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Predictive biomarkers and practical considerations in the management of carfilzomib-associated cardiotoxicity

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Recent advances in the treatment of multiple myeloma have led to significant improvements in overall survival. One contributor to this progress was the 2012 FDA approval of carfilzomib for the treatment of patients with relapsed myeloma. Carfilzomib is a selective proteasome inhibitor that targets and irreversibly binds to the $\beta 5$ subunit of the constitutive 26S proteasome and LMP7 immunoproteasome, resulting in sustained inhibition of chymotrypsin-like activity and apoptosis of myeloma cells. The ASPIRE study showed an unprecedented progression free survival of 26 months in myeloma patients in early relapse

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treated with carfilzomib (20/27mg/m²), lenalidomide and dexamethasone compared to 17.6 months in patients treated with lenalidomide and dexamethasone. However, multiple reports suggested an increased propensity of CV toxicity among patients treated with carfilzomib [1–3]. Analysis of 526 patients on four phase II studies showed that 22% of patients experienced cardiac events, including 9.5% who had a Grade 3 event and 7.2% who experienced cardiac failure, 5.7% of which was Grade 3. Aggregated cardiac failure events included congestive heart failure, pulmonary edema, and decreased ejection fraction [4]. Of note, in the ASPIRE trial, there was no increased risk of CV related deaths among patients treated on the carfilzomib arm versus the control arm[5], while the proportion of nonfatal Grade 3 or higher CV events was 3.8% in the carfilzomib arm versus 1.8% in the control arm. Potential mechanisms of proteasome inhibition related cardiac dysfunction, such as changes in endothelial nitric oxide level, have been proposed and are supported by pre-clinical observations [6,7]. Identifying potential biomarkers of cardiac toxicity has been challenging. In one study, NT-proBNP was found to increase in 72% of patients (n=16) without overt cardiopulmonary symptoms [8]. Another study reported that BNP levels rose by an average of 407 pg/ml after initiation of carfilzomib therapy, however, BNP elevation did not appear to correlate with clinical symptoms [1].

We previously reported on an investigator initiated, single institution Phase II study of high dose carfilzomib (56mg/m²) (NCT01351623). Patients received CFZ at 20mg/m² on Days 1 and 2 of the first cycle of therapy and at 56mg/m² thereafter. Dexamethasone was added for suboptimal response after two cycles of therapy or at progression. None of the patients had prior exposure to carfilzomib. We found that in this heavily pre-treated group 11 of 44 patients (25%) had significant cardiovascular toxicity of any grade. Six of these 11 patients had a clinically significant decrease in left ventricular ejection fraction associated with clinical decompensation [9]. Table 1A. lists characteristics and cardiac risk factors of cases and controls.

To expand our understanding of these observations, we undertook a study to identify potential biomarkers that may predict which patients are at particularly high risk of cardiac toxicity when treated with carfilzomib. On the above mentioned study of high dose carfilzomib ($56\text{mg}/\text{m}^2$) six patients developed treatment-emergent heart failure with a clinically significant drop in LVEF (cases). We had pre-treatment samples on 19 of the patients who did not develop CV toxicity (controls). Using a protein biomarker panel provided by Olink (www.olink.com), we compared 92 cardiac-specific biomarkers in cases and controls, using stored serum obtained at study baseline (i.e. prior to carfilzomib treatment). We used the Proseek Multiplex CVD1 of Olink, a 96-plex immunoassay based on the Proximity Extension Assay technique [10], that allows high throughput detection of protein biomarkers in liquid samples. For each biomarker, a matched pair of antibodies linked to unique oligonucleotides (proximity probes) binds to the respective protein target. Upon binding, the unique proximity probes can hybridize to each other and subsequently be detected and quantified by real-time PCR. Mean biomarker levels were compared using a t-test. False discovery rate was used for multiple comparisons adjustment. The biomarkers in the Proseek Multiplex CVD I assay are associated with cardiac inflammation, remodeling, plaque rupture, hemostasis, and endothelial function, and have been correlated with cardiomyopathy, cardiac remodeling and heart failure in *in vitro* and *in vivo* models

Cardiovascular decompensation was an early event, occurring within the first two weeks of therapy in four of the patients (Patient 1–4). Two patients developed sudden cardiac decompensation after a prolonged period of time on study (Patients 5, 6). Both had a history of cardiomyopathy and borderline left ventricular ejection fraction at the time of study entry. Of these six patients with a documented drop in left ventricular ejection fraction, there was complete recovery of cardiac function in one patient (Patient 3) and at least partial recovery in two others after discontinuation of high dose carfilzomib (Patients 5, 6). The other three patients died within a few weeks of their heart failure event. Despite the small numbers, the two groups (patients with or without clinically significant drop in LVEF) were well-matched. There were no statistically significant differences between the two groups in terms of age, sex, prior autologous or allogeneic stem cell transplant, pre-existing cardiovascular risk factors (hypertension, hyperlipidemia, obesity, diabetes, smoking history) or prior anthracycline exposure. The mean pre-carfilzomib ejection fraction was 57% in the group with CV toxicity versus 60% in the group without (p-value = 0.35). Importantly, baseline echocardiograms were available on all patients and none of the patients with CV toxicity had findings suggestive of cardiac amyloidosis. Post-carfilzomib ejection fraction was not routinely measured in patients who did not have CV toxicity. The mean prior lines of therapy was 5.8 in the group with CV toxicity versus 4.2 in the group without (p-value = 0.12). In an agnostic statistical model we identified eight proteins that were differentially expressed in patients with and without cardiotoxicity (Table 1B). These proteins were significantly altered in univariate analysis; however, as expected, due to the small sample size on multivariate analysis none of the associations remained statistically significant.

Our study has limitations, including the small sample size and confounding factors resulting from our patients having multiply relapsed, refractory disease and therefore multiple lines of prior therapy which itself has been linked to increased incidence of cardiac events. Nevertheless, we observed a trend towards differential baseline expression of some putative cardiac biomarkers in the two groups of patients, suggesting that in a larger cohort, the application of this and similar assays may yield biomarkers that will help identify patients at high risk for carfilzomib-associated cardiotoxicity. Interestingly, the top candidates for putative predictive biomarkers based on our findings include: myoglobin (MB), matrix metalloproteinase-1 (MMP-1), heparin-binding EGF-like growth factor (HB-EGF) and TNF-related apoptosis-inducing ligand (TRAIL). Cardiac myoglobin protects cardiomyocytes via its role as a regulator of nitric oxide bioavailability. Matrix metalloproteinases are a family of proteolytic enzymes responsible, among other functions, for myocardial extracellular protein degradation. Of note, several MMP species, including MMP-1, have been identified within the human myocardium and are thought to be dysregulated in congestive heart failure[11]. HB-EGF is a mitogenic and chemotactic glycoprotein that is essential for maintaining normal cardiac function and is known to play an important role in myocardial remodeling[12]. Therefore, higher expression of these proteins could potentially have a cardio-protective effect. TRAIL, on the other hand, is known to protect the endothelium owing to its anti-inflammatory activity and to the production of nitric oxide by endothelial cells. Therefore, lower levels of TRAIL in patients who did not experience a drop in LVEF is somewhat unexpected. We plan to confirm and expand our findings in a larger prospective

cohort of newly diagnosed myeloma patients who are receiving carfilzomib as induction therapy.

Cardiovascular toxicity has emerged as a rare, but serious side effect of treatment with carfilzomib. In the absence of established biomarkers to better risk stratify patients receiving carfilzomib, we propose a clinical algorithm to minimize the cardiovascular toxicity of carfilzomib in the treatment of patients with multiple myeloma (Table 2). Guidelines for the management of carfilzomib associated cardiotoxicity were previously proposed by our colleagues at other centers [6,13–15]. The guidelines presented here are based on our extensive experience at MSKCC with carfilzomib at standard and at high doses (56mg/m²) and were developed in collaboration with our cardiology colleagues who help us prevent and manage carfilzomib-related cardiac toxicity.

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Baseline characteristics of patients with and without a decrease in LVEF. Adapted from Lendvai et al[9].

Table 1A.

Demographics			Cardiac Risk Factors					Prior Treatments			LVEF Relative to CFZ			Clinical outcome	
AGE/GENDER	RACE	HTN	HLD	OBS	DM	Smoking History	Other	Prior Auto-SCT	Prior Allo-SCT	Prior anthracycline (cumulative dose)	Prior lines of therapy	Pre	Post	Cycles	
Patients with Clinically Significant Decrease in LVEF Following Treatment with Carfilzomib															
1	61F	ASIAN						X	X	LD (120mg/m ²) D (160mg/m ²)	9	64%	22%	0.5	deceased
2	63M	WHITE						X	X	D (40mg/m ²)	6	58%	25%	0.67	deceased
3	70F	BLACK	X				A-fib			LD (40mg/m ²)	6	62%	25–30%	0.67	recovered
4	64F	WHITE		X				X			4	60%	40–45%	0.67	deceased
5	73F	WHITE	X			X	CM	X			7	52%	35%	12	recovered
6	71M	WHITE	X	X		X	CM	X		D (80mg/m ²)	3	49%	19%	12	recovered
Patients without CV event Following Treatment with Carfilzomib															
7	60M	BLACK			X			X			3	57%	N/A	10	N/A
8	64M	BLACK			X			X			6	70%	N/A	0.5	N/A
9	87F	BLACK				X					6	63%	N/A	12	N/A
10	68M	BLACK	X			X		X			4	N/A	N/A	1	N/A
11	64M	WHITE						X			1	65%	N/A	10	N/A
12	72M	BLACK		X		X		X			6	64%	N/A	1	N/A
13	70M	ASIAN	X								3	55%	N/A	15	N/A
14	52M	WHITE			X	X				D (40mg/m ²)	2	64%	N/A	2	N/A
15	56F	BLACK	X								2	55%	N/A	21	N/A
16	76F	WHITE	X		X						4	67%	N/A	21	N/A
17	58F	WHITE		X				X	X	LD (150mg/m ²)	4	60%	N/A	5	N/A
18	50F	BLACK			X			X			2	55%	N/A	3	N/A
19	74F	BLACK	X		X			X		LD (60mg/m ²)	5	55%	N/A	4	N/A
20	45M	WHITE					BOOP; CM	X	X	D (250mg/m ²)	4	55%	N/A	8	N/A
21	69F	BLACK	X		X			X		D (110mg/m ²)	6	51%	N/A	3	N/A
22	85F	WHITE					CAD				6	55%	N/A	21	N/A
23	56F	WHITE			X					D (40mg/m ²)	5	74%	N/A	6	N/A
24	69F	WHITE				X		X			7	55%	N/A	0.5	N/A
25	65F	BLACK	X		X	X		X		D (40mg/m ²)	3	65%	N/A	21	N/A

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Abbreviations: LVEF, left ventricular ejection fraction; CFZ, carfilzomib; BOOP, bronchiolitis obliterans with organizing pneumonia; A-fib, atrial fibrillation; CM, cardiomyopathy; D, doxorubicin; LD, liposomal doxorubicin; HLD, hyperlipidemia; HTN, hypertension; N/A, not applicable; OBS, obesity; DM, diabetes mellitus, Auto-SCT, autologous stem cell transplant, Allo-SCT, allogeneic stem cell transplant, LVEF, left ventricular ejection fraction; M, male; F, female; CAD, coronary artery disease.

Table 1B.

Proteins that were differentially expressed in patients with and without cardiotoxicity are listed based on the p-value associated with the difference with lowest p-value on the top. The top 8 biomarkers are shown.

	CV event	No CV event		
	N=6	N=19		
Proteins Tested	Mean (SD)	Mean(SD)	Unadjusted P-value	Adjusted P-value
TRAIL	8.1 (0.1)	7.5 (0.1)	0.003	0.158
MB	5.2 (0.2)	5.9 (0.2)	0.005	0.158
MMP_1	1.7 (0.2)	2.7 (0.2)	0.006	0.158
HB_EGF	6.9 (0.1)	7.2 (0.1)	0.007	0.158
CD40_L	3.3 (0.3)	4.2 (0.3)	0.024	0.4
PDGF_subunit_B	3.9 (0.3)	5.0 (0.3)	0.027	0.4
HSP_27	2.1 (0.1)	2.7 (0.2)	0.032	0.401
EGF	3.6 (0.4)	4.7 (0.3)	0.041	0.456

Abbreviations: CV, cardiovascular; TRAIL, MB, myoglobin; MMP_1, matrix metalloproteinase 1; HB_EGF, heparin-binding EGF-like growth factor; CD40_L, CD40 ligand; PDGF, platelet derived growth factor; HSP_27, heat shock protein 27; EGF, epidermal growth factor; SD, standard deviation.

Table 2.**MSKCC Guidelines for Minimizing Cardiotoxicity with Carfilzomib****Prior to Initiating Carfilzomib**

Assess patient medical history - hypertension, arrhythmia, congestive heart failure, coronary artery disease, valvular heart disease, renal insufficiency, diabetes, hyperlipidemia

Obtain baseline studies:

- EKG, Transthoracic echocardiogram should be considered in high risk patients (Assess for: Left ventricular systolic dysfunction, Left ventricular diastolic dysfunction (Grade II or higher), Moderate or severe pulmonary hypertension, Moderate or severe valvular disease)
- Brain natriuretic peptide

Consider alternatives to high dose carfilzomib (e.g. standard dose carfilzomib as part of a triplet or alternative proteasome inhibitors) for patients with pre-existing moderate/severe cardiovascular conditions

Manage pre-existing hypertension aggressively

Consider pre-treatment cardiology consult to assess risk and assist with optimization of cardiac comorbidities prior to starting treatment (ie - rate control arrhythmias, optimize cardiovascular conditions and volume status)

During Carfilzomib treatment

Fluid Management

- Minimize IVF. Pre-hydration with 250cc normal saline without post-hydration is generally sufficient (unless specific concern about tumor lysis and high tumor burden).
- Discontinue iv fluids after the first cycle.
- Have patients home monitor their daily weights and report rapid weight gain.
- Treat fluid retention with diuretics and close monitoring of renal function/electrolytes.
- Dexamethasone may be decreased if fluid retention persists.

Give carfilzomib over at least 30 minutes.

- Doses of carfilzomib 36mg/m² or higher should always be given over at least 30 minutes i.v. infusion.
- Doses of 27mg/m² or below can be given over 10 minutes; however, to minimize errors in the chemotherapy suite it may be reasonable to give carfilzomib over 30 minutes regardless of the dose. Establish routine SOPs in chemotherapy infusion centers.

Assess for heart failure development

- Evaluate for signs and symptoms of developing arrhythmias, fluid retention, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, crackles or rales, pitting edema, new murmur development, and profound fatigue/weakness out of proportion to anemia
- Maintain a low threshold for repeat echocardiogram

Assess for ischemia development

- Evaluate for chest pain, chest pressure, cardiovascular symptoms upon exertion, and atypical angina
- Maintain a low threshold for repeat EKG, and draw cardiac biomarkers

Discontinue carfilzomib at the first sign of cardiotoxicity.