Editorial Commentary



# Looking beyond cancer for cabozantinib-induced cardiotoxicity: evidence of absence or absence of evidence?

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The advent of molecular targeted therapy has transformed the scape of medical oncology in the past decades—patients previously deemed terminal now have more treatment options proven to extend survival. An example is renal cell carcinoma (RCC); given its myriad clinical presentation, a significant proportion of patients have locally advanced or metastatic disease at the time of diagnosis. Historically, treatment options for such patients were limited and their prognosis grim. In the past years, however, vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (TKIs), such as bevacizumab, sunitinib and pazopanib, have been shown to improve progression-free survival, although there have been increasing reports of drug cardiotoxicity including hypertension and heart failure (1-5). As a result, there is a growing need for better patient selection, prevention and monitoring of cardiotoxicity during treatment, as well as exploration of alternative safer agents.

Cabozantinib [a small molecule, multi-targeted TKIs against mesenchymal-epithelial transition factor (MET), VEGF receptors (VEGFR) and AXL] has emerged as a promising agent not only for metastatic RCC, but also for medullary thyroid cancer and hepatocellular carcinoma (6-9). In a recent trial, cabozantinib was superior to sunitinib in terms of progression-free survival and response rate in metastatic RCC (8). Accordingly, the 2019 ESMO guidelines consider it as second-line therapy for intermediate to poor risk patients with RCC, after combination therapy of nivolumab and ipilimumab (10). Given the known cardiotoxicity of related VEGF inhibitors and TKIs, and an increasingly robust literature on its clinical significance in patients with otherwise good tumour response, the possible cardiotoxic effects of cabozantinib remain to be elucidated.

The prospective observational study by Iacovelli *et al.* sought to delineate the cardiotoxic effect of cabozantinib in patients with metastatic RCC (11). In total, 22 patients were followed for up to 6 months after initiation of cabozantinib for adverse clinical events, changes in left ventricular ejection fraction (LVEF), N-terminal brain natriuretic peptide (NT-proBNP) and high sensitivity troponin I (hsTnI) levels. Exclusion criteria were pre-existing cardiovascular comorbidities such as uncontrolled hypertension, documented coronary artery disease (although apparently 2 patients had ischemic heart disease), and heart failure. Most of these patients were at International Metastatic RCC Database Consortium (IMDC) intermediate risk and were diagnosed with clear cell RCC. At baseline, 9.1% of the patients had reduced LVEF at 50–55%; 64.7% (11 out of 17 patients available for analysis) had elevated NT-proBNP and 27.3% had elevated hsTnI levels.

At 3 months, among the 18 remaining patients with LVEF data, 33.3% had a decline in LVEF, although none

 

had LVEF <50%. Only 7 patients had 6-month follow-up, and 1 out of 7 patients had decreased LVEF. There was no change in NT-proBNP or hsTnI level in patients with normal baseline levels; for those with elevated baseline NT-proBNP and hsTnI levels, there was no significant correlation between changes in these biomarkers and LVEF at baseline, 3 months or 6 months.

There were 2 adverse cardiovascular events in the entire cohort. One patient died suddenly at 4 months, without a precedent change in LVEF or an increase in NT-proBNP at 3 months of therapy, and therefore it was concluded that the cause of death was not directly related to cabozantinib. Another patient developed LV systolic dysfunction after 6 months of cabozantinib therapy (LVEF declined from 70% at baseline to 60% at 3 months and 47% at 6 months) but remained asymptomatic. Overall, the authors concluded that there was an "extremely modest risk of developing LV systolic dysfunction" with cabozantinib use, and that "routine assessment of the cardiac function should be avoided in asymptomatic patients—given the low probability of a relevant clinical benefit—while reserved at the occurrence of clinical symptoms" (11).

This study by Iacovelli *et al.* was an important first step to evaluating the cardiovascular safety profile of cabozantinib, an agent anticipated to be in more widespread use in the near future. However, a few study limitations are noteworthy. The authors stated that 38 patients were required to achieve 80% power to show the hypothesized LVEF decline of >10% at a 2-sided α level of 0.05, but only 22 patients were enrolled, undermining the power of the study. Because LV dysfunction was defined as a binary (instead of continuous) outcome according to an arbitrary cut-point (decline by ≥10% to below 50%), subtle reductions in LVEF might be omitted. Importantly, only 7 patients had 6-month follow-up. Therefore, the incidence of LV dysfunction would be estimated at 14.3%, with a binominal 95% confidence interval of 0.4% to as high as 57.9%. Even under a tenuous assumption that none of the patients without follow-up LVEF measurement actually developed LV dysfunction (i.e., only 1 of 22 patients had LV dysfunction), the incidence would be still be 4.5%, with a 95% confidence interval of 0.1% to 22.8%. Such imprecise estimates of the rate of LV dysfunction due to the small sample size could not reliably rule out a clinically significant risk of cardiotoxicity. Furthermore, because data might not have been missing completely at random, with such a high drop-out rate, the observed incidence rate could be biased.

As a common imaging modality to monitor LVEF in clinical practice, transthoracic echocardiogram was used to measure LVEF in this study, but there are a few caveats to keep in mind. LVEF measurements by echocardiogram are subject to operator and technical variabilities. It is unclear if there was a single echocardiographer blinded to other clinical information and the order of examinations, and whether 3-dimensional technique or contrast was employed to enhance the accuracy of LVEF measurements (12,13). Furthermore, there is increasing recognition that reduced LVEF is a late manifestation of cardiotoxicity (13,14). For instance, in the more established literature on doxorubicin-induced cardiotoxicity, LVEF correlates poorly with cardiac biopsy grades of myocardial toxicity (15), suggesting that substantial and even irreversible cardiomyocyte injury might have occurred before the onset of LV dysfunction. Current guidelines recommend initiation of cardioprotective therapy with angiotensin-converting enzyme inhibitors (ACEI) as soon as possible for LV systolic dysfunction, even if asymptomatic, due to a potential inverse relationship between treatment delay and degree of LVEF recovery (13,16). There is also evolving evidence that pre-emptive use of ACEI and beta-blockers may prevent cardiotoxicity (17-19). These observations challenge LVEF as the optimal marker of chemotherapy-induced cardiotoxicity. Indeed, recent studies have demonstrated that LV strain may be more sensitive in detecting subclinical myocardial injury and may furnish incremental prognostic information (14,20).

Beyond imaging, biomarkers such as hsTnI and NT-proBNP may play a valuable complementary role in the early detection and monitoring of cardiotoxicity (16,17,21). While the study by Iacovelli *et al.* (11) evaluated hsTnI and NT-proBNP, there were substantial missing data. Only 17 patients and 6 patients (as per the tables provided) had baseline NT-proBNP and hsTnI measurements, respectively, and even fewer patients had follow-up data at 3 and 6 months. Of note, the biomarker data were presented as dichotomous (normal *vs.* abnormal) rather than continuous variables, which further diminished the power to uncover any real changes over time. Finally, as for other VEGF inhibitors and TKIs, cabozantinib can prolong QT interval and cause significant hypertension (6,22). Unfortunately, these key data were not reported in this study.

As cancer outcome continues to improve with novel and more effective systemic chemotherapy, cardio-oncology is a rapidly expanding field aimed to optimize not only progression-free but also overall survival in patients with cancer (4,13,23). We now need to look beyond cancer-

 

related prognoses, with a heightened vigilance on long-term safety profiles of chemotherapeutic agents, and to address cardiovascular risks as competing causes of death in cancer survivors (13,24). Iacovelli *et al.* should be commended for their seminal attempt to assess cardiotoxicity of cabozantinib, an emerging molecular targeted therapy for metastatic RCC, medullary thyroid cancer and hepatocellular cancer. However, given the aforementioned study limitations, the cardiovascular safety of cabozantinib could not be firmly established. It would also be premature to definitively conclude that routine cardiac function monitoring is unnecessary during cabozantinib treatment. We agree with the authors that a real-world cohort study including patients with cardiovascular comorbidities is crucial—while treatment decisions should be individualized by balancing the risks and benefits for each patient, more precise information about the absolute risks and risk factors for cabozantinib-induced cardiotoxicity will better inform shared clinical decision-making. Further studies involving a larger number and broader spectrum of patients, from multiple centres and with extended follow-up, are warranted to determine the cardiovascular safety profile of cabozantinib.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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