



Cardiovascular adverse events in multiple myeloma patients

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Abstract: Multiple myeloma is a malignant disease, caused by an uncontrolled clonal proliferation of a specific group of white blood cells, the plasma cells. Clinical manifestations include bone pain due to osteolysis, hypercalcemia, anemia, and renal insufficiency. Proteasome inhibitors have substantially improved survival of patients suffering from multiple myeloma, providing an efficient treatment option mainly for relapsed and refractory multiple myeloma. Although constituting one substance class, bortezomib, carfilzomib, and ixazomib differ greatly regarding their non-hematologic side effects. This article reviews the clinical and preclinical data on approved proteasome inhibitors in an attempt to decipher the underlying pathomechanisms related to cardiovascular adverse events seen in clinical trials.

Keywords: Multiple myeloma; cardio-oncology; cardiotoxicity; proteasome inhibitors; carfilzomib; bortezomib; ixazomib

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Introduction

Multiple myeloma is caused by an uncontrolled clonal proliferation of a specific group of white blood cells, the plasma cells. Worldwide the incidence rate of multiple myeloma is 2.1 per 100,000 persons. The highest incidence was reported in high-income North-America and Western Europe with 5.2/100,000 persons and 4.6/100,000 persons, respectively. The disease accounted for 2.1 million disability adjusted life years globally in 2016 (1).

Clinical manifestations include bone pain due to osteolysis, hypercalcemia, anemia, and renal insufficiency. Disease-related and therapy-related adverse cardiovascular events demand close interdisciplinary collaboration between cardiologists and oncologists to ensure optimal medical care. Changes in plasma composition and baseline therapy increase the thromboembolic risk to 1–2% (2). The risk might further increase up to 25% depending on the chemotherapeutic/immune agents used (2). Furthermore,

uncontrolled immunoglobulin light-chain production seen in some patients is related to the development of cardiac amyloidosis as a severe complication (3). As multiple myeloma is frequently incurable, its therapy aims at improving overall survival and patients' quality of life. Recent advances in the treatment of refractory stages, including the introduction of modern immunomodulatory drugs and proteasome inhibitors, have increased overall survival tremendously (4). While immunomodulatory drugs such as lenalidomide have been associated with an increase of thromboembolic events, proteasome inhibitors such as carfilzomib have been associated with an increase in heart failure and arrhythmias (2,4).

The following review aims to give an overview of the current literature about therapy-related cardiac events in patients with multiple myeloma. Especially, the last generation of proteasome inhibitors with its most prominent agent “carfilzomib”, has been related to a significant number of cardiac events. Protein quality

control, with which proteasome inhibitors mostly interfere, is an essential part of the molecular machinery of cardiomyocytes, endothelial cells, and presumably all other members of the cardiac environment. Therefore, the second part of the review will give mechanistic insights on the role of the ubiquitin-proteasome pathway in cardiomyocytes with potential cardioprotective targets.

What can we learn from clinical data?

The first proteasome inhibitor approved for the treatment of multiple myeloma was bortezomib. Relying on data of the phase II SUMMIT trial, FDA (US Food and Drug Administration) approval was granted in 2003 (5). Partially reversible neurotoxicity was reported as the main non-hematologic side effect (6,7). Interestingly, cardiovascular events were not closely monitored and not well reported in clinical trials investigating the effects of bortezomib. The Assessment of Proteasome inhibition for Extending Remission (APEX) trial was the first to monitor cardiac events. In this study, similar event rates in the bortezomib and non-bortezomib group were reported (6).

Significantly improved overall response rates, even when compared to bortezomib, lead to FDA and European Medicines Agency (EMA) approval of carfilzomib in 2012 and 2016, respectively (8,9). An increase in hypertension, heart failure, and ischemic heart disease in the carfilzomib arm of the ASPIRE trial (Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for the Treatment of Patients with Relapsed Multiple Myeloma; see *Table 1*) led to the post-marketing requirement to conduct another trial including a subgroup that was closely monitored for significant changes in cardiac function (see FDA Application No. 202714Orig1s000 PMR 1908-2) (8). The ENDEAVOR trial evaluated the efficacy and safety of carfilzomib (464 enrolled patients) in a direct comparison to bortezomib (465 patients). Response rates as well as cardiac side effects (hypertension and heart failure) were significantly higher in the carfilzomib arm, while neurotoxic side effects were more frequently observed under bortezomib treatment (9). In the interpretation of cardiac events in ENDEAVOR, there are some limitations: Only clinically overt heart failure was reported, cardiac biomarkers were not consequently measured, changes in left ventricular function were only sequentially measured in a subpopulation, and not reported in discrete data (9). However, when compared to other randomized controlled trials investigating the effects of proteasome inhibitors in

patients suffering from multiple myeloma, ENDEAVOR gives the most detailed report on cardiac side effects (see *Table 1*). Patients with a left ventricular ejection fraction <40% or clinical symptoms of heart failure (NYHA III or NYHA IV) or recent history of myocardial infarction or symptoms of cardiac ischemia were excluded from the trial.

Ultimately, ixazomib, an orally administered proteasome inhibitor, was approved for the treatment of relapsed and refractory multiple myeloma by the FDA and EMA in 2015. In the largest trial, which randomized ixazomib *vs.* placebo on top of lenalidomide and dexamethasone, gastrointestinal side effects were the most prominent non-hematologic adverse events associated with ixazomib (15). The incidence of hypertension (6% in the placebo *vs.* 5% in the ixazomib group), heart failure (4% in both arms), arrhythmia (16% in placebo *vs.* 15% in the ixazomib group), and myocardial infarction (1% *vs.* 2%) differed not significantly, suggesting less cardiotoxicity. Mechanistically, ixazomib inhibits the proteasome activity reversibly, comparable to the mode of action of bortezomib. Patients with clinical symptoms of arrhythmias, heart failure, or unstable angina were excluded from the trial. Venous thromboembolism was less frequent (8% *vs.* 11%) with the addition of ixazomib (15). Venous thromboembolism was also unexpectedly low in patients treated with bortezomib in combination with lenalidomide and dexamethasone (12).

Further proteasome inhibitors, currently not approved by the FDA or EMA, have been tested with varying results. Delanzomib and oprozomib did show only limited activity against multiple myeloma. Most frequently occurring non-hematologic adverse events were minor neuropathies and gastrointestinal side effects, respectively (16,17). Marizomib, an irreversible proteasome inhibitor, showed promising results regarding anti-tumor activity. Cardiac side effects were not reported so far. Also, parameters indicative of cardiac side effects, such as left ventricular ejection fraction, longitudinal strain, or biomarkers, however, were not reported/measured (18). Some recent studies only report or measure electrocardiogram (ECG) data (16). However, ECG screening is not sufficient to detect cardiotoxicity and did not reveal the inherent cardiotoxicity of carfilzomib (13).

Interestingly, Clinical data also show that proteasome inhibitors might be protective against venous thromboembolism in patients at increased risk. Patients treated with lenalidomide (immunomodulatory drugs) and dexamethasone had less thromboembolic events with the addition of a proteasome inhibitor (11% without ixazomib *vs.* 8% with ixazomib, see *Table 1*) (15). Another phase I

Table 1 Selected published clinical trials on EMA and FDA approved proteasome inhibitors in multiple myeloma

Proteasome inhibitor	Acronym	Phase	No. subjects	Clinical setting	Treatment	ORR	Cardiovascular adverse events	Ref.
Bortezomib	Summit	II	196	Relapsed MM	BTZ	35%	Not reported/measured	(5)
Bortezomib	APEX	III	669	Relapsed MM	BTZ vs. Dexa	38% vs. 18%	Cardiac events 15% vs. 13%; heart failure 2% in both groups	(6)
Bortezomib	MMVAR/IFM 2005-04	III	269	Relapsed MM after AT	BTZ + TH + Dexa vs. TH + Dexa	56% vs. 35%	Cardiac grade 3 and 4 adverse events: 1.5% vs. 0.7%	(10)
Bortezomib	HOVON-65/GMMG-HD4	III	827	Newly diagnosed MM	BTZ + Doxo + Dexa vs. Vinc + Doxo + Dexa	36% vs. 24%	Not reported/measured	(11)
Bortezomib	–	II	64	Relapsed/refractory MM	BTZ + LEN + Dexa	64%	Atrial fibrillation 3%; Hypotension 2%; venous thromboembolism 3%	(12)
Carfilzomib	–	II	50	Relapsed/refractory MM	CFZ	26%	Congestive heart failure 6%; no notable changes on ECG	(13)
Carfilzomib	ASPIRE	III	792	Relapsed MM	CFZ + Len + Dexa vs. Len + Dexa	87% vs. 67%	Hypertension 14.3% vs. 6.9%; cardiac failure 6.4% vs. 4.1%; ischemic heart disease 5.9% vs. 4.6%	(8)
Carfilzomib/Bortezomib	ENDEAVOR	III	929	Relapsed/refractory MM	CFZ + Dexa vs. BTZ + Dexa	54% vs. 29%	Hypertension 24.8% vs. 8.7%; cardiac failure 8.2% vs. 2.8%; ischemic heart disease 2.6% vs. 1.9%; LVEF only measured in sub-study of 151 patients	(9)
Carfilzomib	FOCUS	III	315	Relapsed/refractory MM	CFZ vs. corticosteroids	19% vs. 11%	Hypertension 15% vs. 6%; cardiac failure 5% vs. 1%	(14)
Ixazomib	TOURMALINE-MM1	III	722	Relapsed/refractory MM	IXZ + Len + Dexa vs. Len + Dexa	78% vs. 72%	Hypertension 6% vs. 5%; hypotension 6% vs. 6%; venous thromboembolism 8% vs. 11%; heart failure 4% vs. 4%; arrhythmia 16% vs. 15%; myocardial infarction 1% vs. 2%	(15)

MM, multiple myeloma; BTZ, bortezomib; Dexa, dexamethasone; TH, thalidomide; Vinc, vincristine; Doxo, doxorubicin; Len, lenalidomide; CFZ, carfilzomib; IXZ, ixazomib; ORR, overall response rate; EMA, European Medicines Agency; FDA, Food and Drug Administration.

trial on bortezomib in combination with lenalidomide and dexamethasone only showed a venous thromboembolism rate of 3%, which is strikingly low when compared to lenalidomide and dexamethasone therapy in other studies without proteasome inhibitors (12). Different proteasome inhibitors exhibit distinct non-hematologic side effects. Simplified, with all limitation of the current literature, we can conclude, that bortezomib is mainly associated with neurotoxicity, ixazomib with gastrointestinal side effects, and carfilzomib with cardiotoxicity.

According to a pooled analysis of phase II studies on carfilzomib comprising 526 patients, 22% (n=116) of patients developed cardiac side effects, 13.3% (n=70) showed arrhythmia, mainly atrial fibrillation, 7.2% (n=38) exhibited heart failure, 2% (n=9) developed treatment-associated cardiomyopathy, and 3% (n=18) suffered from ischemic heart disease. Most cardiovascular events occurred early with the first few doses administered (19). A recent retrospective study on 96 patients with multiple myeloma treated with bortezomib or carfilzomib, which sought to identify patients at risk for proteasome inhibitor-related cardiotoxicity, was not able to show any classic cardiovascular risk factor (e.g., hypertension, smoking, diabetes, etc.) to be predictive. History of atrial fibrillation/flutter or heart failure, however, was significantly more prevalent in patients experiencing cardiovascular events, emphasizing the importance of closely monitoring patients under proteasome inhibitor use (20). Concomitant radiation of the chest and anthracycline therapy increases the risk for carfilzomib mediated cardiotoxicity, while baseline biomarkers and echocardiography were not able to identify patients at an increased risk for cardiovascular events (21,22). Serum troponin levels are not indicative of heart failure. However, nt-pro-BNP levels concomitantly rise with decreased ejection fraction (23). Thus, clinical follow up with echocardiography and biomarkers is controversially discussed.

What can we learn from preclinical data?

The proteasome is an essential cellular component, responsible for the recycling of intracellular proteins. Proteasomes are protein complexes responsible for the elimination of misfolded proteins but also a major mechanism by which cells regulate the balance of protein generation and elimination (24). Proteasomes are widely distributed in the cytosol and in the nucleus of all eukaryotic cells. In the cytosol, proteasomes

associate with the centrosomes, the cytoskeleton, and the outer surface of the endoplasmic reticulum. In the nucleus, proteasomes are present throughout the nucleoplasm except for in the nucleoli (25,26). The ubiquitin-proteasome system (UPS) is the main protein degradation system in the heart (27). As much as 30% of newly synthesized proteins are terminally misfolded and therefore degraded by the proteasome shortly after their synthesis (28). Moreover, the UPS allows cells to adapt to changing physiological conditions by controlling the proteins that are in turn responsible for protein expression in response to stress. The UPS is also important for the maintenance of protein turnover of obsolete, oxidized, mutant, denatured, and misfolded proteins (29). Defects in UPS have been linked to cardiovascular disease, including atherosclerosis, familial and idiopathic cardiomyopathies, myocardial ischemia, hypertrophy, reperfusion injury, and heart failure (30-34). Under physiological conditions, the proteasome activity is the highest in cardiac and renal tissue (35). This is not surprising, because non-proliferating cells tightly control their protein turnover for adaptive and maladaptive remodeling.

The proteasome complex consists of more than 45 subunits that are divided into core particles and regulatory particles. Bortezomib, carfilzomib, and ixazomib target the 20S constitutive proteasome, which consists of four heptameric rings: two external alpha rings, which regulate the entrance of protein, and two internal beta rings that contain protease active sites. Proteasome inhibitors mainly target the $\beta 1$, $\beta 2$, and $\beta 5$ subunits of the internal ring (36). The constitutive proteasome is present in all cells. In lymphocytes and monocytes, IFN- γ and TNF- α stimulation leads to the formation of immunoproteasomes, in which the subunits $\beta 1c$, $\beta 2c$, and $\beta 5c$ are replaced by $\beta 1i$, $\beta 2i$, and $\beta 5i$ (see *Figure 1*) (36). All currently-approved proteasome inhibitors are targeting both, the immunoproteasome and the constitutive proteasome, in which carfilzomib more selectively and irreversibly binds to the $\beta 5$ subunit and bortezomib binds reversibly to the $\beta 1$ and $\beta 5$ subunits (24,36).

Interestingly, carfilzomib does also accumulate in the heart and leads to a strong inhibition of the cardiac proteasome as shown in the initial FDA-approval data. Moreover, the inhibition is stronger as in the targeted bone marrow cells. Carfilzomib reduces the 20S chymotrypsin-like activity down to 10% in cardiac cells and down to 45% in bone marrow cells 5 minutes after administration. A dose-dependent inhibition was found down to 28–56% 24

Effect of proteasome inhibition on cardiac function

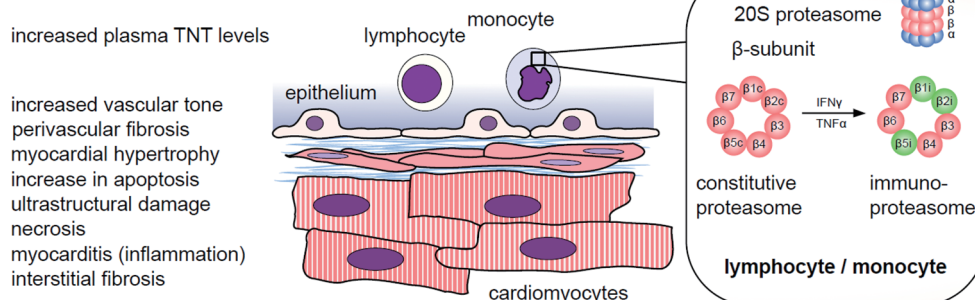


Figure 1 Effect of proteasome inhibition on cardiac function. Pathologic alterations, associated with carfilzomib administration (left-hand side), scheme of the involved compartments (middle), scheme of the 20S proteasome (right-hand side), with the differences between the constitutive proteasome and the immunoproteasome found in TNF- α or IFN- γ activated lymphocytes and monocytes as indicated.

h after last treatment with complete recovery after 28 days in cynomolgus monkeys [see studies TR-0018-171/TXC-004/TR-0011-171/TXC-003/TR-0046-171-PD in FDA: 202714Orig1s000 PHARMACOLOGY REVIEW(s)]. In rats, treatment with carfilzomib led to a reduction of the cardiac chymotrypsin-like activity down to 50% 24 h after treatment, compared to a reduction down to 80% in the bortezomib group (37). Monkeys treated with repeated doses of carfilzomib above 1mg per kg body weight developed hypotension, increased serum troponin T levels, and increased heart rates. Histopathologic analyses showed inflammation, myocyte hypertrophy, and myocardial degeneration [see FDA: 202714Orig1s000 MEDICAL REVIEW(s) Section 4.3]. One could argue, that an increase of cardiotoxic events would be quite expected based on these preclinical data.

Currently, there is a strong effort to decipher the underlying molecular mechanisms of the observed clinical effects. Therapeutic dosages lead to endothelial dysfunction, myocardial hypertrophy, myocarditis, increase in apoptosis, necrosis, and ultrastructural damage in preclinical models (see Figure 1) (38).

Endothelial dysfunction following carfilzomib treatment leads to an increase in vascular tone and vasospasms, which are only partially reversed by the application of nitrates and calcium-antagonists. These effects might explain hypertension, the most frequent cardiovascular side effect, and maybe to some extent the nominal increase in myocardial infarction (38,39). The above mentioned thrombo-protective effects of bortezomib, and presumably carfilzomib, in combination with immune-modulatory drugs is mediated by an increased expression of Kruppel-

like factor 2 (KLF2) (40).

Irreversible inhibition of the 20S proteasome by carfilzomib leads to an imbalance of ubiquitylated and non-ubiquitylated proteins, altering protein function and cell signaling (41). An increase of ubiquitylated major vault proteins and heat shock proteins due to proteasome inhibition has been associated with increased left ventricular apoptosis (42). While low dose bortezomib lead to a downregulation of Akt, Erk1/2, and calcineurin, which implies a cardioprotective and anti-hypertrophic effect, therapeutic dosages lead to mitochondrial dysfunction, a decrease in ATP synthesis, disturbed Ca^{2+} -handling, and ultimately cardiac dysfunction (43,44). Direct cardioprotective effects of carfilzomib have not been described. Carfilzomib treatment led to a number of intracellular events, such as activation of NF- κ B, ERK and JNK, with a subsequent increase in hypertrophic gene expression, increase in caspase-3 activity, p65, and increase in reactive oxygen species (ROS), and a decrease in I κ B α , an inhibitor of NF- κ B (45-47). According to the activation of pro-hypertrophic MAP-kinases, proteasome inhibition does also activate the NFAT-calcineurin pathway, a classical pro-hypertrophic pathway in cardiomyocytes (48). Activation of the intracellular pro-hypertrophic programs is currently understood as an initial event of pathological cardiac remodeling, followed by apoptosis, fibrosis, and cardiac dysfunction. Further synergistic cardiotoxic effects of proteasome inhibitors and anthracyclines can be explained by an additional generation of ROS (49). To sum up, proteasome inhibitors, administered at therapeutic dosages lead to an increase in ubiquitylated proteins, indicating intracellular accumulation of misfolded, potentially toxic

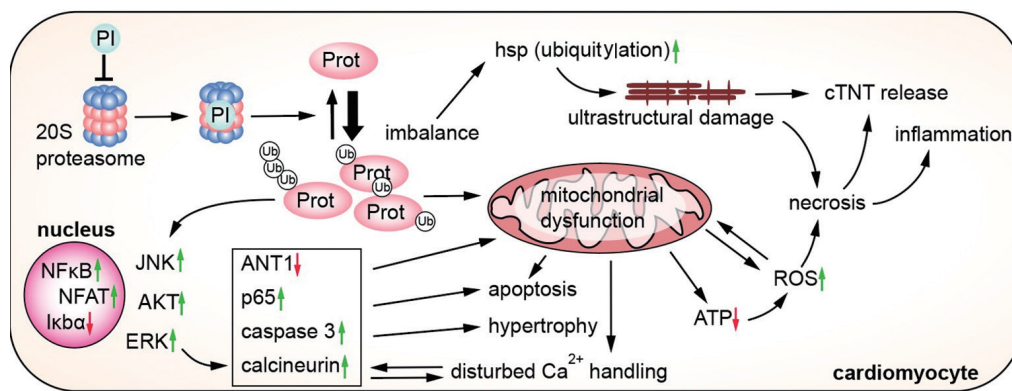


Figure 2 Overview of the involved cardiotoxic pathomechanisms of proteasome inhibitors based on Table 2. PI, protein inhibitor; Prot, protein; Ub, ubiquitin; JNK, c-Jun N-terminal kinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT, nuclear factor of activated T-cells; ERK, extracellular signal-regulated kinase; ANT1, adenine nucleotide translocator 1; p65, transcription factor p65; I κ B α , inhibitory kappa B-alpha; hsp, heat shock proteins; cTNT, cardiac troponin T; ROS, reactive oxygen species; ATP, adenosine triphosphate.

proteins, as well as activation of Akt, NF- κ B, and the NFAT-calcineurin pathways, which lead to myocardial hypertrophy. NF- κ B activation, decreasing ANT1 (adenine nucleotide translocase type 1) expression, and the burden of intracellular, ubiquitylated proteins further affect intracellular signaling and induce mitochondrial dysfunction, ROS production, and ultrastructural changes. Subsequently, this leads to an increase of apoptosis, necrosis, and release of cardiac troponin (see Figure 2) (41,50).

Cardioprotective strategies that have been successfully tested in preclinical studies include the co-administration of dexrazoxane, whereas the underlying mechanism of the protective effect of this chelator is not fully understood. Rutin, a NO scavenger, counteracts increased ROS production; apremilast, a phosphodiesterase 4 inhibitor decreases TNF- α secretion. Another strategy consists of selectively targeting the immunoproteasome (42,45-47,49). Table 2 provides an overview of preclinical studies investigating the cardiovascular effects of proteasome inhibitors and potential cardioprotective strategies.

Discussion

As opposed to other substance classes such as anthracyclines, proteasome inhibitors show distinct non-hematologic side effects. Bortezomib is mainly associated with mostly reversible neuropathy, ixazomib with gastrointestinal side effects, and carfilzomib with cardiotoxicity. Bortezomib-induced neurotoxicity is most likely non-proteasome

mediated (51). This seems plausible, as carfilzomib is a more potent proteasome inhibitor and does not show similar neurotoxicity. Although cardiotoxicity has been shown for both bortezomib and carfilzomib in preclinical data, clinical data did not reveal a significant increase of cardiovascular adverse events in patients treated with bortezomib or ixazomib, while carfilzomib use led to an increase in cardiac biomarkers and heart failure.

The proteasome regulates protein quantity and quality control in maintaining health and preventing heart disease. Given that proper protein turnover is required for cardiac homeostasis and impaired proteasomal function contributes to heart disease, the contribution of proteasome inhibition to cardiac dysfunction is plausible. Preclinical studies have elucidated the underlying cardiac pathomechanisms of irreversible proteasome inhibition by carfilzomib. However, the molecular mechanisms are not yet fully understood, and only few cardioprotective strategies have been tested in preclinical studies and practically none in clinical studies. Few case series have been published indicating that medication withdrawal or dose reduction and heart failure medication might reverse cardiomyopathy in some cases (23,52,53). Some of them report resolved cardiac dysfunction without discontinuation of carfilzomib (53). These findings have to be systematically confirmed in clinical studies. Meanwhile, cardiovascular toxicity under carfilzomib therapy could be addressed by reducing the dose, changing to bortezomib or ixazomib based regimens, and treating the cardiovascular side effects according to

Table 2 Selected preclinical studies investigating the cardiovascular mechanisms related to protein inhibitors

Proteasome inhibitor	Model	Dose used	Proposed pathomechanism	Cardioprotective drug or rationale	Treatment effect	Ref.
Bortezomib	Wistar rat	0.2 mg/kg BW 3×/week	Mitochondrial dysfunction leads to decrease in ATP synthesis, disturbed Ca ²⁺ handling, and ultimately cardiac dysfunction	N/A	N/A	(43)
Bortezomib	Dahl salt sensitive rats	0.050 mg/kg BW per day	Downregulation of Akt, Erk1/2, calcineurin	N/A	N/A	(44)
Carfilzomib	Wistar rat	6× 4 mg/kg BW per day	Activation of NF-κB leads to increase hypertrophic gene expression, oxidative stress, and apoptosis	Rutin 16× 20–40 mg/kg BW per day	Reduced toxicity	(45)
Carfilzomib	Wistar rat	6× 4 mg/kg BW per day	Increase in NF-κB, ERK, JNK leads to increase in caspase-3 and p65 and a decrease in Iκbα	Apremilast 16× 10–20 mg/kg BW per day	Reduced toxicity	(46)
Carfilzomib	Wistar rat	6× 4 mg/kg BW per day	Increase in ROS leads to myocardial damage	Dexrazoxane 16× 20–40 mg/kg BW per day	Reduced toxicity	(47)
Carfilzomib	Rabbit (ex vivo heart + aorta)	10 ⁻⁹ to 10 ⁻⁷ mol/L	Endothelial dysfunction leads to vasospasms and reduced sensitivity to nitroglycerin and nifedipine	Nitroglycerin and nifedipine	Partial reversal of vasospasms	(39)
Carfilzomib	Sprague-Dawley rats (PAH models)	4× 6 mg/kg BW in 2 weeks	Increase in ubiquitylation of major vault and heat shock proteins lead to apoptosis in the left ventricle	Dexrazoxane/pifithrin-α	Reduced left ventricular apoptosis	(42)
MG132 and epoxomicin	LMP7 deficient mice/primary cardiomyocyte	10 μM + 1 μm doxorubicin	Synergistic cardiotoxicity with doxorubicin by inhibiting the β5 proteasome subunit	Selected immunoproteasome inhibition	Reduced toxicity with LMP7 inhibition	(49)
MG262	Mice carrying NFAT binding site-dependent luciferase reporter	5 μmol/kg BW	Activation of NFAT-calcineurin pathway	N/A	N/A	(48)
MLN-273	Domestic pigs	0.08 mg/kg BW per day	Vascular dysfunction, myocyte hypertrophy, increase in apoptosis, and perivascular and interstitial fibrosis lead to hypertrophic cardiomyopathy with diastolic dysfunction	N/A	N/A	(38)

PAH, pulmonary arterial hypertension; BW, body weight; ROS, reactive oxygen species; N/A, not available.

current guidelines (54,55).

So far, there is no risk stratification available. Baseline echocardiography, cardiovascular risk factors, and biomarkers are not conclusive when assessing the individual risk for cardiotoxicity (20,21). Monitoring cardiac function as well as close interdisciplinary collaboration between cardiologist and oncologist is essential to provide optimal medical care for these patients (54).

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Footnote

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