CLINICAL VIGNETTE

A Case of Lenvatinib-Associated Cardiomyopathy

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Case Description

A 70-year-old male with hypertension and hepatitis B-associated cirrhosis and hepatocellular carcinoma (HCC) on lenvatinib therapy presented to the emergency department (ED) with shortness of breath and chest pain for three days. He reported having shortness of breath at rest that worsened with exertion. Initially, his symptoms improved with use of home supplemental oxygen. However, despite oxygen therapy, he developed a constant, left-sided, non-exertional chest pain that did not improve with rest, prompting ED evaluation. At baseline, the patient was able to walk at least one mile without problems but now was only able to walk five feet before developing shortness of breath. He denied orthopnea, paroxysmal nocturnal dyspnea, light headedness, and lower extremity swelling. Of note, the patient was started on lenvatinib one month prior by his oncologist for treatment of his unresectable HCC. However, he recently stopped taking lenvatinib due to dyspnea. Other medications included entecavir and amlodipine. He denied any history of tobacco, alcohol, or illicit substance use and denied any family history of heart disease.

On examination, the patient was afebrile with a heart rate of 88 beats/minute, respiratory rate of 20 respirations/minute, blood pressure of 92/72 mmHg, and oxygen saturation of 97% on room air. Cardiopulmonary examination was notable for a regular rate and rhythm with no murmurs, rubs, or gallops. Chest examines revealed right greater than left bibasilar crackles, and jugular venous distension of 10 cm H_2O. There was 1+ pitting edema to bilateral knees.

Initial laboratory findings were remarkable for sodium of 127 mmol/L, normal creatinine, initial troponin of 0.775 ng/mL that subsequently peaked at 0.953 ng/mL, and a brain natriuretic peptide level of 2,997 pg/mL. Liver chemistries were stable compared to prior and notable for alkaline phosphatase of 197 U/L, aspartate aminotransferase of 197 U/L, normal alanine aminotransferase, and mildly elevated total and direct bilirubin of 2.0 mg/dL and 0.6 mg/dL, respectively. Thyroid stimulating hormone and hemoglobin A1c levels were normal. Electrocardiogram showed nonspecific diffuse T-wave flattening without dynamic changes and chest x-ray revealed moderate cardiomegaly and moderate cardiac decompensation with dense bilateral lung bases with consolidation and/or pleural effusions. CT angiography negative for pulmonary embolism and CT abdomen and pelvis showed an unchanged multilobulated left hepatic lobe HCC.

After his initial evaluation, a transthoracic echocardiogram, revealed a left ventricular ejection fraction of 29%, a 16 x 9 mm left ventricular (LV) thrombus, and regional wall motion abnormalities consistent with multivessel coronary artery disease versus cardiomyopathy. The patient was given aspirin, clopidogrel, intravenous furosemide and started on a heparin drip prior to cardiac catheterization, which showed non-obstructive coronary artery disease. Cardiac magnetic resonance imaging prior to discharge was nondiagnostic for infarct and infiltrative disease. The patient was diagnosed with nonischemic cardiomyopathy due to grade 3 lenvatinib-induced cardiac dysfunction and lenvatinib therapy was discontinued. He was eventually started on guideline-directed medical therapy for heart failure with reduced ejection fraction prior to discharge and therapeutic low molecular weight heparin bridged to warfarin for treatment of his LV thrombus with outpatient cardiology and oncology follow-up.

Discussion

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally.[1] HCC is the most common type of primary liver cancer, with the highest incidence rates in East Asia and sub-Saharan Africa.[1] Patients with advanced HCC have a poor prognosis and are not typically candidates for curative surgical resection, given the elevated perioperative mortality and increased risk of extrahepatic invasion.[1] For more than a decade, sorafenib has been the primary first-line, systemic treatment of advanced HCC.[1] This drug inhibits multiple receptor tyrosine kinases that are over-expressed in cancer cells and involved in cell proliferation and angiogenesis. However, its therapeutic efficacy is limited due to the upregulation of alternate pro-angiogenic pathways, including the fibroblast growth factor signaling pathway.[1]

Multiple clinical trials have evaluated newer systemic treatments for unresectable HCC. Lenvatinib is an oral small molecule inhibitor of vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-

derived growth factor receptor alpha, RET, and KIT. It was recently approved as a first-line treatment for unresectable HCC based on the phase 3 REFLECT trial.[2,3] This trial found lenvatinib was non-inferior to sorafenib for overall survival in patients diagnosed with unresectable HCC. Compared with sorafenib, lenvatinib was associated with significant improvements in all secondary endpoints, including higher objective response rate and longer progression-free survival and time to progression.[2,3] Furthermore, deterioration of multiple health-related quality of life aspects was delayed by lenvatinib versus sorafenib.[3]

Despite the promising results in patients with HCC, lenvatinib is associated with multiple toxicities and side effects. Based on the REFLECT trial, common side effects of lenvatinib include diarrhea, hypertension, decreased appetite, and decreased weight. In HCC patients treated with lenvatinib at a dose of 8 mg or 12 mg once daily, QTc interval prolongation occurred in 8% of patients with QTc interval prolongation of greater than 500 milliseconds observed in 2% of patients.[4] Across multiple clinical trials, 7% of lenvatinib-treated patients experienced cardiac dysfunction including, cardiomyopathy, decreased left or right ventricular ejection fraction, or congestive heart failure, with 2% with grade 3 or higher cardiac dysfunction.[4] Hypertension, which could potentially induce cardiac adverse events, also occurred in 73% of lenvatinib-treated patients compared with 15% of placebo-treated patients in the SELECT trial.[4]

Although multiple studies have explored the mechanism of lenvatinib-induced cardiotoxicity, the exact mechanism remains unclear. Results of a preclinical study showed that lenvatinib caused cardiomyocyte apoptosis through oxidative stress, mitochondrial dysfunction, and cell nucleus damage.[5] Studies that have investigated the mechanism behind sorafenib-induced cardiac dysfunction have suggested that inhibition of RAF-1 and BRAF kinase impact cardiomyocyte survival.[6] The interruption of angiogenesis through the inhibition of vascular endothelial growth factor signaling has also been implicated in the development of hypertension and concentric hypertrophy, which can lead to heart failure.[7]

Research on the management of lenvatinib-associated cardiotoxicity is limited. Currently, there are no medications that are specifically designed to treat tyrosine kinase inhibitor-mediated cardiac dysfunction. American Heart Association guidelines recommend careful monitoring of patients undergoing chemotherapy and suggest that routine monitoring of LV function using serial echocardiograms would be reasonable.[8] Previous literature on the treatment of cardiac dysfunction caused by earlier generation tyrosine kinase inhibitors can also offer valuable insight. Follow-up data from clinical trials have shown that cardiac dysfunction from trastuzumab is reversible with discontinuation of the drug and may be responsive to medical therapy.[9] Wu et al describe a patient admitted for decompensated heart failure four months after initiating treatment with sorafenib for stage IIIC HCC.[7] Sorafenib was discontinued, and the patient was treated with intravenous furosemide and guideline-directed medical therapy. His heart failure was complicated by cardiogenic shock requiring inotropic support, although successful titration of guideline-directed medical therapy led to hemodynamic improvement. Another report described a woman who developed heart failure eight months after the start of lenvatinib treatment for thyroid cancer. Once lenvatinib was discontinued, the patient's cardiac function eventually recovered. She was subsequently able to restart lenvatinib and survived for 15 months after restarting therapy.[10] Further research is necessary to understand the impact of lenvatinib on cardiac function and the time course for resolution of symptoms following discontinuation of lenvatinib in patients who develop lenvatinib-associated cardiotoxicity.

Conclusion

Cardiac dysfunction is a rare side effect of lenvatinib and research on the management of patients who develop lenvatinib-associated cardiomyopathy is limited. As the use of tyrosine kinase inhibitors in the treatment of different types of malignancies increases, the incidence of cardiotoxicity caused by these agents will likely increase. We look forward to future research that will not only assess the risk factors and molecular mechanisms underlying lenvatinib-induced cardiac dysfunction but also guide the management of patients with nonischemic cardiomyopathy associated with lenvatinib therapy.

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