Modified carfilzomib dosing is associated with improved treatment responses and longer time on treatment in patients with multiple myeloma

Carfilzomib is a second-generation proteasome inhibitor (PI) approved for the treatment of patients with multiple myeloma (MM). Compared to bortezomib and ixazomib, carfilzomib is associated with higher rates of cardiovascular (CV) adverse events (AE).[1] For example, compared to bortezomib-lenalidomide-dexamethasone (VRd) in the newly diagnosed setting, carfilzomib-lenalidomide-dexamethasone (KRd) was associated with three-times more frequent grade ≥3 cardiac disorders (2.1% *vs.* 6.3%, respectively).[2] Similarly, in the relapsed/refractory setting, grade ≥3 cardiac failure rates for patients treated with bortezomib-dexamethasone (Vd) were 1.8% compared to 4.8% in the Kd arm.[3]

One proposed mechanism of carfilzomib-induced cardiotoxicity appears to be through the inhibition of the AMPKα/mTORC1 pathways via increased PP2A activity, with downstream effects of autophagy downregulation in the myocardium.[4] Higher doses of carfilzomib may result in decreased phosphorylation and activation of the PI3K/AKT/eNOS pathway. Multi-omics analyses have also revealed the importance of the glutamate-dependent acid resistance and pyruvate oxidation pathways in patients that experience CV AE.[5] Finally, clinicians inexperienced with carfilzomib may overhydrate patients with normal saline during drug administration that may contribute to CV toxicity.[6]

We conducted a retrospective analysis to assess incidence of CV AE and outcomes of MM patients treated with carfilzomib using a step-up titration dosing (TD) schedule (e.g., step-wise C1D1 20 mg/m^2, C1D8 27 mg/m^2, C1D15 36 mg/m^2, for goal C2D1 70 mg/m^2 onwards) compared to standard dosing (SD) schedule (e.g., C1D1 20mg/m^2 and C1D8 70mg/m^2 onwards) (other examples of dosing schedules are given in the *Online Supplementary Table S1*). We included adult MM patients treated with more than one cycle of carfilzomib at the Ohio State University (OSU) from January 1, 2013 to September 1, 2019. Patients were excluded if they were not carfilzomib-naïve when receiving treatment institutionally, received a single dose of carfilzomib while inpatient with no intent to continue treatment outpatient, or had a treatment plan entered but never received it. Patient demographics, disease and carfilzomib-related characteristics, CV AE, and follow-up information were collected.

Of the 166 patient charts analyzed, 36 were treated using a TD method and 130 were treated using a SD method. Baseline demographics and disease characteristics are described in the *Online Supplementary Table S2*. The median age at diagnosis of myeloma was 60 years old and the majority of patients were Caucasian males. There were no differences in International Staging System (ISS) and Revised-ISS scores between the two groups. There was similar use of autologous hematopoietic cell transplantation, immunomodulatory drugs (IMiD), anti-CD38 monoclonal antibodies, and cyclophosphamide prior to the use of carfilzomib in both groups. There was a slight difference in baseline renal function (median creatinine clearance [CrCl]: SD 76 mL/min *vs.* TD 94mL/min; *P*=0.01) and prior PI use (SD 95.4% *vs.* TD 86.1%; *P*=0.048) between the two groups. Pre-existing CV risk factors were similar between the two groups; there was similar incidence of pre-existing hypertension (HTN; n=104; SD 61.5% *vs.* TD 66.7%), congestive heart failure (CHF; n=11; SD 6.9% *vs.* TD 5.6%), ischemic heart disease (IHD; n=17; SD 11.5% *vs.* TD 5.6%), arrhythmia (n=27; SD 16.2% *vs.* 16.7%), prior anthracycline exposure (n=16; SD 10.0% *vs.* TD 8.3%), and prior chest radiation (n=18; SD 10.0% *vs.* TD 13.9%).

The majority of patients were treated with carfilzomib in the relapsed/refractory setting (SD 98.5% *vs.* TD 91.7%) compared to the newly-diagnosed setting (SD 1.5% *vs.* TD 8.3%). Most patients were treated with carfilzomib using the twice-weekly dosing schedule (SD 83.1% *vs.* TD 75.0%) compared to once-weekly dosing schedule (SD 16.9% *vs.* TD 25.0%). Carfilzomib was most often combined with an IMiD (n=84, 50.6%; SD 70% *vs.* TD 30%), with cyclophosphamide in 18.1% (n=30; SD 97% *vs.* TD 3%), and with another agent in 1.8% of patients (n=3; SD 67% *vs.* TD 33%). Carfilzomib and dexamethasone doublet was used in 29.5% of patients (n=49; SD 82% *vs.* TD 18%). Additional carfilzomib therapy details can be found in the *Online Supplementary Table S3*. The provider treatment selection reasoning was not explicitly documented in the charts reviewed. Furthermore, information regarding fluid volumes infused during carfilzomib treatment were not able to be collected.

There were no differences in incidence of HTN (n=137; SD 83.1% *vs.* TD 80.6%), CHF (n=17; SD 10.8% *vs.* TD 8.3%), IHD (n=20; SD 13.1% *vs.* 8.3%), arrythmias (n=28; SD 16.9% *vs.* 16.7%), or pulmonary HTN (n=5; SD 3.1% *vs.* TD 2.8%) between the different dosing schedules. Approximately 80% of patients had documentation of HTN while on carfilzomib, however, the onset of HTN was delayed in the TD

group compared to the SD group. In the SD group, HTN developed earlier within the first five cycles (SD 70.3% *vs.* TD 46.7%) compared to sixth cycle and beyond in the TD group (SD 1.8% *vs.* TD 6.7%; *P*=0.02). Consistent with published reports, patients with pre-existing CV risk factors were more likely to develop CV toxicities associated with carfilzomib use (HTN, *P*=0.005; CHF, *P*=0.04; IHD, *P*=0.004; arrhythmia, *P*<0.001). Furthermore, there was a lower incidence of dyspnea (not included in the definition of CV AE) in the TD group compared to SD group (SD 36.2% *vs.* TD 16.7%; *P*=0.03). There was no statistical difference in CV AE being the cause for treatment discontinuation between the two groups.

The median number of cycles administered to titrated patients was seven (range, 2-56) compared to three (range, 1-44) for standard patients (*P*<0.001) (*Online Supplementary Table S3*). The cumulative carfilzomib dose administered to patients with TD was 1,669 mg compared to 593 mg in the SD group (*P*<0.001). There was a trend towards higher objective response rate in TD group compared to the SD group (SD 42.8% *vs.* TD 63.9%; *P*=0.09). Five-year OS was improved in patients treated with TD than with SD (SD 17.5% *vs.* TD 43.8%; *P*<0.001; Figure 1). In the univariable analysis on association between patient treatment characteristics and overall survival (OS), TD (hazard ratio [HR] =0.43; 95% confidence interval [CI]: 0.27-0.70; *P*=0.001) and carfilzomib being part of triplet therapy (HR=0.64; 95% CI: 0.44-0.93; *P*=0.019) were associated with improved OS (Table 1). In multivariable analysis controlling for age, disease status, and pre-existing CV risk, TD (HR=0.46; 95% CI: 0.28-0.74; *P*=0.002) and carfilzomib being part triplet therapy (HR=0.59; 95% CI: 0.41-0.86; *P*=0.007) retained significance for association with improved OS.

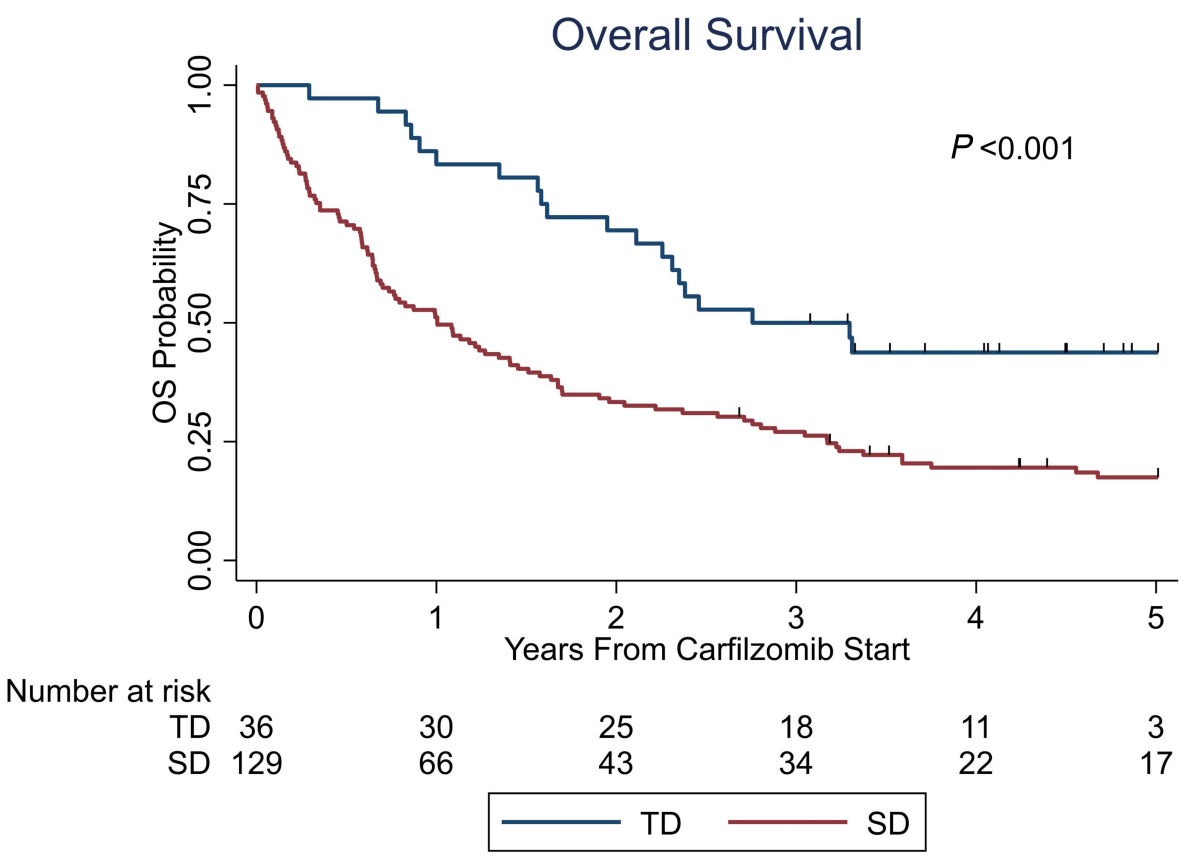

Figure 1. 5-year overall survival for multiple myeloma patients treated with carfilzomib. OS: overall survival; TD: titration dosing; SD: standard dosing.

Table 1. Univariable and multivariable analyses of factors associated with overall survival.

Factor	Univariable analysis				Factor	Multivariable analysis			
	HR	95% CI		*P*		HR	95% CI		*P*
Titration *vs.* standard	0.43	0.27	0.70	0.001	Titration *vs.* standard	0.46	0.28	0.74	0.002
Age at diagnosis	1.03	1.01	1.05	0.007	Age at diagnosis	1.03	1.01	1.05	0.008
CrCl at start of therapy	1	0.99	1	0.112	-	-	-	-	-
Multiple *vs.* doublet	0.64	0.44	0.93	0.019	Multiple *vs.* doublet	0.59	0.41	0.86	0.007
Relapsed *vs.* frontline	5.75	0.8	41.2	0.081	Relapsed *vs.* frontline	4.3	0.59	31.25	0.15
Prior PI	1.47	0.69	3.16	0.321	-	-	-	-	-
Pre-existing CV risk	1.42	0.94	2.15	0.093	Pre-existing CV risk	1.3	0.86	1.97	0.22

Factors with *P*<0.10 in the univariable model were included in the multivariable model. HR: hazard ratio; CI: confidence interval; CrCl: creatinin clearance; PI: proteasome inhibitor; CV: cardiovascular risk.

Overall, a simple modification of carfilzomib titration dosing resulted in significantly reduced perception of dyspnea with carfilzomib-based therapy and did not compromise efficacy. The incidence of HTN while on carfilzomib therapy was similar between the two groups although the patients treated with TD developed HTN later. However, an improvement in OS was observed in the TD group due to prolonged duration of therapy, including both the cumulative carfilzomib dose administered and cycles of therapy. As there were no differences in CV AE being the cause of treatment discontinuation between the two dosing schedules, future pharmacokinetic studies may identify the mechanism by which carfilzomib TD results in improved clinical outcomes compared to SD. Limitations of the study include its retrospective design, different carfilzomib target doses in the various treatment combinations, and choice of dosing schedule potentially being influenced by the aggressiveness of disease. In a large analysis of carfilzomib treated patients, titration dosing allows more time on therapy, similar efficacy, and improved 5-year OS.

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Contributions

KD and AMK collected data. QZ and AMK performed data analysis. AMK, QZ, and AR drafted the manuscript. All authors reviewed the manuscript.

Data-sharing statement

Data are available from the corresponding author upon reasonable request.

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