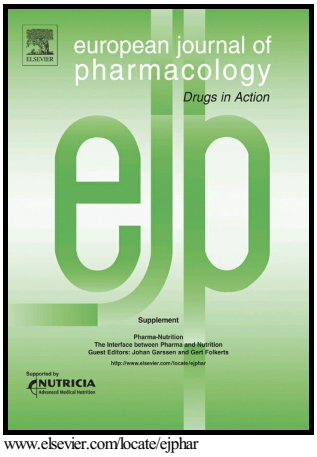
Author's Accepted Manuscript



www.elsevier.com/locate/ejphar

Mechanism of cardiovascular toxicity by proteasome inhibitors: new paradigm derived from clinical and pre-clinical evidence

Mara Gavazzoni, Enrico Vizzardi, Elio Gorga, Ivano Bonadei, Laura Rossi, Angelo Belotti, Giuseppe Rossi, Rossella Ribolla, Marco Metra, Riccardo Raddino

PII: S0014-2999(18)30176-6
DOI: https://doi.org/10.1016/j.ejphar.2018.03.022
Reference: EJP71726

To appear in: *European Journal of Pharmacology*

Received date: 29 December 2017
Revised date: 11 March 2018
Accepted date: 14 March 2018

Cite this article as: Mara Gavazzoni, Enrico Vizzardi, Elio Gorga, Ivano Bonadei, Laura Rossi, Angelo Belotti, Giuseppe Rossi, Rossella Ribolla, Marco Metra and Riccardo Raddino, Mechanism of cardiovascular toxicity by proteasome inhibitors: new paradigm derived from clinical and pre-clinical evidence, *European Journal of Pharmacology,* https://doi.org/10.1016/j.ejphar.2018.03.022

Mechanism of cardiovascular toxicity by proteasome inhibitors: new paradigm derived from clinical and pre-clinical evidence

Mara Gavazzoni[a*], Enrico Vizzardi[a], Elio Gorga[a], Ivano Bonadei[a], Laura Rossi[a], Angelo Belotti[b], Giuseppe Rossi[b] ,Rossella Ribolla[b], Marco Metra[b], Riccardo Raddino[a]

[a]Cardiology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health University, Cardiothoracic Department, Spedali Civili of Brescia, Italy

[b]Department of Hematology, Spedali Civili of Brescia, Brescia, Italy

[*]**Corresponding author.** Dr. Mara Gavazzoni , Piazzale Spedali Civili 1, 25123 Brescia, Italy. Tel.: +390303995573. **gavazzonimara@gmail.com**

Abstract

Proteasome Inhibitors (PI) have now become the cornerstone of treatment of multiple myeloma (MM). Carfilzomib has been demonstrated to cause more frequent cardiovascular side effects such as dyspnea, hypertension, and heart failure. Recent pre-clinical studies have investigated the effects of proteasome on myocardial and vascular cells, but the pathogenic mechanism underlying the effects of proteasome inhibition on these cells is poorly understood. We reviewed the evidence from clinical trials, post-hoc analysis and small observational studies currently available and summarized the data from experimental, focusing on the pathogenic mechanisms potentially implicated in the cardiovascular toxicity of proteasome inhibitor, particularly of carfilzomib that is most responsible for cardiovascular side effects. Finally, we tried to suggest future perspectives for diagnostic and therapeutic approach to this type of cardiovascular damage.