblastic leukemia.

One study has reported heart failure as a possible adverse effect to cabozantinib in a single patient who was previously known to have congestive heart failure.[1] There are several reasons to consider our heart failure case causally related to cabozantinib. First, the patient had normal LV function before cabozantinib exposure, and heart failure was strongly temporally related to cabozantinib initiation. Secondly, there were no other precipitants for his heart failure: his coronary artery disease and atrial fibrillation had been stable for 22 years before decompensation. Thirdly, his heart failure symptoms improved when the drug was held, and then reappeared after rechallenge. Finally, the LVEF promptly recovered fully after discontinuation of cabozantinib.

Cabozantinib is one of several agents that suppress angiogenesis through inhibition of the VEGF signaling pathway (VSP). This class of tyrosine kinase inhibitor collectively has a cardiovascular adverse effect profile that includes systemic hypertension, arterial thromboembolism, cardiac ischemia, and cardiomyopathy.[2] Cardiomyopathy due to inhibition of VSP may be mechanistically related to dysfunction in myocardial microcirculation and induction of hypoxia-induced factor, leading to hibernation.[3] It appears that VSP-induced cardiomyopathy is usually reversible, as shown in mice hearts, and in clinical reports of cardiomyopathy potentially related to VEGF inhibitor use.[3] There is paucity of data to suggest a relationship between VEGF receptor inhibitor dose and the development of cardiotoxicity.

The cardiotoxicity profile for other VEGF-targeting agents has been well described. In a meta-analysis of bevacizumab, the overall relative risk for high-grade heart failure was 4.74 (95% confidence interval [CI], 1.84-12.19; $P = 0.001$).[4] In another meta-analysis, sunitinib was shown to be associated with an increased risk of heart failure. The relative risk for developing high-grade congestive heart failure compared with placebo was 3.30 (95% CI, 1.29-8.45; $P = 0.01$).[5] In the most recent meta-analysis of clinical trials of VSP inhibitors, there were significant increases in the odds of cardiomyopathy (odds ratio [OR] 1.35 [95% CI, 1.06-1.70]) and cardiac ischemia (OR 2.83 [95% CI, 1.72-4.65]), with a trend towards an increased likelihood of heart failure (OR 1.66 [95% CI, 0.84-3.30]).[2]

Interestingly, our patient received pazopanib for nearly 3 years, and he presented with heart failure 8 months after pazopanib discontinuation. Although theoretically possible, we think it is unlikely that pazopanib directly caused his cardiomyopathy, given the strong temporal relationship to cabozantinib observed.

Conclusions

Cabozantinib represents an important advance in the treatment of many cancers and may have other clinical applications in the future. However, the experience of our patient suggests that it may cause cardiotoxicity, similar to other VSP inhibitors. As a result, cabozantinib should be used cautiously, especially in those with cardiac risk factors, even in patients who did not experience such toxicity with previous VSP inhibitors.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.12.025.