Patterns of Cardiac Toxicity Associated With Irreversible Proteasome Inhibition in the Treatment of Multiple Myeloma

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ABSTRACT

Carfilzomib is a novel irreversible proteasome inhibitor (PI) used with increasing frequency to treat patients with relapsed and/or refractory multiple myeloma (RRMM). This agent is an effective treatment for this challenging population, but proteasome inhibition has the potential of significant cardiac toxicity via the accumulation of intracellular protein aggregates. Although large clinical trials have not suggested an excess of heart failure with PI therapy, nonhuman animal studies and case reports in humans with the PI bortezomib have suggested otherwise. We describe the clinical presentation and management of 6 patients with RRMM who experienced significant cardiac toxicity associated with carfilzomib treatment. A common clinical syndrome of dyspnea associated with left ventricular systolic and/or diastolic dysfunction was identified. These abnormalities were largely reversible with prompt cessation of PI therapy and initiation of traditional heart failure treatments. Safe readministration of carfilzomib with dose modification was possible in some cases. (*J Cardiac Fail 2015;21:138–144*)

Key Words: Carfilzomib, proteasome inhibitor, heart failure, chemotherapy.

Proteasome inhibitors (PIs), including carfilzomib and bortezomib, are cornerstones of the management of multiple myeloma.[1–5] These agents are generally well tolerated but have exhibited some specific cardiac toxicities, the epidemiology and mechanisms of which remain largely undefined. Carfilzomib, a novel proteasome inhibitor that irreversibly inhibits the chymotryptic site of the proteasome, is used with increasing frequency for patients with relapsed and/or refractory multiple myeloma (RRMM). This agent has substantially increased survival in patients with RRMM. However, there is increasing evidence that carfilzomib may be associated with detrimental cardiac toxicity.

Cardiomyocyte survival depends on a critical balance of protein synthesis, folding, and turnover regulated by the ubiquitin-proteasome system (UPS). Proteasome activity is elevated in the heart compared with other tissues,[6] and pharmacologic proteasome inhibition leads to intracellular accumulation of misfolded proteins and ultimately apoptosis.[7] There is emerging evidence that abnormal protein homeostasis may also be pathogenic in cardiomyopathies and heart failure (HF).[8] Although large clinical trials have not suggested an excess of HF with bortezomib,[9,10] in vitro and in vivo nonhuman animal studies, as well as case reports, have suggested otherwise.[11–16] A pooled analysis of carfilzomib safety data in 526 clinical trial patients reported that HF occurred in 7% of individuals.[17] However, careful description of cardiac events during PI therapy has not been performed in the clinical trials. In the present case series, we describe the clinical presentation and management of 6 patients with RRMM who experienced significant cardiac toxicity associated with carfilzomib treatment. The intent of this report is to outline potential cardiac toxicity when potent PI therapy is used for the treatment of relapsed myeloma and identify optimal management strategies.

Clinical Case Description

Patient 1

A 59-year-old Haitian woman with hypertension was treated for IgG kappa multiple myeloma for ~10 years with the use of combinations of dexamethasone, melphalan,

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thalidomide, lenalidomide, and bortezomib. In February 2013 she started carfilzomib and dexamethasone for RRMM. A baseline 2-dimensional transthoracic echocardiogram (2D-echo) showed normal left ventricular (LV) systolic function (Table 1). Three months later, she presented with New York Heart Association (NYHA) functional class III HF and signs of volume overload on exam, including jugular venous distension, an S3 gallop, and mild peripheral edema. The electrocardiogram (ECG) demonstrated preexisting left ventricular hypertrophy (LVH) and new anterolateral T-wave inversions. Serial troponin levels were undetectable, but N-terminal pro−B-type natriuretic peptide (NT-proBNP) was elevated at 1,837 pg/mL (normal <125 pg/mL). Repeat 2D-echo revealed a dilated left ventricle, severe LV systolic dysfunction (left ventricular ejection fraction [LVEF] 25%), significantly decreased LV tissue Doppler velocities, and moderate-to-severe mitral regurgitation (Fig. 1A). A nuclear vasodilator stress test demonstrated moderate- to large-size areas of ischemia in the anterior and inferior segments. After diuresis, she underwent cardiac catheterization, which revealed normal coronary arteries, normal biventricular filling pressures, and a cardiac index of 3.0 L min^{-1} m^{-2} (normal >2.5 L min^{-1} m^{-2}). Carfilzomib was discontinued, and carvedilol, lisinopril, and furosemide were initiated. Over the next 4 months, her functional status returned to baseline, NT-proBNP normalized (Table 2), and repeated 2D-echo showed improved LVEF to 40%, a decrease in LV size, and only trace mitral regurgitation (Fig. 1B).

Patient 2

A 51-year-old white woman, with no history of cardiovascular disease (CVD), developed kappa light chain myeloma and received induction chemotherapy with dexamethasone, lenalidomide, and bortezomib followed by D-PACE (dexamethasone, cisplatin, doxorubicin [total cumulative dose (TCD) 80 mg/m^2], cyclophosphamide, and etoposide). She was subsequently treated with a consolidative autologous then allogeneic stem cell transplant with maintenance bortezomib. At relapse, she started carfilzomib, pomalidomide, and dexamethasone chemotherapy. Her prechemotherapy 2D-echo was unremarkable (Table 1). Over the next few months she reported intermittent episodes of dyspnea and cough that were temporally associated with chemotherapy infusions. These episodes were treated with a macrolide antibiotic and inhaled bronchodilators with variable symptom improvement. Five months after starting chemotherapy, her 2D-echo showed a decreased LVEF to 47% (by Simpson method[18]), mild diastolic dysfunction, and mild right ventricular dysfunction. Physical exam, cardiac biomarkers, and ECG were unremarkable. Carfilzomib was discontinued, and a repeated 2D-echo 1 week later showed normal LV and right ventricular function. At the repeated measurement, NT-proBNP was mildly elevated at 170 pg/mL. Her symptoms of dyspnea resolved within 1 month, and NT-proBNP normalized (Table 2). Carfilzomib was restarted at a lower dose of 20 mg/m^2, the infusion time was prolonged, and she was given less hydration with infusions, which mitigated her dyspnea.

Patient 3

A 69-year-old Caucasian man with hypertension, hyperlipidemia, nonobstructive coronary artery disease, paroxysmal atrial fibrillation, and stage III chronic kidney disease was diagnosed with IgG kappa multiple myeloma. He was treated with combinations of lenalidomide, bortezomib, cyclophosphamide, and dexamethasone. At relapse he received dexamethasone and carfilzomib. Pretreatment 2D-echo revealed normal LVEF of 55% (Table 1). During chemotherapy, acceleration of hypertension led to escalating doses of losartan and carvedilol. Despite blood pressure control, after 11 months of carfilzomib, he developed NYHA functional class III HF. Although his examination at that time was unremarkable, his NT-proBNP was elevated at 2,988 pg/mL. 2D-Echo showed mildly reduced LVEF of 50% and diastolic dysfunction with newly developed reduced tissue Doppler velocities. Carfilzomib was discontinued, and his dyspnea resolved within 1 month.

Table 1. Baseline Characteristics of Case Series Patients

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (y)	59	51	69	51	67	62
Sex	Female	Female	Male	Male	Female	Male
Body mass index	31.3	28.1	28.6	18.3	22.4	33.0
Traditional cardiovascular risk factors*						
No. of risk factors	1/5	0/5	3/5	0/5	0/5	1/5
Multiple myeloma history						
Year of diagnosis	1999	2010	2010	2012	1992	2011
Prior stem cell transplant	No	Auto & allo	No	No	No	Auto
No. of prior chemotherapy regimens	7	6	3	2	5	3
Prior anthracycline	No	Yes	No	Yes	Yes	Yes
Total cumulative anthracycline dose (mg/m^2)	n/a	80	n/a	80	267	40
Baseline left ventricular ejection fraction (LVEF) assessment						
LVEF (%)	50−55	60−65	55	55−60	58	68
Months before carfilzomib therapy	16	28	42	3	2	2

*Traditional cardiac risk factors were hypertension, hyperlipidemia, smoking, family history and diabetes mellitus.