COMMENTARY

blood advances

TO THE EDITOR:

Left ventricular diastolic function as a possible predictor of severe carfilzomib-induced cardiovascular events

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Carfilzomib (Cfz) has been associated with severe cardiovascular adverse effects (CVAEs) that usually occur soon after initiation of Cfz.[1-4] Although the incidence is likely higher in the elderly, Asians, and patients with underlying cardiovascular disease,[1,4] these associations have not been fully elucidated. Accordingly, there is no established predictor for severe Cfz-induced CVAEs, making many clinicians hesitant to use Cfz, especially in older patients.

Echocardiography-based assessment of left ventricular (LV) diastolic dysfunction (LVDD) is an emerging, noninvasive tool that is useful for determining the risk of future incidence of cardiovascular events in patients with or without underlying comorbidities.[5-7] We hypothesized that LVDD may possibly cause Cfz-associated cardiotoxicity to progress to symptomatic cardiac dysfunction. Hence, this study aimed to explore the association between severe Cfz-induced CVAEs and underlying LVDD detected by using echocardiography in patients with relapsed/refractory myeloma.

Seventy-two consecutive patients with relapsed/refractory myeloma who were treated with Cfz-based regimens (KRd [Cfz, lenalidomide, and dexamethasone] or Kd [Cfz and dexamethasone]) between August 2016 and September 2018 at our institution were enrolled in this retrospective study. All patients underwent pretreatment echocardiography for evaluating LV diastolic function within 2 weeks before the initiation of Cfz-based chemotherapies. Echocardiography was performed by 2 expert technicians. The likelihood of LVDD in each patient was categorized into 3 groups: negative, intermediate, and definite LVDD. Categorization was performed according to the 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines.[8] Briefly, the following criteria were initially checked: (1) E/e′ (the ratio of early mitral inflow velocity [E] to mitral annular early diastolic velocity [e′]) >14, (2) left atrial volume index >34 mL/m^2 (not to be used in patients with more than mild mitral valve stenosis or regurgitation or those in atrial fibrillation), (3) septal e′ velocity <7 cm/s, and (4) tricuspid regurgitation velocity >2.8 m/s (not to be used in patients with significant pulmonary disease). Then, the following rules were applied to determine the likelihood of LVDD: if $<50\%$ of the measurable parameters met the criteria, LVDD was considered negative; if $>50\%$ of the measurable parameters met the criteria, LVDD was considered definite; and if 50% of the measurable parameters met the criteria, the diagnosis of LVDD was considered intermediate. Cfz administration was based on the ASPIRE or ENDEAVOR studies for patients who received KRd (20/27 mg/m^2) or Kd (20/56 mg/m^2) therapy, respectively.[9,10] Cfz doses were not reduced in any patient before the development of CVAEs. No patient was prehydrated. Adverse events were closely monitored and graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. In this study, severe CVAEs were defined as grade ≥ 3 events, including heart failure, acute coronary syndrome, relative reduction in the LV ejection fraction (LVEF) ($\geq 20\%$ from baseline), QT prolongation (corrected QT ≥ 501 ms), and hypertension (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg, requiring 2 or more additional intensive medications than before) that were observed within 3 months after the initiation of Cfz therapy. Written informed consent was obtained from all participating patients. The study was conducted according to the Declaration of Helsinki and was approved by the review board of our institution. The methods used for statistical analysis are briefly described in the supplemental Methods.

The baseline characteristics of patients are shown in Table 1. The median patient age was 70 years (interquartile range [IQR], 64-76 years). The median number of prior chemotherapy regimens was

Table 1. Baseline clinical characteristics of all patients and comparison between patients with and without severe Cfz-induced CVAEs

Clinical factors	All patients (N = 72)	Severe Cfz-induced CVAEs		P
		Absent (n = 60)	Present (n = 12)	
Background and/or frailty parameters, n (%)				
Age ≥70 y	38 (54.3)	31 (53.4)	7 (58.3)	1.0
Male sex	38 (52.8)	32 (53.3)	6 (50.0)	1.0
ECOG-PS ≥ 3	18 (25.0)	11 (18.3)	7 (58.3)	.008
Cardiovascular risk factors, n (%)				
Smoking	33 (45.8)	26 (43.3)	7 (58.3)	.36
Coronary artery disease	4 (5.6)	2 (3.3)	2 (16.7)	.12
Arrhythmia	5 (6.9)	5 (8.3)	0 (0.0)	.58
Chronic heart failure	6 (8.3)	3 (5.0)	3 (25.0)	.054
Hypertension	35 (48.6)	31 (51.7)	4 (33.3)	.34
Diabetes mellitus	18 (25.0)	15 (25.0)	3 (25.0)	1.0
Hyperlipidemia	17 (24.3)	14 (23.3)	3 (25.0)	1.0
Hyperuricemia	9 (12.5)	8 (13.3)	1 (8.3)	1.0
Stroke	5 (6.9)	4 (6.7)	1 (8.3)	1.0
Medication, n (%)				
ACE inhibitors or ARBs	19 (26.4)	15 (25.0)	4 (33.3)	.72
Calcium channel blockers	24 (33.3)	20 (33.3)	4 (33.3)	1.0
Diuretics	8 (11.1)	5 (8.3)	3 (25.0)	.12
Myeloma-related factors, n (%)				
Heavy chain IgG	36 (50.0)	32 (53.3)	4 (33.3)	.34
AL amyloidosis	4 (5.6)	2 (3.3)	2 (16.7)	.12
Progressive disease	22 (30.6)	16 (26.7)	6 (50.0)	.16
Prior high-dose therapy followed by ASCT	20 (27.8)	17 (28.3)	3 (25.0)	1.0
Prior use of bortezomib	72 (100)	60 (100.0)	12 (100.0)	–
Prior use of immunomodulatory agents	69 (95.8)	57 (95.0)	12 (100.0)	1.0
More than 3 prior treatments	25 (34.7)	17 (28.3)	8 (66.7)	.018
Cfz-containing regimen, KRd/Kd	66 (91.7)/6 (8.3)	55 (91.7)/5 (8.3)	11 (91.7)/1 (8.3)	1.0
Cardiologic parameters				
LV systolic dysfunction, n (%)	3 (4.2)	2 (3.3)	1 (8.3)	.42
Definite LVDD, n (%)	20 (27.8)	11 (18.3)	9 (75.0)	<.001
Median E/e′ (IQR)	11.0 (9.4-15.0)	10.9 (9.2-13.0)	16.35 (9.7-20.6)	.026
Median LAVI, mL/m^2 (IQR)	44.4 (35.8-52.6)	44.4 (35.8-52.6)	45.4 (40.5-52.4)	.52
Median septal e′, cm/s (IQR)	5.5 (4.5-7.1)	5.9 (4.9-7.7)	4.2 (3.4-5.0)	<.001
Median TR velocity, m/s (IQR)	2.4 (2.2-2.6)	2.4 (2.2-2.6)	2.6 (2.3-2.7)	.088

ACE, angiotensin-converting-enzyme; AL amyloidosis, light chain amyloidosis; ARB, angiotensin receptor blocker; ASCT, autologous stem cell transplantation; ECOG-PS, Eastern Cooperative Oncology Group performance status; IgG, immunoglobulin G; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; LAVI, left atrial volume index; TR, tricuspid regurgitation.

3 (IQR, 2-5 regimens). Previous exposure to anthracyclines (eg, doxorubicin) was confirmed in only 1 patient. The median number of cycles of Cfz treatment was 6 (IQR, 3-10 cycles). Pretreatment echocardiography detected LV systolic dysfunction (LVEF, <50%) in 3 patients (4.3%), intermediate LVDD in 25 patients (34.7%), and definite LVDD in 20 patients, (27.8%).

Severe Cfz-induced CVAEs were observed in 12 patients (16.7%). Acute heart failure was the most frequent event observed in 7 patients (3 with reduced LVEF and 4 with preserved LVEF) followed by hypertension (6 patients), LVEF decrease (4 patients), acute coronary syndrome (2 patients), and QT prolongation (2 patients). Three patients died of severe Cfz-induced CVAEs: heart failure (2 patients) and acute myocardial infarction (1 patient). No patient developed severe Cfz-induced CVAEs later than 3 months after the initiation of Cfz.

The associations between the incidence of severe Cfz-induced CVAEs and baseline clinical characteristics are also summarized in Table 1. Severe Cfz-induced CVAEs were significantly more frequent in patients with worse performance status, a higher number of previous treatment regimens, or definite LVDD. Notably, 9 of the

20 patients with definite LVDD developed severe Cfz-induced CVAEs, whereas only 1 with negative LVDD and 2 patients with intermediate LVDD developed severe CVAEs (Figure 1A). Time-to-event curves according to the likelihood of LVDD confirmed that patients with definite LVDD showed a significantly higher cumulative incidence of severe CVAEs than patients with either negative or intermediate LVDD (Figure 1B). Among the 20 patients with definite LVDD, those with severe Cfz-induced CVAEs (compared with those without) had a relatively higher E/e′ (18.0 vs 15.6, respectively; $P = .12$) and significantly lower septal e′ velocity (3.4 vs 4.9 cm/s, respectively; $P = .037$), indicating that they carried more severe LVDD. Because the outcome of interest was rare, a multivariable analysis was not feasible. However, the presence of definite LVDD had the highest odds ratio for severe Cfz-induced CVAEs (odds ratio, 13.4; 95% confidence interval, 3.10-57.6) (Table 2).

Here, we demonstrated that baseline LVDD was associated with the incidence of severe Cfz-induced CVAEs. Our results may harmonize with those of a recent study, which suggested that Cfz-induced CVAEs might be associated with early myocardial diastolic dysfunction after Cfz administration[2]; baseline LVDD could reasonably amplify these early in vivo cardiovascular effects.

As previously suggested, our relatively older Asian cohort presented with a high incidence of severe CVAEs.[4] However, age per se was not predictive in our cohort of heavily pretreated patients. It is possible that the influence of background factors on cardiac tolerability against Cfz might have been canceled by the cumulative cardiotoxicity of antimyeloma agents and subsequent worsening of LVDD.[11] Therefore, the direct evaluations of diastolic functions might be more informative than conventional cardiovascular risk factors.

LV systolic dysfunction was rare and not predictive for Cfz-induced CVAEs either. It is thought that a later change is generally preceded by LVDD.[7] Therefore, LVDD may more sensitively reflect a decrease in cardiac reserve, thereby facilitating the determination of an individual's cardiac vulnerability to Cfz-associated cardiotoxicity. For instance, treatment modifications (ie, dose reduction or longer infusion time)[1] and strengthening of monitoring inspections could be beneficial for some LVDD patients. Moreover, clinical trials for prophylaxis of Cfz-induced CVAEs using potential medications (eg, metformin)[12] according to the likelihood of LVDD may yield positive results in the future.

Table 2. Univariable analysis of factors that may predict severe Cfz-induced CVAEs

	Univariate analysis	
Variables	**Odds ratio (95% CI)**	***P***
Background and/or frailty parameters		
Age ≥70 y	1.20 (0.35-4.30)	.75
Male sex	1.14 (0.33-3.95)	.83
ECOG-PS ≥3	5.98 (1.59-22.4)	.008
Cardiovascular risk factors		
Smoking	1.83 (0.52-6.43)	.34
Coronary artery disease	5.80 (0.73-46.0)	.096
Chronic heart failure	6.33 (1.10-36.4)	.038
Hypertension	0.46 (0.12-1.72)	.25
Diabetes mellitus	1.00 (0.23-4.18)	1.0
Hyperlipidemia	1.10 (0.26-4.61)	.90
Hyperuricemia	0.59 (0.06-5.22)	.63
Stroke	1.27 (0.13-12.5)	.83
Myeloma-related factors		
AL amyloidosis	5.80 (0.73-46.0)	.096
Progressive disease	2.75 (0.77-9.77)	.12
Prior high-dose therapy followed by ASCT	0.84 (0.20-3.50)	.81
More than 3 prior treatments	5.06 (1.34-19.0)	.016
Cfz-containing regimen, KRd/Kd	1.00 (0.11-9.42)	1.0
Cardiologic parameters		
LV systolic dysfunction	2.64 (0.22-31.7)	.44
Definite LVDD	13.4 (3.10-57.6)	<.001

CI, confidence interval.

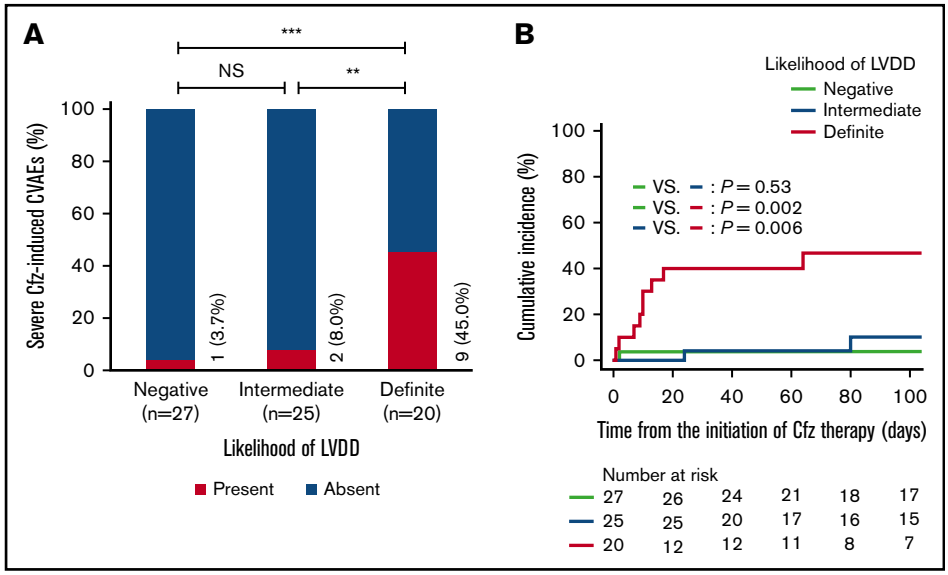

Figure 1. The incidence of severe Cfz-induced CVAEs according to the likelihood of LVDD detected using echocardiography. (A) Among patients with negative LVDD, 1 developed unstable angina that was successfully treated with percutaneous coronary intervention. Among patients with intermediate LVDD, 2 developed severe Cfz-induced CVAEs (acute heart failure and LVEF decrease), which improved immediately after the discontinuation of Cfz. (B) Time-to-event curves for severe Cfz-induced CVAEs according to the likelihood of LVDD: patients with negative, intermediate, and definite LVDD. $^{**}P < .01$; $^{***}P < .001$. NS, not significant.

Although this study has several limitations, including its retrospective nature, heterogeneous treatment, the presence of possible confounding factors, and small sample size, it proposes a promising approach for predicting severe Cfz-induced CVAEs. This has been eagerly sought in real-life clinical settings.

In conclusion, our findings provide what is, to the best of our knowledge, the first evidence that LVDD detected using echocardiography is associated with the incidence of severe Cfz-induced CVAEs, suggesting that LVDD could serve as a robust predictor of these. Assessment of LV diastolic function before treatment may thus have the potential to establish risk-adapted modifications of Cfz-based chemotherapy, monitoring, and prophylaxis strategies.

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