A longitudinal study of right ventricular function of patients with multiple myeloma treated with carfilzomib

Received: 9 July 2024
Accepted: 6 Oct 2024

To the Editor:

We have read with great attention the original article by Grynblat *et al*. [1] showing that patients treated with proteasome inhibitors, especially carfilzomib, should be closely monitored due to an increased risk of pulmonary arterial hypertension (PAH). We commend the authors for carrying out a comprehensive clinical and haemodynamic evaluation of patients of the French pulmonary hypertension (PH) registry with PAH who were exposed to a proteasome inhibitor. The addition of two complementary methods, disproportionality analysis and network meta-analysis, strengthens the causality of these drugs in the development of PAH. Cardiovascular effects of proteasome inhibitors have been documented, with potential impairment of left ventricular (LV) function [2]. A decrease in left ventricular ejection fraction (LVEF) was observed in patients treated with carfilzomib for multiple myeloma [3, 4]. Transthoracic echocardiography (TTE) is therefore recommended prior to initiation of carfilzomib therapy, and during treatment in symptomatic patients [5, 6]. In the most recent recommendations for the diagnosis and treatment of PH [7], carfilzomib is mentioned as having a possible association with the development of PH. In light of the findings of Grynblat *et al*. [1], this assertion holds even greater weight. However, to our knowledge, the right ventricular (RV) function of these patients treated with carfilzomib has never been evaluated in a clinical study.

To evaluate the impact of carfilzomib on RV function, we conducted a longitudinal study in Nancy University Hospital, France. All consecutive patients treated with carfilzomib for multiple myeloma were included. In accordance with French legislation, non-opposition of the patient or their legal representative for use of the data was systematically sought. The study was approved by the ethical committee of Nancy Teaching Hospital (number CO-444). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as most recently amended.

They all had a comprehensive TTE evaluation (including RV-focused apical four-chamber view) before treatment initiation of carfilzomib and during the follow-up. Carfilzomib was mostly prescribed for patients with refractory or relapsed multiple myeloma. All quantitative variables are shown as the median and interquartile range (IQR) (25–75th percentile) and qualitative variables as number and frequency. Comparisons were performed with the Wilcoxon matched pairs signed rank test. Results with p-values <0.05 were considered statistically significant. All the calculation and statistical analyses were performed using GraphPad Prism software version 10.0 for Mac (GraphPad Software, San Diego, CA, USA).

36 patients underwent two TTEs: the first one before initiating carfilzomib and the other at a mean±SD follow-up of 10.2±5.9 months after treatment initiation. The study included a population with a median (IQR) age of 65.5 (58.8–71.5) years, women comprised 53% of the participants and the median body mass index was 24.5 (23.0–26.0) $kg \cdot m^{-2}$. The main comorbidity was systemic hypertension (n=18, 50%). The diagnosis of multiple myeloma was made 2.8 (0.3–5.8) years before the first TTE. 28 (77.8%) patients received at least one line of chemotherapy before carfilzomib and 14 (38.9%) received two or more lines. 28 (77.8%) patients had a performance status of 0 or 1 at inclusion. The International Staging System score (a prognostic score) was I for 12 (33.3%) patients and II for nine (25%) patients.

Shareable abstract (@ERSpublications)
A particular focus on right ventricular function should be suggested in patients during treatment with carfilzomib due to potential RV side-effects. TAPSE follow-up appears to be an interesting tool for close monitoring of these patients. https://bit.ly/4dTedb9

Cite this article as: Basin S, Cezar M, Fraix A, *et al*. A longitudinal study of right ventricular function of patients with multiple myeloma treated with carfilzomib. *ERJ Open Res* 2025; 11: 00861-2024 [DOI: 10.1183/23120541.00861-2024].

Left heart parameters are shown in (table 1). Baseline TTE revealed a median LVEF of 60% (58.8–63.5%) without dilatation of the left cavities (LV end-diastolic diameter of 48.5 (44.0–53.8) mm and left atrial surface of 18.0 (14.2–20.4) cm^2). LVEF was similar during follow-up (59.5% (56.8–61.0%), p=0.12) as well as LV end-diastolic diameter (48.0 (44.0–53.0) mm, p=0.81) and left atrial surface (16.5 (14.0–21.0) cm^2, p=0.32). Diastolic function was evaluated by E/A and E/e′ ratio (respectively 0.84 (0.73–1.02) and 6.88 (5.54–8.93)) without significant evolution after treatment.

Right heart parameters are shown in (table 1). Systolic peak tricuspid regurgitation velocity (peak TRV) was 2.4 (2.2–2.6) $m{\cdot}s^{-1}$ and was not different during follow-up (2.4 (2.3–2.5) $m{\cdot}s^{-1}$, p=0.97). Only two (5.6%) patients had a baseline peak TRV >2.8 $m{\cdot}s^{-1}$. RV outflow tract acceleration time was low before carfilzomib without significant change after the beginning of treatment (105.0 (90.0–125.0) *versus* 102.0 (90.8–120.0) ms, p=0.10). Concerning RV function, baseline tricuspid annular plane systolic excursion (TAPSE) was 24.5 (21.1–27.3) mm and significantly decreased during carfilzomib treatment (21.5 (19.9–25.3), p=0.03). Moreover, 39% of patients had a decreased in TAPSE ⩾3 mm, 50.0% had a change between −3 and 3 mm while only 11.5% had an increase ⩾3 mm. RV fractional area change was within normal range but tended to decrease during treatment. However, lateral tricuspid annulus peak systolic velocity (S′ wave) was similar before and during follow-up (13.0 (11.8–15.0) *versus* 13.0 (11.0–15.0) $cm{\cdot}s^{-1}$, p=0.81). Right atrial surface was measured at 15.0 (11.7–17.5) cm^2 and was not different during follow-up (14.5 (11.7–18.7) cm^2, p=0.74) as well as RV/LV ratio. Cardiac index was in the normal range (>2.5 $L{\cdot}min^{-1}{\cdot}m^{-2}$) in approximately two thirds of the population with no significant change at both TTEs. In patients without kidney failure (n=31, 86.1%), median N-terminal pro-brain natriuretic peptide was stable before and during follow-up (147.5 (53.3–258.5) *versus* 186.0 (83.0–283.0) $pg{\cdot}mL^{-1}$, p=0.38).

These data suggest that baseline LV and RV structure and function were normal despite the patients having multiple comorbidities. However, during treatment with carfilzomib, a significant decrease in TAPSE was observed in many patients. No major medical events that could have altered RV function occurred between baseline and follow-up (*i.e.* pulmonary embolism or acute respiratory failure). Despite the absence of increased RV afterload, patients experienced a decrease in RV systolic function as measured by TAPSE, suggesting potential carfilzomib-induced RV toxicity. Indeed, a simple estimate of RV–pulmonary artery coupling (TAPSE/systolic pulmonary artery pressure ratio) was not altered during treatment. Even though the RV outflow tract acceleration time was low (<150 ms) in half of the patients, there was no worsening after treatment.

TABLE 1 Left and right heart parameters before carfilzomib and during follow-up

	Before carfilzomib	During follow-up	p-value
Left heart parameters			
LVEF, %	60 (58.8–63.5)	59.5 (56.8–61.0)	0.12
End-diastolic diameter, mm	48.5 (44.0–53.8)	48.0 (44.0–53.0)	0.81
Atrial surface, cm^2	18.0 (14.2–20.4)	16.5 (14.0–21.0)	0.32
Cardiac index, $L{\cdot}min^{-1}{\cdot}m^{-2}$	2.90 (2.40–3.23)	2.78 (2.47–3.21)	0.37
E/A ratio	0.84 (0.73–1.02)	0.82 (0.62–0.90)	0.15
E/e′ ratio	6.88 (5.54–8.93)	6.92 (5.18–8.58)	0.13
Right heart parameters			
Peak TRV, $m{\cdot}s^{-1}$	2.4 (2.2–2.6)	2.4 (2.3–2.5)	0.97
TAPSE, mm	24.5 (21.1–27.3)	21.5 (19.9–25.3)	0.03
S′ wave, $cm{\cdot}s^{-1}$	13.0 (11.8–15.0)	13.0 (11.0–15.0)	0.81
TAPSE/sPAP, $mm{\cdot}mmHg^{-1}$	0.94 (0.79–1.11)	0.88 (0.80–1.10)	0.17
Atrial surface, cm^2	15.0 (11.7–17.5)	14.5 (11.7–18.7)	0.74
Fractional area change, %	47.5 (45.0–54.3)	46.0 (42.0–51.0)	0.08
RV/LV ratio	0.70 (0.58–0.76)	0.68 (0.61–0.74)	0.33
RVOT AT, ms	105.0 (90.0–125.0)	102.0 (90.8–120.0)	0.10
Biologics			
NT-pro-BNP[#], $pg{\cdot}mL^{-1}$	147.5 (53.3–258.5)	186.0 (83.0–283.0)	0.38

Data are presented as median (interquartile range) unless otherwise stated. LVEF: left ventricular ejection fraction; TRV: tricuspid regurgitant velocity; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary artery pressure; RV: right ventricle; LV: left ventricle; RVOT AT: right ventricle outflow tract acceleration time; NT-pro-BNP: N-terminal pro-brain natriuretic peptide. [#]: normal range <125 $pg{\cdot}mL^{-1}$.

It is currently accepted that carfilzomib has cardiovascular toxicity that could be mediated by its endothelial effect on cardiomyocytes [8]. In this study, median LVEF was in the normal range and was unchanged after a median exposition of 10 months of carfilzomib. However, previous studies have reported potential cardiotoxic effects of carfilzomib. One study documented a ⩾20% reversible drop in LVEF in 12% of patients [9], while another observed a non-significant decrease in LVEF alongside significant changes in LV global longitudinal strain [3]. However, diastolic dysfunction was observed at baseline in patients without worsening after carfilzomib. Limitations of this study include the relatively small sample size and potentially short treatment duration, which might have masked potential LVEF decline.

The main result of the present study is a statistically significant decrease in TAPSE: 14 (39%) patients (95% CI 23–54%) had a drop of ⩾3 mm in TAPSE. This suggests a relatively common alteration of RV function since it is accepted that TAPSE is a very reproducible measurement with confidence interval of agreement <3 mm [10]. However, the clinical impact of this reduction in TAPSE is unclear. These patients are likely to require close respiratory and cardiological monitoring.

In conclusion, in our study, RV function was normal at baseline among multiple myeloma patients. However, a significant proportion of patients had a decrease in TAPSE after carfilzomib initiation. Thus, a particular focus on RV function should probably be suggested in these patients during treatment with carfilzomib due to potential RV side-effects. TTE, and especially TAPSE follow-up, appears to be an interesting tool for close monitoring of these patients.

Sarah Basin[1], Mathilde Cezar[1], Antoine Fraix[2], Nathalie Pace[2], Laura Filippetti[2], Samantha Schulmann[3], Christine Selton-Suty[2], Olivier Huttin[2], François Chabot[1,4], Ari Chaouat[1,4] and Simon Valentin[1,5]

[1]Centre Hospitalier Universitaire de Nancy, Département de Pneumologie, Vandœuvre-lès-Nancy, France. [2]Service de Cardiologie, Institut Lorrain du Cœur et des Vaisseaux, Centre Hospitalier Universitaire de Nancy, Nancy, France. [3]Centre Hospitalier Universitaire de Nancy, Hématologie, Nancy. [4]INSERM, UMR_S 1116, Université de Lorraine, Nancy, France. [5]INSERM U1254, IADI, Université de Lorraine, Nancy, France.

Corresponding author: Simon Valentin (s.valentin@chru-nancy.fr)

Provenance: Submitted article, peer reviewed.

The study is registered at www.clinicaltrials.gov with identifier number NCT06568952.

Ethics statement: The study was approved by the ethical committee of Nancy Teaching Hospital (number CO-444). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as most recently amended.

Conflict of interest: S. Basin, M. Cezar, A. Fraix, N. Pace, L. Filippetti, S. Schulmann, C. Selton-Suty, O. Huttin and F. Chabot declare no conflicts of interest. A. Chaouat declares invitations to congress from AstraZeneca, Asten Santé, MSD, J&J and Chiesi; an advisory board with Chiesi; and fees from AstraZeneca and MSD. S. Valentin declares invitation to congress from MSD.

References

1 Grynblat J, Khouri C, Hlavaty A, *et al.* Characteristics and outcomes of patients developing pulmonary hypertension associated with proteasome inhibitors. *Eur Respir J* 2024; 63: 2302158.
2 Georgiopoulos G, Makris N, Laina A, *et al.* Cardiovascular toxicity of proteasome inhibitors: underlying mechanisms and management strategies. *JACC CardioOncology* 2023; 5: 1–21.
3 Mingrone G, Astarita A, Airale L, *et al.* Effects of carfilzomib therapy on left ventricular function in multiple myeloma patients. *Front Cardiovasc Med* 2021; 8: 645678.
4 Russell SD, Lyon A, Lenihan DJ, *et al.* Serial echocardiographic assessment of patients (Pts) with relapsed multiple myeloma (RMM) receiving carfilzomib and dexamethasone (Kd) Vs bortezomib and dexamethasone (Vd): a substudy of the phase 3 endeavor trial (NCT01568866). *Blood* 2015; 126: 4250.
5 Curigliano G, Lenihan D, Fradley M, *et al.* Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol Off J Eur Soc Med Oncol* 2020; 31: 171–190.

6 Lyon AR, López-Fernández T, Couch LS, *et al.* ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 2022; 2022: 4229–4361.
7 Humbert M, Kovacs G, Hoeper MM, *et al.* ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2022; 2023: 2200879.
8 Gavazzoni M, Lombardi CM, Vizzardi E, *et al.* Irreversible proteasome inhibition with carfilzomib as first line therapy in patients with newly diagnosed multiple myeloma: early *in vivo* cardiovascular effects. *Eur J Pharmacol* 2018; 838: 85–90.
9 Dimopoulos MA, Roussou M, Gavriatopoulou M, *et al.* Cardiac and renal complications of carfilzomib in patients with multiple myeloma. *Blood Adv* 2017; 1: 449–454.
10 Karatasakis GT, Karagounis LA, Kalyvas PA, *et al.* Prognostic significance of echocardiographically estimated right ventricular shortening in advanced heart failure. *Am J Cardiol* 1998; 82: 329–334.