Proteasome inhibitors as a potential cause of heart failure

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Abstract

Proteasome inhibitors have become an important drug class in the treatment of multiple myeloma, and currently three 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. This article reviews the background to this problem, the incidence of the problem in phase 3 trials and subsequent phase 2 trials in new patient cohorts, and discusses the strategy to detect and manage this emerging problem.

Introduction

Proteasomes are protease complexes which 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 post-translational modifications (1). The ubiquitin proteasome pathway (UPP) 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, and it upregulated in various disease states including myocardial stress, left ventricular hypertrophy and heart failure. It has become increasingly clear that defects within this pathway are associated with a number of non-cardiac 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 USA and Europe for the treatment of multiple myeloma and mantle cell lymphoma (6-8). Bortezomib (Velcade™) is a first-in-class proteasome inhibitor, 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 proteasome inhibitor that preferentially binds to the beta 5 subunit of the 20S proteasome and inhibits its chymotrypsin-like activity.

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

Phase III Randomized controlled trials

BORTEZOMIB

There have been two major phase 3 trials of bortezomib in multiple myeloma including 677 patients receiving bortezomib, usually in combination with dexamethasone and immune modulators e.g. lenalidomide. Bortezomib treatment was also included in the ENDEAVOR trial as the comparator arm to carfilzomib (see below). There has also been a metaanalysis 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 which compared bortezomib with high-dose dexamethasone in patients with multiple myeloma who had had a relapse after one to three 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; $p<0.001$). At one year of follow-up, patients who received bortezomib had a higher rate of overall survival (80%) than those who received dexamethasone (66%, $p=0.003$).

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 to 4% in the dexamethasone arm. This data shows a high rate of cardiac events including heart failure in this patient population, but did not suggest bortezomib was increasing the rate significantly. Dyspnoea is a commonly reported AE in PI trials, and perhaps insufficient data prevents adjudication committees to define as cardiac e.g. heart failure or pulmonary (including pulmonary embolus and pulmonary hypertension). Dyspnoea without cause specified was reported in 20% patients receiving bortezomib and 17% in the control arm.

VISTA Trial (2008)

This 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 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 ($p<0.001$), and the complete-response rates were 30% and 4%, respectively ($p<0.001$). 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, $p=0.008$).

Cardiotoxicity: the rate of all serious adverse events 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: dyspnoea was observed in 15% in the bortezomib group versus 13% in the melphalan group; while peripheral oedema was twice as common in the bortezomib arm (20% vs 10%). It is not clear if the oedema was bilateral (e.g. 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, and what is more relevant is the identification of a high background rate of cardiac events suggesting patients with MM are a high risk population for cardiovascular disease per se.

Meta-analysis

Xiao *et al* in a meta-analysis investigated the incidence and risk of cardiotoxicity in patients treated with bortezomib (15). 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%CI: 2.6–5.6%). The incidence of high-grade cardiotoxicity was ranged from 0% to 7.7% across the trials evaluated, with the highest incidence seen in the trial of elderly patients with mantle cell lymphoma, while no events of cardiotoxicity were observed in three trials. Among patients with bortezomib-

associated high-grade cardiotoxicity, this meta-analysis showed that the mortality of cardiotoxicity was 3.0%. High grade CV toxicity, including heart failure and sudden cardiac death, was seen in 2.3% patients receiving bortezomib. The rate was higher in the multiple myeloma trials (4.3%), perhaps reflecting the higher incidence of pre-existing cardiovascular comorbidities.

CARFILZOMIB

Carfilzomib is a more potent, and irreversible PI. The first two phase 3 trials have demonstrated increased efficacy of carfilzomib as a second line PI in patients with progressive MM despite first line bortezomib against different comparator arms. The latest phase 3 trial recently published compared carfilzomib head-to-head with bortezomib as first line PI strategy, with superior efficacy of the more potent carfilzomib. Aligned to the increased efficacy, the higher potency also is reflected in a higher risk of cardiovascular toxicity in patients receiving carfilzomib treatment compared to bortezomib.

ASPIRE TRIAL (2015)

The ASPIRE trial was a randomized, open-label, multicenter, phase 3 study which evaluated the safety and efficacy of carfilzomib with lenalidomide and weekly dexamethasone (carfilzomib group) compared with lenalidomide and weekly dexamethasone alone (control group)[16]. In this trial, 792 patients with relapsed multiple myeloma were randomly assigned, in a 1:1 ratio.

Efficacy: The median progression-free survival was 26.3 months (95% confidence interval [CI], 23.3 to 30.5) in the carfilzomib group as compared with 17.6 months

(95% CI, 15.0 to 20.6) in the control group (p=0.0001). The Kaplan–Meier 24-month overall survival rates were 73.3% (95% CI, 68.6 to 77.5) in the carfilzomib group and 65.0% (95% CI, 59.9 to 69.5) in the control group.

Cardiovascular toxicity: Cardiac adverse events were common in this trial, and increased in carfilzomib (26.6%) compared to the control arm (15.6%). Severe cardiac AEs (>grade 3) were twice as frequent in the carfilzomib arm (11.4% vs 5.7%). Heart failure related to treatment was reported in 25 patients in the carfilzomib group (6.4%) versus 16 patients in the control arm (4.1%). Severe heart failure was also higher in the carfilzomib arm (3.8% vs 1.8% in the control group).

Vascular toxicity, including ischemic heart disease events, mainly reflecting troponin-positive acute coronary syndromes, were also higher in carfilzomib (5.9% in the carfilzomib group and 4.6% in control arm). Hypertension was another cardiovascular complication increased by carfilzomib (14.3% vs 6.9% in the control group). Dyspnoea without specific cause was very common, and with the assumption that some was cardiac in origin, the overall rate of cardiac AEs plus new dyspnoea was reported in 46% of patients in the carfilzomib arm compared to 30.5% in the control group.

FOCUS Trial (2016)

The FOCUS trial is a phase 3 trial of carfilzomib versus low dose corticosteroids and optional cyclophosphamide in patients with relapsed and refractory multiple myeloma (17). Three hundred and fifteen patients were recruited and randomised to

carfilzomib (n=157) vs control (n=158), with 95% of the control arm receiving cyclophosphamide. All patients had previously received bortezomib treatment, and ~76% of patients recruited had received prior anthracycline chemotherapy.

Efficacy: Median overall survival was similar between study arms (10.2 months Carfilzomib vs 10.0 months in controls). Profession-free survival was also similar, but the overall response rate with significantly higher in the carfilzomib arm (19.1% vs 11.4%).

Cardiovascular toxicity: Hypertension was the most common cardiovascular AE and increased in the carfilzomib arm (15% vs 6% in controls). This may reflect a higher rate of renal failure in the carfilzomib arm (24% vs 9% in controls). Heart failure was reported in 7 patients in the carfilzomib arm (4.5%) and only one patient in the control arm (0.6%), with severe heart failure in 3 patients treated with carfilzomib.

ENDEAVOR TRIAL (2016)

The ENDEAVOR trial is the largest phase 3 trial of PIs and tested carfilzomib head-to-head with bortezomib in advanced MM [18]. In the the ENDEAVOR trial 929 patients with relapsed or refractory MM and a median of two prior lines of therapy were randomized to either carfilzomib with dexamethasone (n=464) or bortezomib–dexamethasone (n=465). Prior PI therapy was allowed providing a partial response had been reported and no prior PI-related serious AEs were reported. Patients with heart failure and reduced LVEF (<40%) or recent MI were excluded.

Efficacy: at a median follow up of 12 months, progression-free survival (PFS) was significantly longer in the carfilzomib arm (median 18.7 months vs. 9.4 months in the bortezomib arm, $p < 0.0001$). The superiority of carfilzomib was seen in both bortezomib-exposed and bortezomib-naïve patients, although PFS was longer in bortezomib-naïve patients in both arms.

Cardiovascular toxicity and general safety: Mortality due to adverse events was relatively high and numerically higher in the carfilzomib arm (4.3% vs 3.1%). Treatment discontinuation due to adverse events was common in patients who had receive 1 prior line of treatment (17.2% vs. 18.5%, respectively), and even higher in those patients enrolled who had received ≥2 prior lines of treatment (22.5% vs 23.1%).

Severe cardiac AEs (grade >3 heart failure, hypertension) and grade 3 dyspnoea occurred in 76 patients in carfilzomib arm (16.3%) compared to 25 patients in the bortezomib arm (5.4%). Serious heart failure (grade 3+) occurred more frequently in carfilzomib-treated patients (10 (2.2%) vs 3 patients (0.6%)). Deep vein thrombosis and pulmonary emboli were also more common in the carfilzomib arm compared to bortezomib (10.2 vs 6.2 %).

In an echocardiographic substudy, serial echocardiograms were performed at baseline (pre-treatment) and 12 weekly intervals from 151 patients (75 from the carfilzomib group and 76 from the bortezomib group). This only identified one patient (in the bortezomib group) with significant left ventricular ejection fraction reduction within the first 24 weeks of study treatment, and yet the rate of

cardiovascular AEs was similar to the overall study, suggesting this strategy failed to detect the carfilzomib-induced left ventricular dysfunction prior to clinical presentation. Further information regarding the data quality and scientific details of the echocardiographic substudy has been presented in abstract form and more details in the main substudy publication are awaited. Three additional patients (two from the carfilzomib group and one from the bortezomib group) had a significant reduction in left ventricular ejection fraction at any time during the study. All patients but one (in the carfilzomib group) had resolution to normal left ventricular ejection fraction on follow-up.

Recent phase II studies

CYCLONE TRIAL

CYKLONE was a multicentre, single-arm, open-label, phase Ib/II study assessing the efficacy and safety of carfilzomib in newly diagnosed MM (19). Patients received carfilzomib by intravenous infusion over 30 min on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle. All patients received cyclophosphamide 300 mg/m^2 orally (PO) on days 1, 8 and 15; thalidomide 100 mg PO on days 1–28; and dexamethasone 40 mg PO on days 1, 8, 15 and 22. Patients received CYKLONE treatment for four cycles or more, followed by stem cell transplant. Sixty-four patients were evaluated for response. Sixteen percent of patients receiving carfilzomib had a cardiovascular AE, with severe cardiac AEs in 6% patients. Dyspnoea (20%) was also common in the MM patients receiving carfilzomib.

Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies.

Siegel *et al* analysed safety data for carfilzomib from 526 patients with advanced multiple myeloma who took part in one of 4 phase II studies (PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005) prior to FOCUS and ENDEAVOR (20).

Overall, 73.6% of patients had a past medical history of cardiovascular events and 70.0% had baseline cardiac risk factors. Cardiac adverse events were reported in 22.1% of patients receiving carfilzomib, and severe ≥ grade 3 cardiac AEs were observed in 9.5% patients treated with carfilzomib. Cardiac failure events were reported in 32 patients (7.2%). The overall mortality rate, including due to disease progression, was the same (7%) in patients who had baseline cardiac risk factors as it was for patients without these risk factors. Hypertension (mainly Grade 1–2) was reported in 14.3% of patients, more than half of whom had a history of hypertension. Dyspnoea was also a commonly reported treatment-emergent AE in patients receiving carfilzomib (42%), raising the question of specific aetiology, with undiagnsoed pulmonary oedema or pulmonary emboli as potential explanations.

In response to a cardiac-related adverse event, 6 patients (1.1%) had a carfilzomib dose reduction. Cardiac events leading to treatment discontinuation were noted in 23 patients (4.4%) and included CHF (1.5%), cardiac arrest (1.0%), and myocardial ischemia (0.6%). The main cluster of cardiovascular toxicity events are early after treatment, with cardiac adverse events occuring within one day of dosing in 62 patients (11.8%).The rate of cardiac adverse events did not increase later in the cycles.

Real world studies

Atrash *et al* reported the cardiotoxicity data associated with carfilzomib in 130 patients with relapsed and/or refractory multiple myeloma, either on a phase 2 compassionate carfilzomib protocol (*n*=118) or as single-patient treatment with an investigational new drug (*n*=12) [21]. Twenty-six patients out of the total 130 patients (20%) developed cardiac adverse events. Eleven patients were hospitalized for congestive heart failure and a further four patients were admitted for congestive heart failure with hypotension – the total new HF incidence of 11.5%. Pulmonary edema led to the hospitalization of two patients and included one case of severe hypertensive crisis. Serious cardiac arrhythmia was also reported. Three patients presented with significant arrhythmias complicated by hypotension, and a fourth patient required hospitalization arrhythmia without hypotension. Among the four patients who were hospitalized for arrhythmia, two had cardiac arrest due to arrhythmias.

Echocardiograms were performed at baseline and as symptom-driven follow-ups (*n*=93 (72%)). The median left ventricular ejection fraction as assessed by echocardiogram reduced from 55% to 33% during carfilzomib treatment. Sixty-nine of 130 patients (53%) also had baseline BNP measurements and measurements during the first cycle of carfilzomib. Among these patients, a median increase of 407 pg/ml BNP from baseline was observed ($P<0.001$). Elevation of BNP did not appear to correlate with clinical symptoms or hospitalization, but may be a useful marker for detecting subclinical carfilzomib cardiotoxicity.

Danhof *et al* in a single-center retrospective study of 22 patients with relapsed/refractory multiple myeloma examined the efficacy and safety of carfilzomib combination therapy in a non-trial clinical practice setting (22). All patients received carfilzomib with a starting dose of 20 mg/m^2 on days 1, 2, 8, 9, 15, and 16 during the first 28-d cycle and a target dose of 27 mg/m^2 per scheduled treatment day thereafter. All patients also received concomitant low-dose dexamethasone at a maximum of 160 mg per cycle and 5 patients received lenalidomide with a target dose of 25 mg on days 1 through 21.

The second most common group of non-hematologic severe AEs was cardiac. Five patients developed symptomatic heart failure. They presented with shortness of breath, weight gain, edema, and pleural effusions and had increased NTproBNP levels (median: 28447, range: 23018–31620 pg/mL) and reduced LVEF (median: 30, range 18–45%). All patients required oxygen and intravenous diuretic therapy. In some patients, inotropic support was given and two patients required intensive care treatment. The period to full recovery was usually short after suspension of myeloma treatment. One patient who had experienced a myocardial infarction 25 years previously had persistent LV impairment with reduced LVEF of 30%.

Finally, Grandin *et al* described the clinical presentation and management of 6 patients with relapsed and/or refractory multiple myeloma who experienced significant cardiac toxicity associated with carfilzomib treatment (23). According with the authors elevated BNP levels appeared to correlate with the development of cardiac dysfunction, and BNP levels declined with recovery of cardiac function.

Oral proteasome inhibitor

The safety and efficacy of ixazomib were demonstrated in the TOURMALINE-MM1 study, an international, phase 3, double-blind clinical trial (24). More than 720 patients with relapsed and/or refractory multiple myeloma were randomized to ixazomib plus lenalidomide and dexamethasone or to placebo plus lenalidomide and dexamethasone.

The median time to response was 1.1 months in the ixazomib group and 1.9 months in the placebo group, and the corresponding median duration of response was 20.5 months and 15.0 months. At a median follow-up of approximately 23 months, the median overall survival has not been reached in either study group, and follow-up is ongoing. The rates of serious adverse events were similar in the two study groups (47% in the ixazomib group and 49% in the placebo group), as were the rates of death during the study period (4% and 6%, respectively). The rate of HF related symptoms were similar in both groups, with a trend to higher rates in the ixazomib arm (25% vs 18%).

Discussion

Proteasome inhibitors are associated with an elevated risk of cardiovascular toxicity, probably as a direct result of reduced proteasome activity in the cardiac myocytes, given the important role of the proteasome in protein degradation in both normal metabolism and in particular in the ventricular myocardium following myocardial stress.

Bortezomib is the first therapeutic proteasome inhibitor to be licensed for treatment, and carfilzomib is a more potent, irreversible proteasome inhibitor, which appears to be more effective in treating refractory MM, but also portends a greater cardiovascular risk. Ixazomib is a new oral PI and may also have an increased cardiovascular risk.

Bortezomib has been reported to be cardiotoxic, but with over ten years of wide-scale use this incidence is apparently very low. Carfilzomib-associated cardiac toxicity was reported as any of the following: new-onset or worsening congestive heart failure, arrhythmia (mostly of low grade), myocardial infarction, pulmonary hypertension, deep vein thrombosis and pulmonary emboli, sudden cardiac death, and an asymptomatic decrease in left ventricular ejection fraction. Elevation in the cardiac biomarkers (BNP, NT-proBNP) from baseline was reported in most patients treated with carfilzomib, but with no apparent correlation to symptoms.

A head-to-head comparison of cardiovascular toxicity with carfilzomib and bortezomib is available through the ENDEAVOR trial (18). In that trial in the setting of relapsed/refractory disease, any cardiac event of any grade was reported in 12% of patients in the carfilzomib arm compared to 4% in the bortezomib arm.

Regarding the cardiotoxicity of Ixazomib, the clinical experience regarding is very limited and further trials required for safety data, but concerns regarding cardiotoxicity are present given the class-associated risk and results from the TOURMALINE-MM1 trial [24].

Most cardiac adverse events occurred relatively early in the course of treatment (2–3 months from treatment initiation) and mostly in patients with cardiovascular co-morbidities or prior exposure to other cardiotoxic agents, raising the possibility of synergistic effect with background cardiac risk factors which are common in this patient group [25].

Treatment strategies should involve risk stratification at baseline diagnosis before starting PI treatment, and medical optimisation of pre-existing cardiovascular comorbidities including hypertension, ischaemic heart disease and pre-existing left ventricular dysfunction. Minimizing fluid loads associated with treatments, avoiding concomitant cardiotoxic and nephrotoxic drugs, and use of diuretics to optimise fluid balance are pragmatic approaches which can be delivered in current clinical practice. Cardio-Oncology services have been developed to develop expertise in manageing cardiovascular toxicity and complications in patients receiving cancer therapies. Cardio-Oncology services are supporting haemato-oncology specialists to help manage PI-associated cardiotoxicity, with an important emphasis on communication and education between cardiologists and haemato-oncologists. The role of echocardiography and cardiac biomarkers including natriuretic peptides in patients treated with PIs for cardiotoxicity surveillance and optimal treatment of cardiotoxicity to support ongoing PI tretment in patients with responsive disease remain to be determined and are important goals of future work.

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