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LETTER TO THE EDITOR

Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib

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Carfilzomib is a novel, highly selective, tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, which is the proteolytic core particle within the 26S proteasome, as compared with bortezomib, which reversibly inhibits the 20S proteasome.[1] *In vitro*, carfilzomib has demonstrated antiproliferative and proapoptotic activities in solid and hematologic tumor cells.[2]

In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic and solid tumors.[1] Proteasome inhibition was maintained for $\geqslant 48$ h following the first dose of carfilzomib in each week of dosing.[1] In addition, carfilzomib administration resulted in the inhibition of the low-molecular mass polypeptide two and multicatalytic endopeptidase complex-like one subunit of the immunoproteasome ranging from 26 to 32% and 41 to 49%, respectively, at a dose of 20 mg/m^2 (ref. 3).

In patients, carfilzomib has demonstrated efficacy and tolerability as a single agent and in combination regimens in patients with relapsed and/or refractory multiple myeloma (MM) in phase 2 studies.[4–7] In 2012, based on these results, carfilzomib was approved in the United States for single-agent use in the treatment of patients with MM who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy.[8]

Carfilzomib has the advantage of a favorable safety profile—most notably a low incidence of peripheral neuropathy, which is a common complication with bortezomib-based regimens. However, recent studies and case reports suggest that treatment with proteasome inhibitors may be associated with cardiac events.[9–11] An increasing body of evidence supports the assertion that deficient proteasome activity has a crucial role in the impairment of cardiac function. This effect may be mediated by several mechanisms, the most important of which is putatively the accumulation of unfolded, damaged and undegraded proteins inside myocytes.[11–13] However, limited data are currently available on cardiac adverse events associated with carfilzomib treatment.

Between 2009 and 2012, which was before regulatory approval of carfilzomib in the United States, we treated 130 patients with relapsed and/or refractory MM, either on a phase 2 compassionate carfilzomib protocol ($n = 118$) or as single-patient treatment with an investigational new drug ($n = 12$). We herein report data on those patients who developed a significant cardiovascular adverse event, which was defined as hospitalization owing to a cardiac complication during the first two cycles of therapy with carfilzomib either alone or with dexamethasone. Patients with hospitalization attributed to other causalities, such as infections, or who received concomitant anti-MM drugs were excluded from this analysis. We also describe subsets of patients with baseline echocardiogram findings from before and during carfilzomib treatment and with brain natriuretic peptide (BNP) measurements gathered at baseline and during follow-up.

Patients were orally hydrated with ~30 ml/kg/day of liquid (~6 to 8 cups of liquid per day) starting 48 h before the first dose of carfilzomib. Patients were also given intravenous prehydration with 250 ml of normal saline. Carfilzomib was then coadministered with dexamethasone; dexamethasone was typically given at a dose of 4 mg, but dose escalation was allowed. The addition of other anti-MM agents was permitted after cycle 1 in absence of at least partial response per International Myeloma Working Group criteria. Descriptive statistics were performed on the study cohort and clinical and echocardiographic results. Levels of BNP were evaluated as markers for myocardiac dysfunction or excessive stretching of cardiomyocytes. To compare BNP values from before and during treatment, we used a Wilcoxon signed-rank test with continuity correction, using the software R, v2.15.1.[14] All patients had creatinine levels < 3.0 mg/dl before treatment.

Within our cohort study, we identified 26 patients out of the total 130 patients who met the previously discussed criteria for significant cardiac adverse events (Table 1; Supplementary Table 1). The population was composed of 58% males and 42% females, and the median age was 65 years (range, 47–86 years). The median number of previous lines of treatment was 6 (range, 1–24). Patients had a median of 1 transplantation (range, 1–4 transplantations). Patients received a median of two cycles of carfilzomib (range, 1–24 cycles) and a median dose of 36 mg/m^2 carfilzomib (range, 20–45 mg/m^2). The median total previous lifetime dose of doxorubicin was 120 mg/m^2 (range, 40–280 mg/m^2). More than half of the identified patients ($n = 14$; 54%) had a history of cardiac events, including hypertension ($n = 7$), atrial fibrillation ($n = 5$), supraventricular tachycardia ($n = 4$) and congestive heart failure ($n = 3$).

Although receiving treatment with carfilzomib, 11 patients were hospitalized for congestive heart failure alone and 4 patients were admitted for congestive heart failure with hypotension (Supplementary Table 1). Five patients were admitted for hypotension alone. Hypotension was also reported with arrhythmia in three patients. Pulmonary edema led to the hospitalization of two patients and included one case of severe hypertensive crisis. Arrhythmia alone resulted in hospitalization for one patient. Among the 12 patients who were hospitalized for hypotension, 7 had severely low blood pressure. Among the four patients who were hospitalized for arrhythmia, two had cardiac arrest due to arrhythmias.

The initial carfilzomib clinical trials[4–6] were designed with carfilzomib administered as a 2–10 min infusion, based on preclinical pharmacokinetic and pharmacodynamic data. The recently reported FOCUS trial demonstrated a cardiac event rate of ~4.5% with the carfilzomib 20/27 mg/m^2 schedule,[15] which is consistent with data reported in the carfilzomib registration phase 2 study.[8] Between 2009 and 2010, we observed an increased incidence of cardiac events, leading us to arbitrarily change the infusion time for all carfilzomib dosing levels to 30 min. Interestingly, 20 of the 26 cases of serious cardiac events reported here occurred in patients receiving the 2–10 min infusion and included 15 patients being treated at doses higher than the 27 mg/m^2.

Owing to concerns regarding cardiopulmonary adverse events, we also performed echocardiograms at baseline and as

Table 1. Patient characteristics

Patient	*Doxorubicin dose, mg*	*Transplants,* n	*CFZ cycles,* n	*Maximum CFZ dose, mg/m²*	*Cardiac history*
1	120	4	1	20	None
2	200	2	14	36	HTN
3	160	0	1	27	SVT, HTN
4	80	0	1	27	None
5	200	3	1	27	None
6	160	2	1	20	None
7	280	3	3	36	None
8	80	0	3	27	Atrial fibrillation, SVT, mitral regurgitations
9	40	2	1	27	Atrial fibrillation
10	80	2	2	36	CAD, bradycardia
11	40	1	12	36	CHF
12	120	2	1	45	None
13	40	1	24	45	HTN
14	40	0	2	36	None
15	280	3	2	45	LVH
16	200	1	2	36	Atrial fibrillation
17	240	2	2	36	None
18	120	0	1	27	CHF, HTN
19	160	3	1	20	None
20	120	0	3	45	None
21	280	4	5	36	None
22	80	1	3	36	CHF, SVT, atrial fibrillation
23	80	1	1	36	Atrial fibrillation, HTN
24	—	1	3	27	None
25	120	1	6	45	HTN, SVT
26	80	1	2	27	HTN

Abbreviations: CAD, coronary artery disease; CFZ, carfilzomib; CHF, congestive heart failure; HTN, hypertension; LVH, left ventricular hypertrophy; SVT, supraventricular tachycardia.

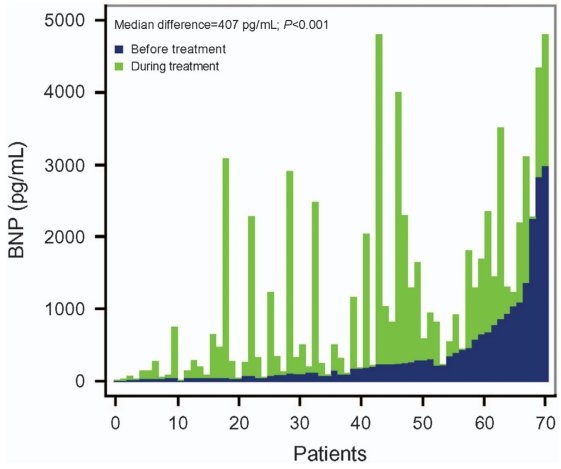

Figure 1. BNP levels. BNP levels were compared before and during treatment with carfilzomib. BNP, brain natriuretic peptide.

symptom-driven follow-ups ($n = 93$). Among these patients, the median ejection fraction as assessed by echocardiogram dropped from 55 to 33%. Sixty-nine of 130 patients also had baseline BNP measurements and measurements during the first cycle of carfilzomib. Among these patients, a median increase of 407 pg/ml BNP from baseline was observed ($P < 0.001$; Figure 1). Elevation of BNP did not appear to correlate with clinical symptoms or hospitalization.

In conclusion, this retrospective, single-center study observed that among patients receiving carfilzomib, a number experienced increased BNP levels, cardiac events confirmed by echocardiogram and/or serious cardiovascular events that required hospitalization. Proteasome inhibition has been shown to impair cardiac function, as evidenced in murine models and clinical studies of bortezomib[9–11]; this, however, is the first clinical study of cardiac dysfunction following carfilzomib treatment. The SWOG 1304 phase 2 study, which compares standard-dose (20/27 mg/m^2) with high-dose (20/56 mg/m^2) carfilzomib, included serial cardiac profiling in its study design to better examine any cardiac events (https://clinicaltrials.gov/ct2/show/NCT01903811); similar end points are included in the ENDEAVOR phase 3 trial that compares carfilzomib–dexamethasone with bortezomib–dexamethasone (http://clinicaltrials.gov/show/NCT01568866).

Most patients in our study who reported a serious cardiovascular event also had a history of cardiac events and exposure to doxorubicin. The authors advise that caution should be exercised when using carfilzomib in patients with cardiac comorbidities and prior therapy with cardiotoxic agents. Increasing the infusion time to 30 min across all dosing levels may lead to a decrease in the occurrence of cardiac events, as we observed in our single-center experience.

CONFLICT OF INTEREST

SZU is a consultant to Celgene, Millennium, Onyx and Sanofi. He has received research funding from ArrayBioPharma, Celgene, Onyx, Janssen and Pharmacyclics and speaking honoraria from Celgene, Millennium and Onyx. BB has received research funding from Celgene and Novartis. He is a consultant to Celgene and Genzyme and has received speaking honoraria from Celgene and Millennium. BB is a coinventor on patents and patent applications related to use of gene expression profiling in cancer medicine. The remaining authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Blood Cancer Journal website (http://www.nature.com/bcj)