Cardiovascular events during carfilzomib therapy for relapsed myeloma: practical management aspects from two case studies

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Introduction

Multiple myeloma (MM) is a challenging disease to manage with a number of age- and disease-related comorbidities [1–4]. While renal and bone disease are among the most common comorbidities, patients with MM are also at a higher risk for developing cardiovascular comorbidities due to the interaction of patient-related (e.g. diabetes, diet, lipid levels, weight), disease-related, and treatment-related risk factors [4]. An observational retrospective cohort study (2006–2011) reported a significantly higher prevalence of cardiovascular events in previously treated patients with MM versus those without MM (52% vs 35% p < 0.0001), including elevated rates of arrhythmias, congestive heart failure, cardiomyopathies, and conduction disorders [4]. Therapies for MM, including anthracyclines, corticosteroids, alkylating agents, immunomodulatory agents, proteasome inhibitors, histone deacetylase inhibitors, and stem cell transplantation, have all been associated with cardiovascular adverse events (AEs) [5–9].

Proteasome inhibitors, including bortezomib and carfilzomib, are backbone therapies for MM and have contributed to significant improvements in disease outcomes. Although generally well tolerated, these agents are associated with cardiovascular-specific toxicity, the mechanisms of which are not yet fully elucidated. Several published case reports and literature reviews have described cardiovascular events induced by bortezomib, a first-generation, reversible proteasome inhibitor [10–19]. A recent systematic review and meta-analysis of 12 MM trials by the Cochrane group reported that there is high quality of evidence for increased risk of cardiac disorders with bortezomib treatment (odds ratio: 1.74, 95% confidence interval [CI] 1.17–2.58) with grade 3 and 4 cardiac disorders identified in 70 of 1093 (6.4%) patients in the bortezomib group and 42 of 1098 (3.8%) patients in the control group [20]. These results are consistent with those from another systematic review and meta-analysis, which found a higher incidence of all-grade and high-grade cardiotoxicity with bortezomib among patients with MM than among patients without MM [21].

Carfilzomib is a second-generation, irreversible proteasome inhibitor approved in the United States for use in combination with dexamethasone or lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory MM (1–3 previous lines of therapy) and as a single agent for the treatment of
patients with relapsed or refractory MM (≥1 previous lines). An integrated safety analysis of four single-arm phase two studies using carfilzomib monotherapy in 526 heavily pretreated patients (median four prior regimens) with significant medical history of cardiovascular events at baseline reported any cardiovascular serious events in 7.8% of patients and aggregated heart failure serious AEs in 4.9% of patients, regardless of causality. Hypertension (mainly grade 1–2) was reported in 14.3% of patients, half of whom had a baseline history of hypertension. Additionally, the incidence of treatment discontinuations or dose reductions due to cardiovascular AEs was low [22].

Recently, the ENDEAVOR study, a head-to-head phase three superiority study comparing carfilzomib with dexamethasone (Kd) versus bortezomib with dexamethasone (Vd) in patients with relapsed or refractory MM (1–3 prior lines of therapy), demonstrated a significant progression-free survival (PFS) benefit for Kd versus Vd (median PFS, 18.7 vs 9.4 months, respectively; hazard ratio, 0.53; 1-sided p < 0.0001) [23]. The incidence of cardiac failure serious AEs (grouped term including cardiac failure, ejection fraction decreased, pulmonary edema, acute cardiac failure, congestive cardiac failure, acute pulmonary edema, acute left ventricular [LV] failure, chronic cardiac failure, right ventricular failure, and LV failure) was higher in the Kd arm (3.7%) compared with the Vd arm (1.3%); however, cardiac failure appeared to be clinically manageable as evidenced by the low rates of dose reductions (<1%) or treatment discontinuations (<1%) in the Kd arm [23]. In contrast, a retrospective analysis of 96 consecutive patients treated for MM with bortezomib and carfilzomib at Vanderbilt University from 2011 to 2014 reported a similar cumulative incidence of cardiovascular AEs with these agents [24].

With more patients receiving carfilzomib-based regimens as part of their disease treatment, clinical experiences are accumulating to inform preventative measures and guide management of patients experiencing cardiovascular AEs. Herein, two adapted cases, reflective of clinical practice at the University of Chicago Medicine, of treatment-emergent cardiovascular events in patients receiving the approved regimen of carfilzomib for relapsed and refractory MM are presented and discussed.

Case studies

Case 1

A 68-year-old African-American female was diagnosed with immunoglobulin G (IgG) kappa MM, Durie-Salmon stage IIA, in 2012. The patient’s medical history included hypertension and stage II chronic kidney disease (creatinine level of 1.1 mg/dL). She received two prior lines of MM therapy with combinations of bortezomib, lenalidomide, liposomal doxorubicin (cumulative dose of 150 mg/m²), and dexamethasone. At her second relapse, treatment with Kd was initiated. Prior to starting the treatment, a cardiovascular evaluation was performed and the echocardiogram revealed a normal LV ejection fraction (LVEF) of 65% and grade 2 LV diastolic dysfunction with no evidence of cardiac amyloidosis. Blood pressure was 138/85 mmHg. Chest X-ray (CXR) and lab values were normal.

The patient began receiving carfilzomib 20 mg/m² intravenously (IV) titrated to 56 mg/m² IV on a twice-weekly schedule with dexamethasone 20 mg orally (PO). She also received 500 mL normal saline pre-infusion and 500 mL normal saline post-infusion during cycle 1 and day 1 cycle 2.

Twelve hours after receiving her carfilzomib dose on day 2 of cycle 2, she presented to the emergency room with complaints of acute onset dyspnea, orthopnea, and demonstrated hypoxemia (pulse oximetry: 86% in room air). Physical exam revealed mild tachypnea, with clinical signs of volume overload including weight gain (9 lbs), jugular vein distention, 2+ pitting pedal edema, hepatomegaly, mild tachycardia, and pulmonary rales. Blood pressure was 165/92 mmHg.

Laboratory results

N-terminal pro-B-type natriuretic peptide (NT-proBNP), 1240 pg/mL (normal range <125 pg/mL); blood urea nitrogen (BUN), 28 mg/dL (normal range 7–20 mg/dL); creatinine, 1.3 mg/dL (normal range 0.5–1.1 mg/dL); K+, 4.5 mEq/L (normal range 3.5–5.0 mEq/L); Na+, 136 mEq/L (normal range 135–145 mEq/L); troponin-T, 0.009 ng/mL (normal range <0.01 ng/mL).

ECG

Sinus tachycardia and non-specific ST-T wave changes. No signs of ischemia, myocardial infarction, rhythm, or conduction abnormalities.

CXR

Mild cardiomegaly with LV enlargement with interstitial markings consistent with pulmonary congestion.

Echocardiogram

Decreased LVEF (42%) with mild-moderate global LV hypokinesis, grade 3 LV diastolic dysfunction, mild right atrial enlargement (4.0 cm) with mild mitral regurgitation.

Clinical course and medical management

The diagnostic was acute congestive cardiac failure with fluid overload. The next carfilzomib dose was held. The patient was diuresed with IV Lasix 40 mg twice-daily and placed on IV Nitroglycerin 5 mcg/min up-titrated to 10 mcg/min. Subsequently, she was switched to oral Lasix 40 mg daily and initiated on an angiotensin-converting enzyme inhibitor (Enalapril 2.5 mg twice-daily, subsequently up-titrated to 5 mg twice-daily)
plus a beta-blocker (Carvedilol 3.125 mg twice-daily, up-titrated to 6.25 mg twice-daily). Her symptoms dramatically improved with these interventions. Prior to discharge, she underwent a left heart catheterization and a coronary angiography. Findings demonstrated no significant coronary atherosclerosis, LVEF of 45%, and showed mild to moderate global LV hypokinesis. One week later, her cardiologist recommended she maintain her current cardiac medications. Two weeks later, she had significantly improved without any symptoms or signs of heart failure. Blood pressure was normal (114/74 mmHg) and a repeat echocardiogram 3 weeks after carfilzomib was withhold showed LVEF improved to 62%. Repeat NT-proBNP was normal at 87 pg/mL. Repeat ECG was normal.

The patient restarted carfilzomib at a reduced dose of 45 mg/m² twice-weekly. Pre-infusion hydration was reduced to 250 mL and post-infusion hydration omitted for the remainder of treatment. She received therapy for 16 months before discontinuation due to disease progression.

**Case 2**

A 70-year-old white male was diagnosed with IgA kappa MM, International Staging System stage III in 2013. The patient’s significant medical history included a grade 1 peripheral neuropathy, stage III chronic renal insufficiency, and long-standing history of hypertension, treated and well controlled with amlodipine 5 mg daily and losartan 100 mg daily. He received first-line treatment with bortezomib, cyclophosphamide, and dexamethasone induction, followed by autologous stem cell transplant and bortezomib maintenance.

Two years later, he presented with chest pain, pallor, and dyspnea. Skeletal survey demonstrated diffuse osteoporosis, with a fracture in the 5th and 6th left ribs with no evidence of cord compression revealed by imaging. His laboratory values showed an M spike of 1.87 g/dL, and a bone marrow biopsy revealed 55% plasma cell infiltration. He received Kd as second-line therapy. Prior to initiating this therapy, his physical examination was normal and blood pressure was 140/86 mmHg.

**Labs**

BUN, 27 mg/dL; creatinine, 1.62 mg/dL; estimated glomerular filtration rate, 45 mL/min; K+, 4.4 mEq/L; Na+, 144 mEq/L; Hb, 9.1 g/dL; calcium, 12.6 mg/dL.

**ECG**

Sinus rhythm, moderate voltage criteria for LV hypertrophy (LVH) with nonspecific T wave abnormality.

**CXR**

Prominent left atrium, LV prominence, calcification of the aortic arch, no active pulmonary disease.

**Echocardiogram**

Mild concentric LVH, mild left atrial enlargement (4.2 cm), normal LV chamber size and systolic function, ejection fraction 68%, mild aortic valvular thickening without stenosis, trace to mild aortic regurgitation. No evidence of cardiac amyloidosis was detected.

**Treatment with carfilzomib**

The patient began receiving carfilzomib 20 mg/m² IV and dexamethasone 20 mg PO. His carfilzomib dose was increased to 56 mg/m² on day 8 of cycle 1, on a twice-weekly schedule and infused over 30 min, with pre- and post-dose intravenous hydration (500 mL).

On day 9 of cycle 1, pre-infusion blood pressure was 155/93 mmHg. After completion of carfilzomib administration, the patient’s blood screening showed creatinine had risen to 2.48 mg/dL and BUN to 69 mg/dL. Three days following his last carfilzomib dose (day 12 of cycle 1), the patient was admitted to the hospital with acute renal failure, nausea, vomiting, and dizziness. On admission, his blood pressure was 184/110 mmHg (equal both arms). Physical examination was normal with no signs or symptoms of cardiac decompensation. Laboratory findings were not conclusive to confirm tumor lysis syndrome. The reported symptoms seemed to be primarily related to hypertension and acute renal failure.

**Laboratory results**

Creatinine, 4.22 mg/dL; BUN, 79 mg/dL; K+ 5.4 mg/dL; Na+, 148 mg/dL; Cl, 111 mEq/L (normal range 98–108 mEq/L); CO₂, 17 mEq/L (normal range 22–32 mEq/L).

**Urinalysis**

1+ protein, a few hyaline casts only.

**ECG**

Sinus rhythm, no changes from prior tracing noted.

**CXR**

No active pulmonary disease, no changes from previous film noted.

**Repeat echocardiogram**

Mild LVH, ejection fraction 70%, grade III LV diastolic dysfunction.

**Clinical course and medical management**

The patient received IV hydration with normal saline, followed by a single dose of IV furosemide 40 mg. Carfilzomib doses on days 15 and 16 of cycle 1 were omitted. Renal ultrasound and renal flow scan were unremarkable. His amlodipine dose was increased to 10 mg daily. Losartan was discontinued. Metoprolol Succinate 25 mg daily was initiated and increased to
50 mg daily. He responded well and was discharged with a creatinine level of 1.68 mg/dL and blood pressure of 140/84 mmHg. He resumed treatment on day 1 of cycle 2 at a dose of 45 mg/m² twice-weekly. His hydration protocol included 250 mL normal saline pre-carfilzomib infusion. Post-infusion hydration was omitted. He continues to receive treatment with stable hemodynamics and is currently in complete remission after 11 cycles.

Discussion

Based on standard practices employed at the University of Chicago Medicine, suggestions for practical management and mitigation of cardiovascular events during carfilzomib therapy are summarized in Table 1 and detailed below.

Baseline cardiovascular risk assessment

Patients receiving carfilzomib should be assessed for the presence of cardiovascular risk factors at baseline. Although both patient cases presented with preexisting renal impairment, initial dosage adjustment for carfilzomib may not be necessary based on renal function [25]. Hypertension should be well controlled before initiating treatment with carfilzomib. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or uncontrolled arrhythmias may be at increased cardiovascular risk, and patients aged ≥ 75 years are at an increased risk of cardiac failure [26,27]. Before starting carfilzomib, these patients should have a comprehensive medical assessment and be closely followed for the duration of carfilzomib therapy [27]. A consultation with a cardiologist before initiating carfilzomib treatment should be considered for patients with a history of cardiovascular risk factors, especially if those factors are uncontrolled [28], and for those with an abnormal baseline echocardiogram, especially when cardiac amyloidosis is suspected.

Hydration

Hydration is required prior to carfilzomib dosing in cycle 1, particularly in patients considered at high risk for tumor lysis syndrome or renal toxicity [27]. In general, hydration should be tailored to patient needs, especially for those at risk for cardiac failure [27]. Volume status should be closely monitored [27], and the volume of hydration should be adjusted as clinically appropriate when there is any evidence of weight gain or fluid retention. If fluid retention is confirmed, a short course of diuretics may be considered. In both cases described here, pre-infusion volumes were reduced from 500 to 250 mL, with post-infusion hydration omitted in the first case. Keeping a fluid volume of 250 mL after carfilzomib dosing may also be appropriate as in the second case in order to prevent renal injury.

Cardiovascular monitoring

During treatment, patients should be monitored on an ongoing basis for signs and symptoms of cardiac failure or ischemia, volume overload due to pre- and post-infusion hydration, and abnormal blood pressure. Closely monitor volume status and adapt hydration as clinically appropriate when there is evidence of weight gain or fluid retention. Use a reduced fluid volume of 250 mL for patients with high cardiovascular risk in cycle 1 and evaluate the need for further hydration post carfilzomib infusion and in subsequent cycles. Identify emerging cardiovascular problems by evaluating patients in the first cycle of treatment for early signs and symptoms of fluid retention and dyspnea.

Table 1. Suggestions for proactive monitoring and clinical management of cardiovascular events with carfilzomib.

| Baseline cardiovascular risk assessment | Identify and assess patients at risk for cardiovascular events with consideration for patients with NYHA Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, uncontrolled arrhythmias, and general cardiovascular risk factors (including ≥ 75 years of age, weight, lipid levels, diabetes) |
| Hydration | Administer appropriate hydration prior to carfilzomib dosing in cycle 1 but reevaluate over time to determine individualized hydration needs |
| Cardiovascular monitoring | Monitor for signs and symptoms of cardiac failure or ischemia, volume overload due to pre- and post-infusion hydration, and abnormal blood pressure |
| Intervention | Promptly assess patients presenting with suspected cardiovascular signs or symptoms |
| Education | Educate patients on recognition and prompt reporting of symptoms of cardiovascular decompenensation such as shortness of breath, dizziness, confusion, impaired thinking, coughing or wheezing, swelling of the feet or legs, sudden weight gain, chest pain, fatigue or weakness, nausea or lack of appetite, and increased heartbeat |

BNP, B-type natriuretic peptide; NT, N-terminal; NYHA, New York Heart Association.
infusion hydration, and abnormal blood pressure. In the event of suspected cardiovascular events, patients should undergo a cardiovascular assessment promptly [27]. In the first case, the patient initially reported dyspnea, a symptom that could be related to cardiac failure due to volume overload, which merited additional evaluation and revealed ventricular dysfunction. It is not uncommon for subtle symptoms or signs of fluid retention and dyspnea to be present in early treatment cycles. Patient evaluation with the aim to identify these early signs and symptoms, particularly in the first cycle of treatment, may help identify an emerging problem.

In the second case, the patient had a worsening of his baseline pre-existing hypertension with renal impairment. Blood pressure should be controlled at baseline and routinely monitored in all patients receiving carfilzomib, especially those with a history of hypertension. For patients with uncontrolled blood pressure with renal impairment, it is important to involve a cardiologist or cardio-oncologist (if available) and a nephrologist, for best assessment of the underlying cause of the renal disease and to help establish the best anti-hypertensive intervention in order to reduce the risk of further renal dysfunction.

### Interventions

Primary focus should be on monitoring and early intervention to prevent events for patients with multiple cardiovascular risk factors and for those with poorly controlled or newly uncontrolled cardiovascular risk factors. When grade 3 or 4 cardiovascular events do occur in patients treated with carfilzomib, carfilzomib should be held until recovery, after which consideration to restart therapy with a dose reduction should be based on a benefit-risk analysis [27]. If the patient has not already been under a cardiologist’s care during carfilzomib therapy, consultation is warranted at the time of the event and upon resuming carfilzomib therapy. A multi-disciplinary approach to care involving both the cardiologist and oncologist should be implemented to design and adjust the patient’s treatment plan during therapy. Based upon the cardiologist’s recommendation, additional follow-up studies, including echocardiograms and/or biomarkers such as BNP or NT-pro-BNP, may be performed for subsequent cycles of treatment.

In the two cases presented, the observed events were manageable and did not prevent resumption and continuation of carfilzomib treatment after appropriate patient management. In the first case, the heart failure event was reversible, an observation which is consistent with the findings from a cardiac sub-study of the ENDEAVOR trial. In this sub-study, of the six patients who had a significant decrease in LVEF (Kd, n = 3; Vd, n = 3), all but one in the Kd arm had a resolution to normal LVEF after treatment discontinuation [29]. Notably, this study found limited value in serial screening with echocardiograms for unselected patient populations.

### Patient education

Effective patient education involves a concerted effort by the treating physician, nurses, pharmacists, consulting cardiologist, and others. Early recognition is critical as many of these cardiovascular events have been reported to be resolvable. Patients should be educated to promptly report potential signs or symptoms of cardiovascular AEs to their healthcare providers, especially shortness of breath, headache, dizziness, confusion, impaired thinking, coughing or wheezing, swelling of the feet or legs, sudden weight change, chest pain, fatigue or weakness, nausea or lack of appetite, or increased heartbeat. Patients should also be encouraged to monitor their blood pressure and promptly report any significant increase to their healthcare provider; emergency medical treatment should be sought for a systolic reading ≥150 mmHg or a diastolic reading ≥90 mmHg after repeated measurements.

### Conclusions

Carfilzomib is an effective anti-MM agent with demonstrated efficacy and an overall tolerable safety profile in relapsed or refractory MM [23,30]. It is associated with a low incidence of cardiovascular-related AEs, primarily hypertension and cardiac failure that appear to be manageable as evidenced by low reported rates of treatment discontinuations or dose reductions due to cardiovascular AEs [22,23]. Careful application of practical management and mitigation strategies by the multi-disciplinary treatment team, supported by patient education focused on prompt recognition and reporting of symptoms, are critical to reduce delay in the management of cardiovascular events. Adopting these proactive approaches may help maximize the benefits of carfilzomib treatment, leading to improved outcomes for patients with relapsed MM.

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