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A retrospective analysis of 3954 patients in phase 2/3 trials of bortezomib for the treatment of multiple myeloma: towards providing a benchmark for the cardiac safety profile of proteasome inhibition in multiple myeloma

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Summary

This retrospective analysis aimed to establish the overall cardiac safety profile of bortezomib using patient-level data from one phase 2 and seven phase 3 studies in previously untreated and relapsed/refractory multiple myeloma [MM]. Seven clinically relevant primary (congestive heart failure [CHF], arrhythmias, ischaemic heart disease [IHD], cardiac death) and secondary (hypertension, dyspnoea, oedema) cardiac endpoints were defined based on MedDRA v16.0 preferred terms.

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2509 bortezomib-treated patients and 1445 patients in non-bortezomib-based control arms were included. The incidence of grade ≥3 CHF was 1·3–4·0% in studies in relapsed/refractory MM and 1·2–4·7% in previously untreated MM (2·0–7·6% all grades), with no significant differences between bortezomib- and non-bortezomib-based arms in comparative studies. Incidences of arrhythmias (1·3–5·9% grade ≥2; 0·6–4·1% grade ≥3), IHD (1·2–2·9% all grades; 0·4–2·7% grade ≥3) and cardiac death (0–1·4%) were low, with no differences between bortezomib-based and non-bortezomib-based arms. Higher rates of oedema (mostly grade 1/2) were seen in bortezomib-based *versus* non-bortezomib-based arms in one study and a pooled transplant study analysis. Logistic regression analyses of comparative studies showed no impact on cardiac risk with bortezomib-based *versus* non-bortezomib-based treatment. Bortezomib-based treatment was associated with low incidences of cardiac events.

Keywords

bortezomib; cardiac; cardio-oncology; multiple myeloma

Introduction

Due to recent treatment advances, patients with multiple myeloma (MM) are living longer (Anderson, 2012; Kumar et al, 2014; Liwing et al, 2014), underscoring the importance of patient quality of life and management of adverse events (AEs) related to therapy. MM patients are at risk of cardiac events due to age and disease-related factors (Kistler et al, 2012; McBride et al, 1988; Inanir et al, 1998; Robin et al, 2008; Kwaan, 2013); there is also a risk of cardiac events due to cardiotoxicity from treatments including anthracyclines (Ky et al, 2013), proteasome inhibitors (Bockorny et al, 2012; Herndon et al, 2013; Honton et al, 2013; Lonial et al, 2012; Siegel et al, 2013) and high-dose therapy (Chow et al, 2011; Sureddi et al, 2012; Fatema et al, 2009).

The United States Food and Drug Administration (US FDA)-approved proteasome inhibitors, bortezomib, carfilzomib and ixazomib, have been associated with cardiac events in MM patients (Bockorny et al, 2012; Herndon et al, 2013; Honton et al, 2013; Lonial et al, 2012; Siegel et al, 2013; Moreau et al, 2016). Cardiac toxicity and cardiac adverse reactions are included under ‘Warnings and Precautions’ in the respective US labels for bortezomib and carfilzomib (http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf). Case reports have described cardiac failure and other cardiotoxicity with bortezomib treatment in patients with MM and other cancers (Bockorny et al, 2012; Dasanu, 2011; Enrico et al, 2007; Hacihanefioglu et al, 2008; Lee et al, 2011; Takamatsu et al, 2010; Voortman & Giaccone, 2006; Gupta et al, 2012; Subedi et al, 2014). However, case reports do not provide a comprehensive picture of the cardiovascular risk profile of bortezomib. More than 550 000 patients worldwide have been treated with bortezomib; its development involved numerous large, randomised, controlled clinical trials in relapsed and/or refractory MM (RRMM) (Moreau et al, 2011; Orlowski et al, 2007; Richardson et al, 2005) and newly diagnosed MM (NDMM) (Cavo et al, 2010; Harousseau et al, 2010; Rosinol et al, 2012; San Miguel et al, 2008; Sonneveld et al, 2012). This large, accumulated experience offers the

opportunity to define a benchmark for describing the cardiovascular profile of proteasome inhibitors in MM.

We conducted a retrospective analysis of the risk of heart failure, arrhythmias, ischaemic heart disease (IHD), cardiac death, hypertension, dyspnoea and oedema associated with bortezomib, using patient-level data from MM studies that supported US and European Union (EU) regulatory approvals (Cavo et al, 2010; Harousseau et al, 2010; Richardson et al, 2003; Richardson et al, 2005; Rosinol et al, 2012; San Miguel et al, 2008; Sonneveld et al, 2012; Sonneveld et al, 2013; Moreau et al, 2011; Orlowski et al, 2007). The aim was to establish the overall cardiac safety profile of bortezomib, using a clearly defined, standardised and replicable reporting method. This approach aimed to reconcile discrepancies between the National Cancer Institute's (NCI) Common Terminology Criteria for AEs (CTCAE) and the Medical Dictionary for Regulatory Activities (MedDRA) regarding AE reporting, and used Standardised MedDRA Queries (SMQ) as the basis for grouping preferred terms to specified cardiovascular entities.

Patients and methods

Studies analysed

This pooled analysis included data on male/female patients in all phase 3 MM studies that led to US/EU regulatory approval, plus the original phase 2 registration study for US/EU regulatory approval, and represented all such studies with patient-level data available (Table I). RRMM studies included: phase 2 Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) study of bortezomib with/without dexamethasone (M34100-025) (Richardson et al, 2003); phase 3 APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial of single-agent bortezomib *versus* dexamethasone (NCT00048230) (Richardson et al, 2005); phase 3 MMY-3001 trial of bortezomib plus liposomal doxorubicin *versus* single-agent bortezomib (NCT00103506) (Orlowski et al, 2007); phase 3 MMY-3021 trial of subcutaneous (SC) *versus* intravenous (IV) bortezomib (with/without dexamethasone; NCT00722566) (Moreau et al, 2011). NDMM studies included the phase 3 VISTA (Velcade® as Initial Standard Therapy in Multiple Myeloma) trial of bortezomib-melphalan-prednisone (VMP) *versus* melphalan-prednisone (MP) in elderly transplant-ineligible patients (NCT00111319) (San Miguel et al, 2008), and a pooled analysis based on patient-level data from 3 phase 3 trials of bortezomib-based *versus* non-bortezomib-based induction therapy in transplant-eligible patients (FM 2005-01, NCT00200681; GEM2005MENOS65, NCT00461747; HOVON-65/GMMG-HD4: EudraCT 2004-000944-26) (Sonneveld et al, 2013). Unfortunately, it was not possible to obtain patient level data from the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) study (NCT01134484) (Cavo et al, 2010).

Analyses of cardiac AEs

Seven clinically relevant cardiac entities/disease states were selected for analysis (Table SI). The 4 primary endpoints for this analysis were heart failure (congestive heart failure [CHF]), arrhythmia(s), IHD and cardiac death. For arrhythmias, only AEs of grade 2 severity or greater were included (based on clinical relevance and to improve specificity); ventricular

arrhythmias were described as a distinct subgroup. Incidences of hypertension, dyspnoea and oedema were included as secondary endpoints; dyspnoea AEs occurring in conjunction with CHF were analysed as a distinct subgroup.

Patient-level data from study databases were analysed retrospectively for treatment-emergent AEs (AEs occurring up to 30 days after last dose of study drug [20 days in SUMMIT], or regardless of start date for drug-related events) within the 7 cardiac endpoints. Different studies used different terminology criteria for recording and grading AEs: NCI Common Toxicity Criteria version 2.0 and CTCAE version 3.0. Relevant AEs were analysed and re-coded for consistency across studies. MedDRA SMQ version 16.0 was used for developing lists of preferred terms for inclusion in the primary and secondary cardiac endpoints, which were mapped to older versions of MedDRA. All terms were reviewed by 2 cardiologists and included, excluded or mapped to another cardiac endpoint on the basis of clinical relevance (Table SI), a methodology that has been previously employed (Basaria et al, 2010).

Statistical methods

For each endpoint, the primary descriptive analysis was incidence of events (patients with AE/total patients). Hazard of events over time was analysed using Kaplan–Meier methodology; each patient contributed 1 (first) event. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with statistical significance determined ($\alpha = 0.05$ level) using the log-rank test. Logistic regression models were used for each comparative study to determine parameters independently affecting risk of each cardiac endpoint. Parameters included treatment assignment, age (≤70 vs. >70 years), cardiac history (yes/no, defined as ‘any abnormal finding in the cardiovascular system organ class’, and per individual study definitions of cardiac history, Table I), interaction of treatment assignment and age, interaction of treatment assignment and cardiac history, and interaction of age and cardiac history. Due to marked heterogeneity across patient populations (transplant eligible, transplant ineligible and RRMM) and treatments (single-agent bortezomib, various combination regimens), data were not combined across studies except for transplant induction studies, which were conducted in the same patient population.

Results

Patients

Data from 3954 patients (2509 bortezomib treated, 1445 non-bortezomib treated) were included (Table I). In comparative studies, cardiac risk factors (age, prior cardiac history) were balanced between bortezomib- and non-bortezomib-based arms. Median age ranged from 57 years in the pooled transplant induction analysis to 71 years in VISTA; rate of prior cardiac history, defined in Table I, ranged from 21% to 74%, respectively.

Cardiac events

Primary endpoints: The incidence of grade ≥3 CHF across bortezomib-based arms was 1·3–4·0% in RRMM studies and 1·2–4·7% in NDMM (Table II); overall incidences were 2·0–7·4% in RRMM and 3·1–7·6% in NDMM. There were no significant differences in the

hazard of CHF over time between bortezomib- and non-bortezomib-based arms in comparative studies (Fig 1). The incidence of all-grade CHF was higher with bortezomib plus liposomal doxorubicin *versus* bortezomib in MMY-3001 (HR 0·42, $P = 0·017$) due to the difference in grade 1/2 events (5·9% vs. 1·6%). However, there was minimal difference in the incidence of grade ≥3 CHF between bortezomib plus liposomal doxorubicin and bortezomib (1·3% vs. 1·6%) in the overall population of the MMY-3001 study.

The incidence of grade ≥3 arrhythmias across bortezomib-based arms was 0·6–1·8% in RRMM studies and 1·7–4·1% in NDMM (Table III); incidences of grade ≥2 events were 1·3–4·1% in RRMM and 3·5–5·9% in NDMM. No significant differences between bortezomib- and non-bortezomib-based arms were seen. Most events were supraventricular arrhythmias; only 7 cases of ventricular arrhythmias were identified across all studies (5 in bortezomib-treated and 2 in non-bortezomib-treated patients; incidences of 0–0·5%; data not shown).

Grade ≥3 IHD was seen in 0·5–2·7% of bortezomib-treated patients in RRMM studies and 0·4–1·5% in NDMM (Table IV); overall incidences in individual studies were 1·5–2·7% in RRMM and 1·2–2·9% in NDMM. No significant differences between bortezomib- and non-bortezomib-based arms were seen.

Incidences of cardiac death were low; no meaningful statistical comparisons between treatment arms/groups were feasible. In RRMM, the incidence was 1·0% ($n = 2$) with bortezomib ± dexamethasone in SUMMIT, 0·6% ($n = 2$) *versus* 0 with bortezomib *versus* dexamethasone in APEX, 0·6% ($n = 2$) in both arms of MMY-3001, and 0·7% ($n = 1$) *versus* 1·4% ($n = 1$) with SC *versus* (IV bortezomib in MMY-3021. In NDMM, incidences were 0 *versus* 0·9% ($n = 3$) with VMP *versus* MP in VISTA, and 0·3% ($n = 2$) *versus* 0 with bortezomib-based *versus* non-bortezomib-based induction therapy in the pooled transplant analysis.

Secondary endpoints: Grade ≥3 hypertension was reported in 0–2·0% of bortezomib-treated patients in RRMM and 1·5–2·9% in NDMM; overall incidences were 3·5–9·5% in RRMM and 5·1–13·5% in NDMM (Table V). Rates appeared numerically higher with bortezomib *versus* non-bortezomib treatment in comparative studies, with a trend towards increased rates of all-grade (HR 1·54, $P = 0·0656$) and grade ≥3 (HR 2·94, $P = 0·0881$) hypertension with VMP *versus* MP in VISTA.

Grade ≥3 dyspnoea (regardless of cause) was reported in 0·9–5·4% of bortezomib-treated patients in RRMM studies and 1·2–3·8% in NDMM, with overall incidences of 7·5–22·3% in RRMM and 6·4–15·3% in NDMM (Table SII). No significant differences were seen in rates of dyspnoea between bortezomib- and non-bortezomib-based arms in comparative studies (Fig 1). Incidences of dyspnoea occurring in conjunction with CHF were low with bortezomib-based treatment (0–3·9% overall; 0–1·2% grade ≥3; Table SIII), with a significantly greater rate of all-grade events with bortezomib *versus* dexamethasone in APEX (HR 6·10, $P = 0·0066$).

Incidences of grade ≥3 oedema (regardless of cause) were low with bortezomib-based treatment (0–0·3% in RRMM; 0·6–1·2% in NDMM). Overall incidences were 3·0–11·9% in RRMM and 23·5% in NDMM (Table SIV), with significantly higher rates with VMP *versus* MP in VISTA (HR 2·24, $P < 0·0001$) and with bortezomib- *versus* non-bortezomib-based induction therapy in the pooled transplant analysis (HR 1·54, $P = 0·0002$).

Analysis of risk factors

In APEX, logistic regression model analysis showed no added risk of any cardiac endpoint with bortezomib compared with dexamethasone. In patients aged ≤70 years, independent of treatment, there was a significantly higher risk of dyspnoea occurring in conjunction with CHF in patients with *versus* without prior cardiac history. In patients randomised to dexamethasone, patients aged >70 years had a significantly higher risk of hypertension. Logistic regression model analysis identified no independent parameters that significantly affected the incidence of any cardiac endpoint in the MMY-3001, MMY3021 and VISTA studies. In the pooled transplant analysis, patients with prior cardiac history had a significantly higher risk of CHF, oedema and hypertension, independent of treatment.

Discussion

Bortezomib-based treatment was associated with generally low incidences of all-grade and grade ≥3 cardiac AEs across studies included in this analysis in NDMM and RRMM, supporting guidance in the current prescribing information that cardiac monitoring is most appropriate in those patients with risk factors for heart disease, or who have existing heart disease. No significant differences were seen in comparative studies of bortezomib- *versus* non-bortezomib-based treatment in CHF, arrhythmias, IHD and cardiac death (primary endpoints). The same was true for the secondary endpoints, except for a higher rate of all-grade oedema with VMP in VISTA and with bortezomib-based induction in the pooled transplant analysis, a higher rate of all-grade dyspnoea in conjunction with CHF with bortezomib in APEX, and a trend towards higher rates of hypertension with VMP in VISTA. Additionally, there was a significantly higher rate of any-grade CHF with bortezomib plus liposomal doxorubicin *versus* bortezomib in MMY-3001, possibly associated with the cardiac safety profile of anthracyclines; this differs from the primary manuscript findings (Orlowski et al, 2007), probably due to the broader range of preferred terms incorporated in this analysis. Prior meta-analysis has shown that bortezomib combination treatment did not increase the cardiac toxicity compared with bortezomib monotherapy (Xiao et al, 2014). Furthermore, data from the MMY-3021 study of SC *versus* IV bortezomib did not show any consistent differences between arms in cardiac risk; however, patient and event numbers are very small.

Notably, the absence of differences in all primary and most secondary endpoints between bortezomib- and non-bortezomib-based treatment was not affected in logistic regression model analyses of risk factors. These findings indicate that relative cardiac risk is not modified by bortezomib treatment and suggest that proteasome inhibition therapy with bortezomib may be an appropriate option in patients with cardiac risk factors, such as older age and cardiac history (acknowledging the cardiac study eligibility criteria, discussed

below). These findings are particularly valuable when considering older patients, as they include not only grade 3 and higher events but also grade 1 and 2 events, which may be clinically relevant in elderly patients. A limitation of our analysis was that non-specific definitions of cardiac history precluded a detailed assessment of the impact of pre-existing cardiac conditions.

Due to the large number of patients included from rigorously conducted trials, and comprehensive adjudication of cardiac endpoints, this analysis provides an important benchmark of cardiac safety for proteasome inhibitors and MM drugs in general, and represents a reference point for future clinical studies. It provides criteria to define cardiotoxicity based upon individual MedDRA preferred terms and SMQs, plus data on multiple distinct, clinically relevant cardiac endpoints. Furthermore, the analysis addresses the challenges of mapping AEs consistently across studies utilising different AE definitions, and differences between NCI CTCAE (terms commonly encountered in oncology interventions, with a severity rating scale) and MedDRA (clinically validated, multidisciplinary list of >66 000 preferred terms, but without definitions or severity ratings). Although inherent discrepancies between NCI CTCAE and MedDRA may represent a limitation of our approach (Groarke et al, 2013), careful and diligent reclassification of relevant cardiac AEs across the 2 systems (and their various iterations), as well as the inclusive approach used, ensured a consistent and rigorous methodology.

To our knowledge, this is the first large analysis using patient-level data from multiple phase 2 and 3 studies of bortezomib. This approach incorporated analysis of hazards and logistic regression for assessment of the influence of specific risk factors. It was assumed that each cardiac AE could occur independently, other than cardiac death, and, therefore, we did not conduct competing risks analyses; such analyses were not required due to the very low rates of cardiac deaths in the included studies. A recent pooled analysis employing only published study-level data and AEs reported in the respective publications provides supportive evidence that bortezomib does not significantly increase cardiotoxicity risk (Xiao et al, 2014). Additionally, regarding the feasibility of bortezomib in the setting of cardiovascular risk, reports have indicated that bortezomib-based therapy may be administered successfully to amyloidosis patients, specifically patients with cardiac amyloid involvement (Charaf et al, 2009; Dubrey et al, 2011; Freeman et al, 2012; Gatt et al, 2016; Mikhael et al, 2012; Reece et al, 2011; Tamaki et al, 2010), noting that all patients with existing heart disease or risk factors for heart disease should be closely monitored (http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf). Indeed, in the phase 1 trial by Dubrey et al (2011), logitudinal echocardiographic study reported no cardiac responses to bortezomib therapy in patients with relapsed AL amyloidosis. However, it should be highlighted that in the studies in the present analysis, patients with New York Heart Association class II/III–IV CHF and/or known amyloidosis were excluded and, except in VISTA, median ages were generally relatively lower *versus* the overall patient population; thus, a standard MM patient population may include more patients at higher risk of cardiovascular complications. While our findings may be broadly applicable to the wider MM patient population, due to employing data from selected clinical trial populations with specific cardiac exclusion criteria (Table I), they are not necessarily generalisable to patients with a higher burden of cardiovascular disease or recent/ongoing cardiac comorbidities.

The apparent overall higher incidence of cardiac events in VISTA compared with other studies may be due to patients being approximately 10 years older, based on median ages, or having a higher rate of prior cardiac history. Transplant-ineligible patients aged ≥65 years represent the majority of MM patients – approximately two-thirds – at initial diagnosis (Mateos & San Miguel, 2013), underlining the importance of understanding cardiac profiles of MM drugs. There were no differences between VMP and MP in VISTA, except for incidence of oedema, which does not appear to have a cardiac aetiology. This finding, combined with logistic regression results, suggests bortezomib can be used safely in this patient population. VISTA data challenge the common perception that RRMM patients may *per se* have higher risk of cardiac events in addition to the higher age of patients. However, these findings may have been a result of patients having a more complete medical history in VISTA *versus* other trials. Potential differences in AE reporting and eligibility criteria must be considered when assessing safety data across different studies.

We speculate on several possible reasons for the higher incidence of oedema with VMP *versus* MP in VISTA and in the pooled transplant analysis, and the trend towards higher incidences of hypertension. There may be some contribution directly via proteasome inhibition (http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf), including potentially a low-level cardiac effect, and there may be other, less serious types of oedema included. There may be an element of endothelial leak and fluid retention, associated with activity of proteasome inhibition on the endothelium and its anti-angiogenic effects (Belloni et al, 2010; Roccaro et al, 2006), and possibly potentiated by the synergy between proteasome inhibition and alkylating agents (Ma et al, 2003; Mitsiades et al, 2003) and the long exposure to prednisone (San Miguel et al, 2008).

All proteasome inhibitors have unique characteristics, with potentially distinct mechanistic differences, pharmacological characteristics and safety profiles (Moreau et al, 2012; Allegra et al, 2014; McBride & Ryan, 2013). Respective relative effects on the central/peripheral nervous system, gastrointestinal system, bone marrow and cardiovascular system may differ (Cavo et al, 2010; Harousseau et al, 2010; Richardson et al, 2003; Richardson et al, 2005; Rosinol et al, 2012; San Miguel et al, 2008; Sonneveld et al, 2012; Sonneveld et al, 2013; Moreau et al, 2011; Orlowski et al, 2007; Lonial et al, 2012; Siegel et al, 2013; Touzeau et al, 2013). Further studies are needed to better define these differences. No comparisons can be made with this analysis or conclusions drawn from available findings. Data on cardiac AEs in early-phase carfilzomib studies have been published, and the phase 3 ENDEAVOR (Carfilzomib and dexamethasone versus bortezomib and dexamethasone for RRMM patients) trial reported that 2 patients in each arm had significant left ventricular ejection fraction reductions during the study and that rates of grade ≥3 cardiac failure were 1·8% *versus* 4·8%, grade ≥3 pulmonary hypertension were <1% *versus* <1% and grade ≥3 IHD were 1·5% *versus* 1·7%, respectively (Dimopoulos et al, 2016). In the ASPIRE (Carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma) phase 3 trial, rates of grade ≥3 cardiac failure were 3·8% *versus* 1·8%, and grade ≥3 hypertension rates were 4·3% *versus* 1·8% (Stewart et al, 2015). A pooled analysis of phase 2 studies in 526 RRMM patients (70% with baseline cardiac risk factors [use of ≥1 prior cardiovascular or anti-diabetic medication]), 53% of whom received the approved 20/27 mg/m^2 dose, reported 7·2% cardiac failure (5·7% grade

≥3), 13·3% (2·3%) cardiac arrhythmia, 3·4% (1·3%) IHD, 42·2% (4·9%) dyspnoea and 14·3% hypertension, with 1·5% cardiac-related deaths (Lonial et al, 2012; Siegel et al, 2013). Other cardiac AE data have been reported from a phase 1/2 study of carfilzomib-MP (Touzeau et al, 2013), a compassionate-use analysis of carfilzomib in RRMM (Atrash et al, 2015), and a phase 2 study of carfilzomib 56 mg/m^2 with/without dexamethasone in RRMM (Lendvai et al, 2014). Phase 3 data on the oral proteasome inhibitor ixazomib in combination with lenalidomide and dexamethasone in RRMM have recently been published (Moreau et al, 2016); rates of heart failure with ixazomib + lenalidomide/dexamethasone were 4% (2% grade 3; <1% grade 4), arrythmia 16% (5% grade 3; <1% grade 4), hypertension 6% (3% grade 3) and myocardial infarction 1% (<1% grade 4). A recent case report also described an instance of acutely decompensated heart failure that was considered as being induced by ixazomib; the patient's cardiac function did not improve within 6 months of ixazomib discontinuation, but no further episodes of systolic heart failure were observed (Jouni et al, 2016). Data on cardiac AEs with the investigational proteasome inhibitors oprozomib and marizomib are limited. These findings provide support for the methodological approach taken in these analyses, which focus not just on CHF but other specific endpoints of cardiac aetiology that are relevant in MM treatment.

Non-clinical studies have suggested possible links between proteasome inhibition and the cardiovascular system, with studies demonstrating the importance of the ubiquitin-proteasome system, including in heart remodelling (Li & Wang, 2011; Portbury et al, 2012; Su & Wang, 2010; Willis & Patterson, 2013). Furthermore, studies have identified multiple effects of proteasome inhibition on the cardiovascular system, with a differential impact of different proteasome inhibitors on cardiac proteasome subtypes (Kloss et al, 2010; Powell et al, 2012; Scruggs et al, 2011) in 1 study (Kloss et al, 2010). These data further highlight the importance of analysing the cardiovascular risk associated with proteasome inhibitors and other novel agents for MM treatment (Groarke et al, 2013).

In conclusion, these data from bortezomib studies provide a benchmark for evaluating cardiovascular risk associated with proteasome inhibition in MM; data from ongoing prospective and comparative studies are necessary to determine whether proteasome inhibitors have different cardiotoxicity profiles. A better understanding of the mechanism of proteasome inhibitor-induced cardiotoxicity, risk factors and potential biomarkers identifying at-risk patient populations will be critical. Furthermore, it will be important to improve reporting of baseline cardiac risk factors, cardiac AEs and detection of cardiotoxicity in the context of oncology clinical trials. The NCI CTCAE provide for standardised AE reporting in cancer trials, but the methodology differs compared with cardiovascular trials; thus, early, asymptomatic cardiac changes may not be identified using NCI CTCAE. To facilitate assessment of cardiac AEs, there may be a need for improved cardiac monitoring in future studies of proteasome inhibitors and other drugs to elucidate any differential cardiac effects of these agents, especially as combination approaches in MM with other novel agents are pursued (Lonial et al, 2011). More broadly, in the context of the abundance of novel agents either already approved or in development for the treatment of MM, it will be critical to gain an improved understanding of cardiac events associated with individual agents. Our analyses represent a broadly applicable, comprehensive, reproducible and consistent methodology for the standardised assessment of cardiac toxicity in MM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Allegra A, Alonci A, Gerace D, Russo S, Innao V, Calabro L, & Musolino C (2014) New orally active proteasome inhibitors in multiple myeloma. Leukemia Research, 38, 1–9. [PubMed: 24239172]

Anderson KC (2012) The 39th David A. Karnofsky Lecture: bench-to-bedside translation of targeted therapies in multiple myeloma. Journal of Clinical Oncology, 30, 445–452. [PubMed: 22215754]

Atrash S, Tullos A, Panozzo S, Bhutani M, Van RF, Barlogie B, & Usmani SZ (2015) Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib. Blood Cancer Journal, 5, e272. [PubMed: 25594159]

Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, & Bhasin S (2010) Adverse events associated with testosterone administration. New England Journal of Medicine, 363, 109–122. [PubMed: 20592293]

Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, Citrome L, Gurr JA, Mooney LA, Moore BJ, Peña T, Sanes-Miller CH, Veitch K, Woolley KL, Yarker YE & International Society for Medical Publication Professionals. (2015) Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. Ann Intern Med, 163, 461–464. [PubMed: 26259067]

Belloni D, Veschini L, Foglieni C, Dell'Antonio G, Caligaris-Cappio F, Ferrarini M, & Ferrero E (2010) Bortezomib induces autophagic death in proliferating human endothelial cells. Experimental Cell Research, 316, 1010–1018. [PubMed: 19917281]

Bockorny M, Chakravarty S, Schulman P, Bockorny B, & Bona R (2012) Severe heart failure after bortezomib treatment in a patient with multiple myeloma: a case report and review of the literature. Acta Haematologica, 128, 244–247. [PubMed: 22964848]

Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, Di RF, Crippa C, Zamagni E, Palumbo A, Offidani M, Corradini P, Narni F, Spadano A, Pescosta N, Deliliers GL, Ledda A, Cellini C, Caravita T, Tosi P, & Baccarani M (2010) Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet, 376, 2075–2085. [PubMed: 21146205]

Charaf E, Iskandar SB, Blevins A, Abi-Saleh B, & Fahrig S (2009) Cardiac amyloidosis responding to bortezomib: case report and review of literature. Current Cardiology Reviews, 5, 228–236. [PubMed: 20676282]

Chow EJ, Mueller BA, Baker KS, Cushing-Haugen KL, Flowers ME, Martin PJ, Friedman DL, & Lee SJ (2011) Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. Annals of Internal Medicine, 155, 21–32. [PubMed: 21727290]

Dasanu CA (2011) Complete heart block secondary to bortezomib use in multiple myeloma. Journal of Oncology Pharmacy Practice, 17, 282–284. [PubMed: 20406745]

Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hajek R, Facon T, Ludwig H, Oriol A, Goldschmidt H, Rosinol L, Straub J, Suvorov A, Araujo C, Rimashevskaya E, Pika T, Gaidano G, Weisel K, Goranova-Marinova V, Schwarer A, Minuk L, Masszi T, Karamanesht I, Offidani M, Hungria V, Spencer A, Orlowski RZ, Gillenwater HH, Mohamed N, Feng S, & Chng WJ (2016) Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncology, 17, 27–38. [PubMed: 26671818]

Dubrey SW, Reece DE, Sanchorawala V, Hegenbart U, Merlini G, Palladini G, Fermand JP, Vescio RA, Blade J, Heffner LT, Hassoun H, Liu X, Enny C, Ramaswami P, Elsayed Y, van de Velde H, Mortimer S, Cakana A, & Comenzo RL (2011) Bortezomib in a phase 1 trial for patients with relapsed AL amyloidosis: cardiac responses and overall effects. QJM, 104, 957–970. [PubMed: 21752867]

Enrico O, Gabriele B, Nadia C, Sara G, Daniele V, Giulia C, Antonio S, & Mario P (2007) Unexpected cardiotoxicity in haematological bortezomib treated patients. British Journal of Haematology, 138, 396–397. [PubMed: 17561972]

Fatema K, Gertz MA, Barnes ME, Eisinger AD, Ness SA, Gersh BJ, Micallef IN, Seward JB, Cha SS, Bailey KR, & Tsang TS (2009) Acute weight gain and diastolic dysfunction as a potent risk complex for post stem cell transplant atrial fibrillation. American Journal of Hematology, 84, 499–503. [PubMed: 19565646]

Freeman B, Sloan JM, Seldin DC, Cowan AJ, Ruberg FL, & Sanchorawala V (2012) Multiple arterial and venous thromboembolic complications in AL amyloidosis and cardiac involvement: a case report and literature review. Amyloid, 19, 156–160. [PubMed: 22680044]

Gatt ME, Hardan I, Chubar E, Suriu C, Tadmor T, Shevetz O, Patachenco P, Dally N, Yeganeh S, Ballan-Haj M, Cohen Y, Trestman S, Muchtar E, Magen H, Jakubinsky J, & Avivi I (2016) Outcomes of light-chain amyloidosis patients treated with first-line bortezomib: a collaborative

retrospective multicenter assessment. European Journal of Haematology, 96, 136–143. [PubMed: 25827161]

Groarke JD, Cheng S, & Moslehi J (2013) Cancer-drug discovery and cardiovascular surveillance. New England Journal of Medicine, 369, 1779–1781. [PubMed: 24180496]

Gupta A, Pandey A, & Sethi S (2012) Bortezomib-induced congestive cardiac failure in a patient with multiple myeloma. Cardiovascular Toxicology, 12, 184–187. [PubMed: 21952908]

Hacihanefioglu A, Tarkun P, & Gonullu E (2008) Acute severe cardiac failure in a myeloma patient due to proteasome inhibitor bortezomib. International Journal of Hematology, 88, 219–222. [PubMed: 18633693]

Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, Lenain P, Hulin C, Facon T, Casassus P, Michallet M, Maisonneuve H, Benboubker L, Maloisel F, Petillon MO, Webb I, Mathiot C, & Moreau P (2010) Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. Journal of Clinical Oncology, 28, 4621–4629. [PubMed: 20823406]

Herndon TM, Deisseroth A, Kaminskas E, Kane RC, Koti KM, Rothmann MD, Habtemariam B, Bullock J, Bray JD, Hawes J, Palmby TR, Jee J, Adams W, Mahayni H, Brown J, Dorantes A, Sridhara R, Farrell AT, & Pazdur R (2013) U.S. Food and Drug Administration approval: carfilzomib for the treatment of multiple myeloma. Clinical Cancer Research, 19, 4559–4563. [PubMed: 23775332]

Honton B, Despas F, Dumonteil N, Rouvellat C, Roussel M, Carrie D, Galinier M, Montastruc JL, & Pathak A (2013) Bortezomib and heart failure: case-report and review of the French Pharmacovigilance database. Fundamental & Clinical Pharmacology, e-pub ahead of print; doi: 10.1111/fcp.12039.

Inanir S, Haznedar R, Atavci S, & Unlu M (1998) Arteriovenous shunting in patients with multiple myeloma and high-output failure. Journal of Nuclear Medicine, 39, 1–3. [PubMed: 9443728]

Jouni H, Aubry MC, Lacy MQ, Rajkumar SV, Kumar SK, Frye RL, & Herrmann J (2016) Ixazomib Cardiotoxicity: A Possible Class Effect of Proteasome Inhibitors. Am J Hematol, e-pub ahead of print; doi: 10.1002/ajh.24608.

Kistler KD, Rajangam K, Faich G, & Lanes S (2012) Cardiac event rates in patients with newly diagnosed and relapsed multiple myeloma in US clinical practice. Blood, 120, 2916.

Kloss A, Meiners S, Ludwig A, & Dahlmann B (2010) Multiple cardiac proteasome subtypes differ in their susceptibility to proteasome inhibitors. Cardiovascular Research, 85, 367–375. [PubMed: 19564153]

Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, Kapoor P, Dingli D, Hayman SR, Leung N, Lust J, McCurdy A, Russell SJ, Zeldenrust SR, Kyle RA, & Rajkumar SV (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia, 28, 1122–1128. [PubMed: 24157580]

Kwaan HC (2013) Hyperviscosity in plasma cell dyscrasias. Clinical Hemorheology and Microcirculation, 55, 75–83. [PubMed: 23455837]

Ky B, Vejpongsa P, Yeh ET, Force T, & Moslehi JJ (2013) Emerging paradigms in cardiomyopathies associated with cancer therapies. Circulation Research, 113, 754–764. [PubMed: 23989717]

Lee WS, Kim DH, Shin SH, Woo SI, Kwan J, Park KS, Park SD, Yi HG, & Jeon SH (2011) Complete atrioventricular block secondary to bortezomib use in multiple myeloma. Yonsei Medical Journal, 52, 196–198. [PubMed: 21155055]

Lendvai N, Hilden P, Devlin S, Landau H, Hassoun H, Lesokhin AM, Tsakos I, Redling K, Koehne G, Chung DJ, Schaffer WL, & Giralt SA (2014) A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed or refractory multiple myeloma. Blood, e-pub ahead of print; doi: 10.1182/blood-2014-02-556308.

Li YF & Wang X (2011) The role of the proteasome in heart disease. Biochimica et Biophysica Acta, 1809, 141–149. [PubMed: 20840877]

Liwing J, Uttervall K, Lund J, Aldrin A, Blimark C, Carlson K, Enestig J, Flogegard M, Forsberg K, Gruber A, Haglof KH, Johansson P, Lauri B, Mellqvist UH, Swedin A, Svensson M, Nasman P, Alici E, Gahrton G, Aschan J, & Nahi H (2014) Improved survival in myeloma patients: starting to

close in on the gap between elderly patients and a matched normal population. British Journal of Haematology, 164, 684–693. [PubMed: 24313224]

Lonial S, Mitsiades CS, & Richardson PG (2011) Treatment options for relapsed and refractory multiple myeloma. Clinical Cancer Research, 17, 1264–1277. [PubMed: 21411442]

Lonial S, Niesvizky R, McCulloch L, Rajangam K, & Vij R (2012) Cardiac and pulmonary safety profile of single-agent carfilzomib from four phase 2 studies in patients with relapsed and/or refractory multiple myeloma. Blood, 120, 4037.

Ma MH, Yang HH, Parker K, Manyak S, Friedman JM, Altamirano C, Wu ZQ, Borad MJ, Frantzen M, Roussos E, Neeser J, Mikail A, Adams J, Sjak-Shie N, Vescio RA, & Berenson JR (2003) The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. Clinical Cancer Research, 9, 1136–1144. [PubMed: 12631619]

Mateos MV & San Miguel JF (2013) How should we treat newly diagnosed multiple myeloma patients? Hematology American Society of Hematology Education Program, 2013, 488–495. [PubMed: 24319223]

McBride A & Ryan PY (2013) Proteasome inhibitors in the treatment of multiple myeloma. Expert Review Anticancer Therapy, 13, 339–358.

McBride W, Jackman JD Jr., Gammon RS, & Willerson JT (1988) High-output cardiac failure in patients with multiple myeloma. New England Journal of Medicine, 319, 1651–1653. [PubMed: 3200279]

Mikhael JR, Schuster SR, Jimenez-Zepeda VH, Bello N, Spong J, Reeder CB, Stewart AK, Bergsagel PL, & Fonseca R (2012) Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood, 119, 4391–4394. [PubMed: 22331188]

Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, Fanourakis G, Gu X, Bailey C, Joseph M, Libermann TA, Schlossman R, Munshi NC, Hideshima T, & Anderson KC (2003) The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. Blood, 101, 2377–2380. [PubMed: 12424198]

Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, Rekhtman G, Masliak Z, Robak T, Shubina A, Arnulf B, Kropff M, Cavet J, Esseltine DL, Feng H, Girgis S, van de Velde H, Deraedt W, & Harousseau JL (2011) Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncology, 12, 431–440. [PubMed: 21507715]

Moreau P, Richardson PG, Cavo M, Orlowski RZ, San Miguel JF, Palumbo A, & Harousseau JL (2012) Proteasome inhibitors in multiple myeloma: 10 years later. Blood, 120, 947–959. [PubMed: 22645181]

Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, Sandhu I, Ganly P, Baker BW, Jackson SR, Stoppa AM, Simpson DR, Gimsing P, Palumbo A, Garderet L, Cavo M, Kumar S, Touzeau C, Buadi FK, Laubach JP, Berg DT, Lin J, Di BA, Hui AM, van de Velde H, & Richardson PG (2016) Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. New England Journal of Medicine, 374, 1621–1634. [PubMed: 27119237]

Orlowski RZ, Nagler A, Sonneveld P, Blade J, Hajek R, Spencer A, San MJ, Robak T, Dmoszynska A, Horvath N, Spicka I, Sutherland HJ, Suvorov AN, Zhuang SH, Parekh T, Xiu L, Yuan Z, Rackoff W, & Harousseau JL (2007) Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. Journal of Clinical Oncology, 25, 3892–3901. [PubMed: 17679727]

Portbury AL, Ronnebaum SM, Zungu M, Patterson C, & Willis MS (2012) Back to your heart: ubiquitin proteasome system-regulated signal transduction. Journal of Molecular and Cellular Cardiology, 52, 526–537. [PubMed: 22085703]

Powell SR, Herrmann J, Lerman A, Patterson C, & Wang X (2012) The ubiquitin-proteasome system and cardiovascular disease. Progress in Molecular Biology and Translational Science, 109, 295–346. [PubMed: 22727426]

Reece DE, Hegenbart U, Sanchorawala V, Merlini G, Palladini G, Blade J, Fermand JP, Hassoun H, Heffner L, Vescio RA, Liu K, Enny C, Esseltine DL, van de Velde H, Cakana A, & Comenzo RL

(2011) Efficacy and safety of once-weekly and twice-weekly bortezomib in patients with relapsed systemic AL amyloidosis: results of a phase 1/2 study. Blood, 118, 865–873. [PubMed: 21562045]

Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar SV, Srkalovic G, Alsina M, Alexanian R, Siegel D, Orlowski RZ, Kuter D, Limentani SA, Lee S, Hideshima T, Esseltine DL, Kauffman M, Adams J, Schenkein DP, & Anderson KC (2003) A phase 2 study of bortezomib in relapsed, refractory myeloma. New England Journal of Medicine, 348, 2609–2617. [PubMed: 12826635]

Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, San-Miguel JF, Blade J, Boccadoro M, Cavenagh J, Dalton WS, Boral AL, Esseltine DL, Porter JB, Schenkein D, & Anderson KC (2005) Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. New England Journal of Medicine, 352, 2487–2498. [PubMed: 15958804]

Robin J, Fintel B, Pikovskaya O, Davidson C, Cilley J, & Flaherty J (2008) Multiple myeloma presenting with high-output heart failure and improving with anti-angiogenesis therapy: two case reports and a review of the literature. Journal of Medical Case Reports, 2, 229. [PubMed: 18627621]

Roccaro AM, Hideshima T, Raje N, Kumar S, Ishitsuka K, Yasui H, Shiraishi N, Ribatti D, Nico B, Vacca A, Dammacco F, Richardson PG, & Anderson KC (2006) Bortezomib mediates antiangiogenesis in multiple myeloma via direct and indirect effects on endothelial cells. Cancer Research, 66, 184–191. [PubMed: 16397231]

Rosinol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, Granell M, Besalduch J, Palomera L, Gonzalez Y, Etxebeste MA, Diaz-Mediavilla J, Hernandez MT, de AF, Gutierrez NC, Martin-Ramos ML, Cibeira MT, Mateos MV, Martinez J, Alegre A, Lahuerta JJ, San MJ, & Blade J (2012) Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood, 120, 1589–1596. [PubMed: 22791289]

San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, Spicka I, Petrucci MT, Palumbo A, Samoilova OS, Dmoszynska A, Abdulkadyrov KM, Schots R, Jiang B, Mateos MV, Anderson KC, Esseltine DL, Liu K, Cakana A, van de Velde H, & Richardson PG (2008) Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. New England Journal of Medicine, 359, 906–917. [PubMed: 18753647]

Scruggs SB, Ping P, & Zong C (2011) Heterogeneous cardiac proteasomes: mandated by diverse substrates? Physiology (Bethesda, Md), 26, 106–114.

Siegel D, Martin T, Nooka A, Harvey RD, Vij R, Niesvizky R, Badros AZ, Jagannath S, McCulloch L, Rajangam K, & Lonial S (2013) Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica, 98, 1753–1761. [PubMed: 23935022]

Sonneveld P, Schmidt-Wolf IG, van der Holt B, El JL, Bertsch U, Salwender H, Zweegman S, Vellenga E, Broyl A, Blau IW, Weisel KC, Wittebol S, Bos GM, Stevens-Kroef M, Scheid C, Pfreundschuh M, Hose D, Jauch A, van de Velde H, Raymakers R, Schaafsma MR, Kersten MJ, van Marwijk-Kooy M, Duehrsen U, Lindemann W, Wijermans PW, Lokhorst HM, & Goldschmidt HM (2012) Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. Journal of Clinical Oncology, 30, 2946–2955. [PubMed: 22802322]

Sonneveld P, Goldschmidt H, Rosinol L, Blade J, Lahuerta JJ, Cavo M, Tacchetti P, Zamagni E, Attal M, Lokhorst HM, Desai A, Cakana A, Liu K, van de Velde H, Esseltine DL, & Moreau P (2013) Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. Journal of Clinical Oncology, 31, 3279–3287. [PubMed: 23897961]

Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, Hajek R, Rosinol L, Siegel DS, Mihaylov GG, Goranova-Marinova V, Rajnics P, Suvorov A, Niesvizky R, Jakubowiak AJ, San-Miguel JF, Ludwig H, Wang M, Maisnar V, Minarik J, Bensinger WI, Mateos MV, Ben-Yehuda D, Kukreti V, Zojwalla N, Tonda ME, Yang X, Xing B, Moreau P, & Palumbo A (2015)

Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. New England Journal of Medicine, 372, 142–152. [PubMed: 25482145]

Su H & Wang X (2010) The ubiquitin-proteasome system in cardiac proteinopathy: a quality control perspective. Cardiovascular Research, 85, 253–262. [PubMed: 19696071]

Subedi A, Sharma LR, & Shah BK (2014) Bortezomib-induced acute congestive heart failure: a case report and review of literature. Annals of Hematolgy, e-pub ahead of print; doi: 10.1007/s00277-014-2026-z.

Sureddi RK, Amani F, Hebbar P, Williams DK, Leonardi M, Paydak H, & Mehta JL (2012) Atrial fibrillation following autologous stem cell transplantation in patients with multiple myeloma: incidence and risk factors. Therapeutic Advances in Cardiovascular Disease, 6, 229–236. [PubMed: 23047326]

Takamatsu H, Yamashita T, Kotani T, Sawazaki A, Okumura H, & Nakao S (2010) Ischemic heart disease associated with bortezomib treatment combined with dexamethasone in a patient with multiple myeloma. International Journal of Hematology, 91, 903–906. [PubMed: 20458563]

Tamaki H, Naito Y, Lee-Kawabata M, Taniguchi Y, Hao H, Hirota S, Hasegawa S, Masuyama T, & Ogawa H (2010) Sustained improvement in cardiac function with persistent amyloid deposition in a patient with multiple myeloma-associated cardiac amyloidosis treated with bortezomib. International Journal of Hematology, 92, 655–658. [PubMed: 20976630]

Touzeau C, Kolb B, Hulin C, Caillot D, Benboubker L, Tiab M, Leleu X, Roussel M, Chaleteix C, Attal M, Facon T, & Moreau P (2013) Effect of CMP, carfilzomib (CFZ) plus melphalan-prednisone (MP), on response rates in elderly patients (pts) with newly diagnosed multiple myeloma (NDMM): Results of a phase (Ph) I/II trial. Journal of Clinical Oncology, 31, 8513.

Voortman J & Giaccone G (2006) Severe reversible cardiac failure after bortezomib treatment combined with chemotherapy in a non-small cell lung cancer patient: a case report. BMC Cancer, 6, 129. [PubMed: 16689991]

Willis MS & Patterson C (2013) Proteotoxicity and cardiac dysfunction--Alzheimer's disease of the heart? New England Journal of Medicine, 368, 455–464. [PubMed: 23363499]

Xiao Y, Yin J, Wei J, & Shang Z (2014) Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. PLoS One, 9, e87671. [PubMed: 24489948]

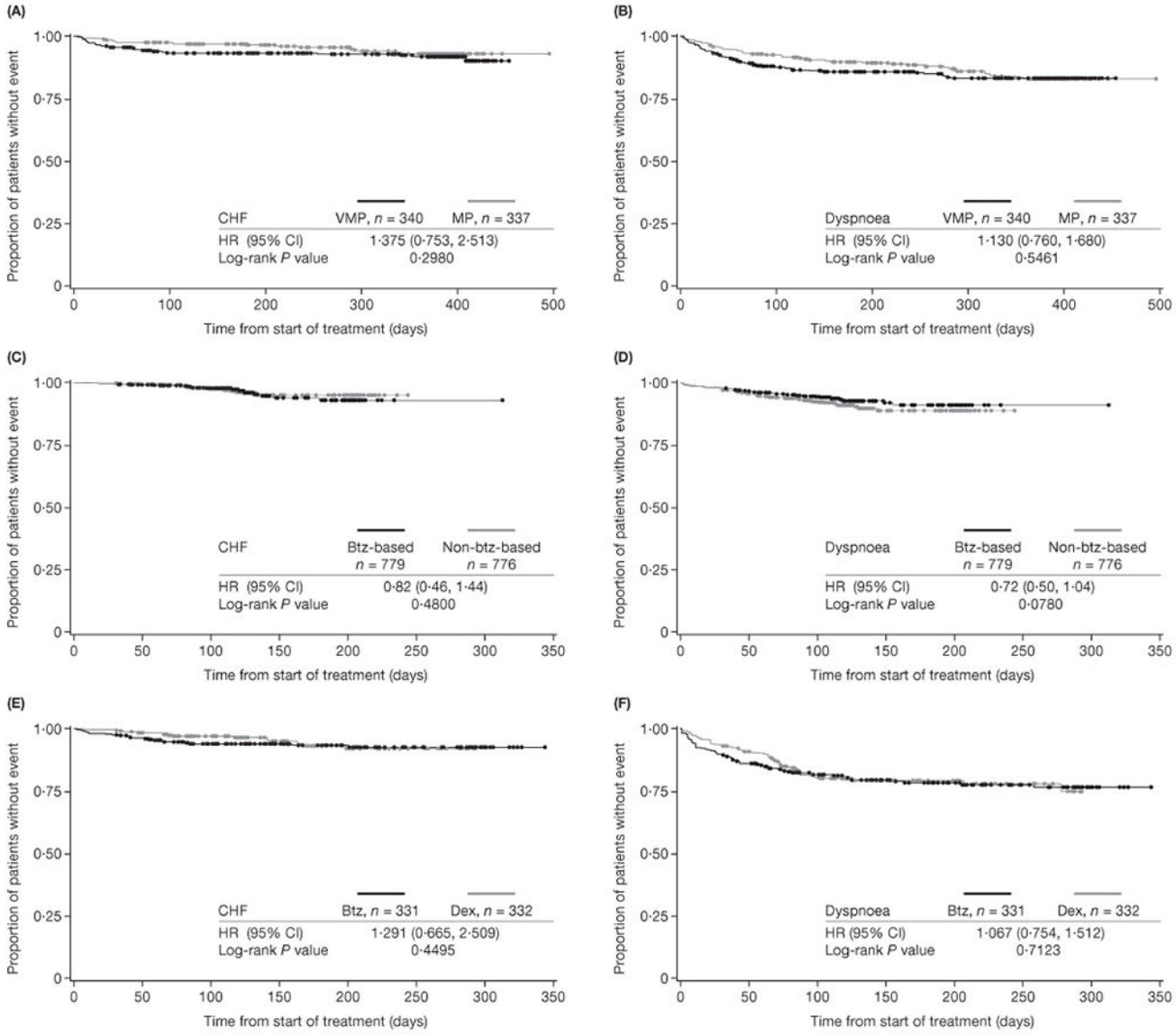

Fig 1.

Time to first onset of CHF and dyspnoea in (A, B) VISTA (San Miguel et al, 2008), (C, D) the pooled transplant analysis and (E, F) APEX.

HR shown for time to first onset of CHF or dyspnoea. Circles represent individual censored observations.

APEX, Assessment of Proteasome Inhibition for Extending Remissions study;Btz, bortezomib; CHF, congestive heart failure; Dex, dexamethasone; HR, hazard ratio; MP, melphalan-prednisone; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

Table I.

Patient characteristics, cardiac history and cardiac exclusion criteria used in the bortezomib studies included in this analysis of cardiac events. Studies in the pooled transplant analysis were IFM 2005-01 (bortezomib-dexamethasone vs. vincristine-doxorubicin-dexamethasone [VAD] induction) (Harousseau et al, 2010), HOVON-65/GMMG-HD4 (bortezomib-doxorubicin-dexamethasone vs. VAD) (Sonneveld et al, 2012) and PETHEMA GEM2005MENOS65 (bortezomib-thalidomide-dexamethasone vs. thalidomide-dexamethasone vs. combination chemotherapy plus single-agent bortezomib) (Rosinol et al, 2012).

Study	Arm	*N*[*]	Age, years[†]	Prior lines[†]	Prior anthra, *n* (%)	Cardiac history, *n* (%)	Cardiac exclusion criteria
RRMM							
SUMMIT (Richardson et al, 2003)	Btz ± dex	202	59 (34–84)	6 (2–15)	163 (81)	94 (47)[‡]	NYHA Class III/IV; Acute ischaemia by ECG; Clinically significant conduction abnormalities; MI within 6 months
APEX (Richardson et al, 2005)	Btz	331	62 (33–84)	2 (1–≥4)	255 (77)	192 (58)[‡]	As SUMMIT, plus: Uncontrolled angina; Severe uncontrolled ventricular arrhythmias
	Dex	332	61 (27–86)		253 (76)	190 (57)[‡]	
MMY-3001 (Orlowski et al, 2007)	Btz + Dox	318	61 (28–85)	2 (NR)	220/324 (68)	181 (57)[§]	As APEX/SUMMIT, but NYHA Class II–IV, plus: Clinically significant pericardial disease
	Btz	318	62 (34–88)		216/322 (67)	173 (54)[§]	
MMY-3021 (Moreau et al, 2011)	SC btz ± dex	147	64 (42–88)	1 (1–3)	58 (39)	97 (66)[¶]	As APEX/SUMMIT
	IV btz ± dex	74	64.5 (38–86)		32 (43)	44 (59)[¶]	
Previously untreated MM							
VISTA (San Miguel et al, 2008)	VMP	340	71 (57–90)	0	0	252 (74)[#]	As SUMMIT, plus: Uncontrolled angina; Clinically significant pericardial disease; Cardiac amyloidosis
	MP	337	71 (48–91)			250 (74)[#]	
Pooled transplant analysis (Sonneveld et al, 2012)	Btz based	779	57 (31–65)	0	0	165 (21)[**]	IFM 2005-01 and PETHEMA GEM2005MENOS65: as APEX, plus: Heart failure HOVON-65/GMMG-HD4: Severe cardiac dysfunction (NYHA Class II–IV)
	Non-btz based	776	57 (25–65)			169 (22)[**]	

anthra, anthracyclines; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; Dex, dexamethasone; Dox, liposomal doxorubicin; ECG, electrocardiogram; GMMG, German Multicentre Myeloma Group; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Group; IFM, Intergroupe Francophone du Myélome; IV, intravenous; MI, myocardial infarction; MM, multiple myeloma; MP, melphalan-prednisone; NR, not reported; NYHA, New York Heart Association; PETHMA, Programme for the Study and Treatment of Haematological Malignancies; SC,

subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

*Safety population.

†Median (range).

Cardiac history defined as ‘any abnormal finding in the cardiovascular system organ class’, and per individual study definitions, as follows:

‡Recorded medical history on case report form under cardiovascular category

§Abnormal cardiovascular history

¶History of heart failure

#History of cardiac condition.

**For IFM 2005-01, all patients with history of any general cardiac condition; for HOVON-65/GMMG-HD4, all patients with history of any cardiac arrhythmia or general cardiac condition; for PETHEMA GEM2005MENOS65, based on clinical review of medical history terms considered related to history of cardiac failure.

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Table II.

Incidence of congestive heart failure reported in phase 2 and phase 3 trials of bortezomib.

				Incidence, *n* (%)		Incidence rate, *n*/pt-yr		HR (95% CI)	
Study	**Arm**	***N***	**Exposure, pt-yr**	**All AE**	**Grade ≥3**	**All AE**	**Grade ≥3**	**All AE**	**Grade ≥3**
Relapsed and/or refractory MM									
SUMMIT (Richardson et al, 2003)	Btz ± dex	202	59·5	15 (7·4)	8 (4·0)	0·336	0·151	NA	NA
APEX (Richardson et al, 2005)	Btz	331	129·2	21 (6·3)	7 (2·1)	0·224	0·07	1·29 (0·67, 2·51)	0·89 (0·31, 2·53)
	Dex	332	100·9	15 (4·5)	7 (2·1)	0·198	0·079		
MMY-3001 (Orlowski et al, 2007)	Btz + dox	318	101·3	23 (7·2)	4 (1·3)	0·247	0·039	0·42 (0·20, 0·88) *	1·21 (0·32, 4·49)
	Btz	318	101·4	10 (3·1)	5 (1·6)	0·099	0·049		
MMY-3021 (Moreau et al, 2011)	SC btz	147	63·3	3 (2·0)	3 (2·0)	0·047	0·047	0·50 (0·10, 2·49)	1·50 (0·16, 14·45)
	IV btz	74	30·9	3 (4·1)	1 (1·4)	0·097	0·032		
Previously untreated MM									
VISTA (San Miguel et al, 2008)	VMP	340	254·2	26 (7·6) †	16 (4·7)	0·161	0·083	1·38 (0·75, 2·51)	1·14 (0·55, 2·37)
	MP	337	226·7	18 (5·3)	13 (3·9)	0·097	0·066		
Pooled analysis (Sonneveld et al, 2012)	Btz based	779	254·6	24 (3·1)	9 (1·2)	0·110	0·043	0·82 (0·46, 1·44)	2·08 (0·64, 6·80)
	Non-btz based	776	254·7	25 (3·2)	4 (0·5)	0·110	0·016		

AE, adverse event; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

* $P = 0{\cdot}017$ (log-rank test).

† One patient with missing grade.

Table III.

Incidence of at least grade 2 arrhythmia reported in phase 2 and phase 3 trials of bortezomib.

				Incidence, *n* (%)		Incidence rate, *n*/pt-yr		HR (95% CI)	
Study	**Arm**	***N***	**Exposure, pt-yr**	**Grade ≥2**	**Grade ≥3**	**Grade ≥2**	**Grade ≥3**	**Grade ≥2**	**Grade ≥3**
Relapsed and/or refractory MM									
SUMMIT (Richardson et al, 2003)	Btz ± dex	202	59·5	3 (1·5)	3 (1·5)	0·05	0·05	NA	NA
APEX (Richardson et al, 2005)	Btz	331	129·2	13 (3·9)	6 (1·8)	0·132	0·046	0·93 (0·43, 2·01)	0·93 (0·30, 2·88)
	Dex	332	100·9	13 (3·9)	6 (1·8)	0·139	0·069		
MMY-3001 (Orlowski et al, 2007)	Btz + dox	318	101·3	9 (2·8)	3 (0·9)	0·109	0·03	0·45 (0·14, 1·45)	0·71 (0·12, 4·31)
	Btz	318	101·4	4 (1·3)	2 (0·6)	0·049	0·02		
MMY-3021 (Moreau et al, 2011)	SC btz	147	63·3	5 (3·4)	2 (1·4)	0·079	0·032	0·83 (0·20, 3·47)	1·00 (0·09, 11·06)
	IV btz	74	30·9	3 (4·1)	1 (1·4)	0·097	0·032		
Previously untreated MM									
VISTA (San Miguel et al, 2008)	VMP	340	254·2	20 (5·9)	14 (4·1)	0·126	0·087	1·28 (0·66, 2·51)	1·47 (0·64, 3·39)
	MP	337	226·7	15 (4·5)	9 (2·7)	0·088	0·049		
Pooled analysis (Sonneveld et al, 2012)	Btz based	779	254·6	27 (3·5)	13 (1·7)	0·126	0·051	1·17 (0·67, 2·04)	1·19 (0·53, 2·65)
	Non-btz based	776	254·7	23 (3·0)	11 (1·4)	0·094	0·043		

APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

Table IV.

Incidence of ischaemic heart disease reported in phase 2 and phase 3 trials of bortezomib.

				Incidence, *n* (%)		Incidence rate, *n*/pt-yr		HR (95% CI)	
Study	**Arm**	***N***	**Exposure, pt-yr**	**All AE**	**Grade ≥3**	**All AE**	**Grade ≥3**	**All AE**	**Grade ≥3**
Relapsed and/or refractory MM									
SUMMIT (Richardson et al, 2003)	Btz ± dex	202	59·5	4 (2·0)	1 (0·5)	0·067	0·017	NA	NA
APEX (Richardson et al, 2005)	Btz	331	129·2	5 (1·5)	3 (0·9)	0·077	0·031	0·54 (0·18, 1·65)	0·53 (0·13, 2·23)
	Dex	332	100·9	8 (2·4)	5 (1·5)	0·099	0·059		
MMY-3001 (Orlowski et al, 2007)	Btz + dox	318	101·3	6 (1·9)	2 (0·6)	0·059	0·02	0·90 (0·27, 2·99)	1·86 (0·30, 11·66)
	Btz	318	101·4	5 (1·6)	3 (0·9)	0·079	0·049		
MMY-3021 (Moreau et al, 2011)	SC btz	147	63·3	3 (2·0)	2 (1·4)	0·047	0·032	0·75 (0·13, 4·49)	0·50 (0·07, 3·53)
	IV btz	74	30·9	2 (2·7)	2 (2·7)	0·065	0·065		
Previously untreated MM									
VISTA (San Miguel et al, 2008)	VMP	340	254·2	10 (2·9)	5 (1·5)	0·047	0·02	1·20 (0·48, 3·05)	0·96 (0·28, 3·31)
	MP	337	226·7	8 (2·4)	5 (1·5)	0·04	0·022		
Pooled analysis (Sonneveld et al, 2012)	Btz based	779	254·6	9 (1·2)	3 (0·4)	0·039	0·016		
	Non-btz based	776	254·7	14 (1·8)	3 (0·4)	0·055	0·012	0·72 (0·31, 1·71)	1·50 (0·25, 8·98)

AE, adverse event; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; NE, not estimable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

Table V.

Incidence of hypertension reported in phase 2 and phase 3 trials of bortezomib.

				Incidence, *n* (%)		Incidence rate, *n*/pt-yr		HR (95% CI)	
Study	**Arm**	***N***	**Exposure, pt-yr**	**All AE**	**Grade ≥3**	**All AE**	**Grade ≥3**	**All AE**	**Grade ≥3**
Relapsed and/or refractory MM									
SUMMIT (Richardson et al, 2003)	Btz ± dex	202	59·5	10 (5·0)	3 (1·5)	0·202	0·05	NA	NA
APEX (Richardson et al, 2005)	Btz	331	129·2	22 (6·6)	6 (1·8)	0·201	0·046	1·14 (0·60, 2·15)	1·25 (0·35, 4·49)
	Dex	332	100·9	17 (5·1)	4 (1·2)	0·178	0·04		
MMY-3001 (Orlowski et al, 2007)	Btz + dox	318	101·3	11 (3·5)	2 (0·6)	0·168	0·02	1·65 (0·78, 3·49)	1·49 (0·25, 8·91)
	Btz	318	101·4	18 (5·7)	3 (0·9)	0·187	0·03		
MMY-3021 (Moreau et al, 2011)	SC btz	147	63·3	14 (9·5)	3 (2·0)	0·348	0·095	2·33 (0·67, 8·12)	NE
	IV btz	74	30·9	3 (4·1)	0	0·097	0		
Previously untreated MM									
VISTA (San Miguel et al, 2008)	VMP	340	254·2	46 (13·5)	10 (2·9)	0·26	0·043	1·54 (0·97, 2·46) *	2·94 (0·80, 10·80) †
	MP	337	226·7	30 (8·9)	4 (1·2)	0·212	0·022		
Pooled analysis (Sonneveld et al, 2012)	Btz based	779	254·6	40 (5·1)	12 (1·5)	0·165	0·047		
	Non-btz based	776	254·7	29 (3·7)	6 (0·8)	0·122	0·024	1·38 (0·85, 2·24)	1·95 (0·73, 5·20)

AE, adverse event; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; NE, not estimable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

* $P = 0{\cdot}0656$ (log-rank test).

† $P = 0{\cdot}0881$ (log-rank test).