Case Report

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Carfilzomib-associated pulmonary arterial hypertension in multiple myeloma

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Abstract

Drug-induced pulmonary arterial hypertension (PAH) is constantly evolving as new drugs are developed. Carfilzomib is a recently approved therapy for relapsed and refractory multiple myeloma. While it has been associated with cardiovascular adverse events, such as ischemic heart disease and heart failure, PAH has not been a well-described side effect. We present two patients who developed PAH associated with initiation of carfilzomib. They both initially presented with severe dyspnea, had elevated right ventricular systolic pressure on transthoracic echocardiography and ultimately underwent right heart catheterization. With discontinuation of carfilzomib, both patients had improvement in hemodynamics. However, one patient required initiation of PAH-targeted therapies and has had worsening right ventricular function again despite permanent discontinuation of carfilzomib. It is important to recognize the association between carfilzomib and PAH. Echocardiography can be an important initial screening tool. PAH from carfilzomib therapy may be reversible, especially if diagnosed early; however, extended follow-up is essential.

Keywords

cardio-oncology, drug toxicity, multiple myeloma, pulmonary hypertension

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Introduction

Our understanding of drugs linked with the development of pulmonary arterial hypertension (PAH) continues to evolve. For many years, anorexigens were the main culprits, but as research and awareness surrounding PAH increase, other drugs have been reported to cause PAH as well.

Carfilzomib is a second-generation selective proteasome inhibitor and was approved in 2012 for the treatment of relapsed and refractory multiple myeloma. Carfilzomib is increasingly used in regimens for multiple myeloma, as studies have shown improved complete response rates, progression-free survival, and reduced risk of death compared to prior treatment regimens.[1] However, cardiovascular adverse effects have also been reported with carfilzomib.[2] Herein, we present two cases of carfilzomib-associated PAH.

Case 1

A 59-year-old woman with multiple myeloma was referred for an abnormal transthoracic echocardiogram (TTE). A year prior to her presentation, she had received an autologous stem cell transplant for multiple myeloma. However, she had relapse of her disease approximately 10 months later, so was started on salvage therapy, which consisted of carfilzomib, daratumumab, and dexamethasone. Prior treatments had included bortezomib and lenalidomide. TTE prior to initiating this regimen showed normal right ventricular systolic function and a right ventricular systolic pressure (RVSP) of 34 mmHg.

After the fourth cycle of carfilzomib, the patient noted dyspnea on exertion. A new TTE was obtained, which demonstrated reduced right ventricular systolic function with a RVSP of 74 mmHg (Video 1(a) and (b)). Therefore, she was referred to the pulmonary vascular clinic. Vitals were

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Table 1. Results of right heart catheterization.

Patient	Timing of RHC	RA (mmHg)	PAP, sys/dias (mmHg)	Mean PAP (mmHg)	PCWP (mmHg)	CO (L/min)	CI (L/min/m^2)	PVR (WU)
1	1 month after carfilzomib	4	39/14	23	10	3.6	2.3	3.6
2	On carfilzomib	12	85/33	52	11	2.7	1.8	15.2

CI: cardiac index; CO: cardiac output; L/min: liters/minute; mmHg: millimeters of Mercury; PAP: pulmonary artery pressures; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RA: right atrial pressure; RHC: right heart catheterization; Sys/dias: systolic/diastolic; WU: Wood units.

normal and she had a room air saturation of 97%. Physical examination was unremarkable. Hemoglobin was 14.8 gm/dL, platelets were 140,000 mm,^{3} and creatinine was 0.74 mg/dL. Electrocardiography confirmed a normal sinus rhythm without signs of ischemia, and ventilation-perfusion scan was not consistent with thromboembolic disease. On further review of her TTE, there was consideration for amyloidosis given interventricular septal thickening, so she was referred for right heart catheterization with possible cardiac biopsy. Carfilzomib was discontinued, and no PAH-targeted therapies were started. Right heart catheterization performed approximately one month later showed resolution of pulmonary hypertension (Table 1). She also reported improvement in her symptoms, and three months later, her dyspnea entirely resolved.

Case 2

A 56-year-old woman with multiple myeloma was evaluated for dyspnea. She had underwent an autologous stem cell transplant several years prior but had relapse of disease approximately two years later. Subsequently, she was treated with multiple regimens, including bortezomib, chimeric antigen receptor T-cell therapy, and most recently carfilzomib.

After four months of treatment with carfilzomib, she developed significant dyspnea. TTE showed RVSP of 120 mmHg with severely enlarged right ventricle and depressed function (Video 2(a) to (c)). Her baseline TTE had normal right ventricular size and function, with RVSP of 43 mmHg. Given her TTE findings and worsening symptoms, she was admitted for urgent work up. Vital signs were within normal limits. Physical examination revealed elevated jugular venous pressure and mild abdominal distention. Hemoglobin was 8.6 gm/dL, platelets 87,000 mm^3, and creatinine 0.77 mg/dL which were all near her baseline. Chest radiography reported no cardiopulmonary abnormality; ventilation-perfusion scan was not consistent with thromboembolic disease; and electrocardiography showed normal sinus rhythm with a rightward axis. Right heart catheterization confirmed PAH (Table 1). Combination PAH-targeted therapy was started with sildenafil and macitentan, and carfilzomib was discontinued.

At two-month follow-up, the patient's dyspnea had resolved. Repeat TTE showed a RVSP of 38 mmHg, normalization of right ventricular size and function (Video 3(a) and (b)), and improved tricuspid annular plane systolic excursion from 1.37 cm to 2.33 cm. Macitentan was discontinued. One month later, repeat TTE showed an increased RVSP to 70 mmHg with enlarged right ventricular size. Therefore, she was restarted on macitentan and has ongoing follow-up with the pulmonary vascular clinic.

Discussion

Carfilzomib has improved the treatment of relapsed and refractory multiple myeloma. However, serious adverse events have been observed, especially related to the cardiovascular system. Prior reports have described heart failure, hypertension, and ischemic heart disease related to carfilzomib.[2,3] While there are several mechanisms for pulmonary hypertension in multiple myeloma,[4] including thromboembolic disease and amyloidosis, drug-associated pulmonary arterial hypertension may become increasingly common, especially as novel medications are emerging. These two cases demonstrate that in addition to ruling out other causes of pulmonary hypertension related to multiple myeloma, drug therapy for myeloma should be carefully monitored.

Although there are reports of bortezomib associated with PAH,[5] the temporal correlation of PAH in both patients appeared to be with carfilzomib. The underlying mechanism of carfilzomib-induced PAH is unclear. One hypothesis is that carfilzomib may lead to dose-dependent changes in endothelial nitric oxide synthase activity, leading to less bioavailable nitric oxide and thus impairing vasodilation.[2] Patient 1 had a cumulative carfilzomib dose of 496 mg/m^2 while patient 2 had received a cumulative dose of 6133 mg/m^2 of carfilzomib. Given this theory of dose-dependent changes in nitric oxide synthase activity, the higher total cumulative dose of carfilzomib in patient 2 may have contributed to why her PAH was not reversible with drug cessation alone. An alternative theory is that the non-targeted proteasome inhibition of the endothelium and subsequent oxidative stress lead to vascular dysfunction and increased vascular tone.[6] Although the pathogenesis of carfilzomib-induced PAH remains unclear, the growing number of case reports[7,8] highlights the importance of screening echocardiograms and close symptom monitoring after initiation of carfilzomib.

Given the limited cases of PAH associated with carfilzomib, prognosis and treatment are ill-defined. Our first

patient highlights that PAH associated with carfilzomib may be potentially reversible if diagnosed early and the offending agent is stopped. She had complete resolution of pulmonary hypertension with just discontinuation of carfilzomib. On the contrary, PAH-targeted therapies were prescribed in our second patient. Despite permanent discontinuation of carfilzomib, she failed a trial off combination PAH therapies. Similarly, in the experience with dasatinib-induced PAH, about a third of patients had persistent PAH despite discontinuation of dasatinib.[9] Therefore, extended follow-up of these patients is essential. We acknowledge the lack of complete hemodynamics in both patients before and after carfilzomib cessation is a limitation in this series, but believe this is still an important association to highlight.

Conclusion

Carfilzomib has been revolutionary for patients with multiple myeloma, but there is an emerging association with PAH. These cases highlight the importance of echocardiographic and symptom screening during treatment with carfilzomib, as well as the need for extended follow-up for these patients even after discontinuation of carfilzomib. While pulmonary hypertension associated with carfilzomib may be reversible with drug discontinuation, there may also be patients who require long-term treatment with PAH-targeted therapies. Larger studies are needed to help further define the incidence, characteristics, and long-term effects of pulmonary hypertension in this population.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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Supplemental Material

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