Proteasome Inhibitors as a Potential Cause of Heart Failure

Georgios Koulaouzidis, MD[a], Alexander R. Lyon, MD, PhD[a,b,*]

KEYWORDS

• Proteasome inhibitors • Heart failure • Myocardium • Multiple myeloma

KEY POINTS

- Proteasome inhibitors have become an important drug class in the treatment of multiple myeloma, and currently 3 have received regulatory approval.
- In addition to its role in myeloma cells, the proteasome plays a critical role in the myocardium, particularly in the context of cardiac stress.
- The growing awareness of the cardiovascular toxicity of proteasome inhibitors is emerging following the phase 3 trials and the transition into real-world practice.

INTRODUCTION

Proteasomes are protease complexes that are responsible for degrading endogenous proteins and protein recycling within cellular metabolism. Proteins to be destroyed are recognized by proteasomes because of the presence of ubiquitin moieties as posttranslational modifications.[1] The ubiquitin proteasome pathway represents the major intracellular pathway for intracellular protein degradation, with more than 80% of cellular proteins degraded through this pathway as part of natural turnover in cellular metabolism.[2,3] This pathway is active in the cardiomyocytes of ventricular myocardium under basal conditions; it is upregulated in various disease states, including myocardial stress, left ventricular hypertrophy, and heart failure (HF). It has become increasingly clear that defects within this pathway are associated with several noncardiac diseases, including several cancers.[4,5]

Proteasome inhibitors (PIs) have been developed to block the action of proteasomes. PIs have been studied in the treatment of cancer, and they are approved for use in both the United States and Europe for the treatment of multiple myeloma and mantle cell lymphoma.[6–8] Bortezomib (Velcade) is a first-in-class PI, acting as a reversible inhibitor, and has been approved for the treatment of multiple myeloma and also relapsed and refractory mantle cell lymphoma.[9] Carfilzomib (Kyprolis) is a modified epoxyketone PI that selectively targets the proteasome enzymes within the cell. It is more potent than bortezomib and irreversibly binds to the active sites of the 20S proteasome as well as the core component within the 26S proteasome.[10,11] Ixazomib (Ninlaro) is the first oral PI and has recently received a license for relapsed and refractory multiple myeloma.[12] It is a reversible PI that preferentially binds to the beta 5 subunit of the 20S

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[a] NIHR Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, London SW3 6NP, UK; [b] Imperial College London, London, UK
* Corresponding author. Department of Cardiology, Royal Brompton Hospital, London SW3 6NP, UK.
E-mail address: a.lyon@imperial.ac.uk

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proteasome and inhibits its chymotrypsinlike activity.

The aim of this article is to review the cardiovascular toxicity in patients receiving PIs.

PHASE III RANDOMIZED CONTROLLED TRIALS

Bortezomib

There have been 2 major phase 3 trials of bortezomib in multiple myeloma including 677 patients receiving bortezomib, usually in combination with dexamethasone and immune modulators, for example, lenalidomide. Bortezomib treatment was also included in the ENDEAVOR trial as the comparator arm to carfilzomib (see later discussion). There has also been a meta-analysis of 25 trials and 4330 patients treated with bortezomib, which provides the most accurate estimate of cardiotoxicity rates in patients with multiple myeloma.

APEX Trial (2005)

The APEX trial was a phase 3 randomized trial that compared bortezomib with high-dose dexamethasone in patients with multiple myeloma who had a relapse after one to 3 other therapies.[13] A total of 669 patients with relapsed multiple myeloma were randomly assigned to receive bortezomib (n = 333) or high-dose dexamethasone (n = 336).

Efficacy

The median time to disease progression was 6.22 months in the bortezomib group and 3.49 months in the dexamethasone group (hazard ratio for the bortezomib group, 0.55; $P<.001$). At 1 year of follow-up, patients who received bortezomib had a higher rate of overall survival (80%) than those who received dexamethasone (66%, $P = .003$).

Cardiotoxicity

The incidence of cardiac events during treatment with bortezomib and dexamethasone was 15% and 13%, respectively. Five percent of patients in the bortezomib arm developed congestive cardiac failure compared with 4% in the dexamethasone arm. These data show a high rate of cardiac events including HF in this patient population but did not suggest bortezomib was increasing the rate significantly. Dyspnea is a commonly reported adverse event (AE) in PI trials; perhaps insufficient data prevent adjudication committees to define as cardiac, for example, HF or pulmonary (including pulmonary embolus and pulmonary hypertension). Dyspnea without cause specified was reported in 20% of patients receiving bortezomib and 17% in the control arm.

VISTA Trial (2008)

This trial was a phase III trial for comparison bortezomib plus melphalan-prednisone (bortezomib group) with melphalan-prednisone alone (control group) in patients with newly diagnosed myeloma who were ineligible for high-dose therapy.[14] This study was an open-label study in which 344 patients were randomly assigned in the bortezomib group and 338 in the control group.

Efficacy

The rates of partial response or better were 71% in the bortezomib group as compared with 35% in the control group ($P<.001$), and the complete-response rates were 30% and 4%, respectively ($P<.001$). After a median follow-up of 16.3 months, 45 patients (13%) in the bortezomib group and 76 patients (22%) in the control group had died (hazard ratio in the bortezomib group, 0.61, $P = .008$).

Cardiotoxicity

The rate of all serious AEs in the bortezomib group was higher than that in the control group (46% vs 36%). HF-related symptoms were more common in the bortezomib group: dyspnea was observed in 15% in the bortezomib group versus 13% in the melphalan group, whereas peripheral edema was twice as common in the bortezomib arm (20% vs 10%). It is not clear if the edema was bilateral (eg, cardiac or renal) or unilateral, raising the possibility of deep vein thrombosis. Together with data from the APEX trial, there is a suggestion that bortezomib may increase the risk of cardiac events and these trials may have been underpowered to detect a significant effect. The absolute increase, if real, is relatively modest; what is more relevant is the identification of a high background rate of cardiac events suggesting patients with multiple myeloma are a high-risk population for cardiovascular disease per se.

Meta-analysis

Xiao and colleagues[15] in a meta-analysis investigated the incidence and risk of cardiotoxicity in patients treated with bortezomib. They included in their analysis 4330 patients who received bortezomib from 11 phase III and 14 phase II trials, for the purpose of analysis. The incidence of all-grade cardiotoxicity was ranged from 0% to 17.9% with the highest incidence observed in elderly patients with mantle cell lymphoma. Using a random-effects model, the summary incidence of all-grade cardiotoxicity in all patients was 3.8% (95% confidence interval [CI]: 2.6%–5.6%). The incidence of high-grade cardiotoxicity ranged from 0% to 7.7% across the trials evaluated, with