Multiple myeloma (MM) is a plasma cell malignant abnormality characterized by uncontrolled clonal plasma cell proliferation in the bone marrow, production of monoclonal protein in the blood and/or urine, and associated organ dysfunction. It is the second most common hematological malignant abnormality, with an annual age-adjusted incidence of 6.3 per 100,000 persons in the United States. The overall survival (OS) of patients with MM has improved in the last decade, predominantly owing to the introduction of novel therapies, including immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs). The risk of cardiovascular (CV) and thrombotic events is an important consideration in treating patients with MM for several reasons. First, CV risk factors and CV disease are prevalent in the population affected by MM, becoming more relevant given patients’ improved cancer prognosis. Second, CV and thrombotic complications are associated with MM itself as well as MM therapies (eFigure 1 in the Supplement). This review will provide an overview of CV and thrombotic complications in MM patients with a focus on complications that can arise owing to IMiDs and PIs. We propose preventive and management strategies but recognize the dearth of high-quality evidence in this area.

**CV Comorbidities and Thromboembolic Risks in MM Patients**

Cardiovascular issues have emerged as relevant considerations in patients with MM given the increased survival in this population. In patients younger than 65, for example, the median 5-year OS is nearly 60%. Nevertheless, MM is typically a disease that affects older individuals with a median age of diagnosis of approximately 70 years; CV comorbidities are common in this age group. A large retrospective analysis of 32,193 patients with newly diagnosed MM (NDMM) or relapsed or refractory MM (RRMM) showed that nearly two-thirds of patients had CV disease at baseline, with ischemic heart disease (IHD), arrhythmia, and congestive heart failure (CHF) most frequently seen. Seventy percent had adverse CV events, including arrhythmia, IHD, CHF, cardiomyopathy, and conduction disorders, during a 6-year follow-up period. Cardiovascular events also contribute to early mortality in patients with MM. In an analysis of 3107 NDMM patients in United Kingdom Medical Research Council MM trials from 1980 to 2002, myocardial infarction (MI) or cerebrovascular accident accounted for 8% of early deaths (death within 60 days of trial entry) and cardiac failure was implicated in 13% of these deaths.

Patients with MM are at increased risk for thromboembolic disease. Two large population-based studies have demonstrated significantly increased thromboembolic risk in patients with MM compared with the general population. In a study of more than 4 million US military veterans, patients with MM demonstrated a 9.2-fold increase in venous thromboembolic events (VTE) risk compared with all other patients in the database. In a second
study, which included 18,627 Swedish patients with MM and 70,991 matched controls, the risks of VTE in patients with MM increased by 7.5-fold, 4.6-fold, and 4.1-fold at 1-year, 5-year, and 10-year follow up, respectively.7 Multiple myeloma is also associated with a higher arterial thromboembolic (ATE) risk, including MI, transient ischemic attack (TIA), and ischemic stroke. In the Swedish study, the risks of ATE were 1.9-, 1.5-, and 1.5-fold at 1-year, 5-year, and 10-year follow-up, respectively.8

Both VTE and ATE are associated with decreased survival in patients with MM. In a cohort of 9399 patients with MM, patients with VTE had a higher mortality at 1-year, 5-year, and 10-year of follow up, with hazard ratios (HRs) of 2.9, 1.6, and 1.6, respectively. There was also an increased mortality among patients with MM who had ATE, with HRs of 3.4, 2.2, and 2.1 at 1-year, 5-year, and 10-year follow up, respectively.8

Given these considerations, it is important to recognize baseline CV comorbidities and risk factors in patients with MM and treat them effectively. Furthermore, a better understanding of how MM itself may contribute to cardiac and vascular events is critical. Defining the baseline and MM-associated CV comorbidities becomes important, given the advent of novel MM therapies where it becomes challenging to distinguish treatment-induced CV toxic effects from MM-related CV issues. Finally, understanding potential CV toxic effects associated with treatments can help maximize the benefits from these novel agents.

Immunomodulatory Drugs (IMiDs) and Thrombosis

Thromboembolic Risks Associated With IMiD Therapy

Prior to the introduction of IMiDs, approximately 10% of MM patients treated with chemotherapy experienced VTE complications.9 In the early clinical trials, when used as a single agent, neither thalidomide nor lenalidomide appeared to increase VTE risk. However, significantly elevated VTEs were observed when IMiDs were combined with dexamethasone and/or cytotoxic chemotherapy. Reported incidences of VTE were variable in clinical trials, even with the same drug combinations (Table 1). In 2001, 2 separate phase II clinical trials of NDMM involving thalidomide-dexamethasone and thalidomide-dexamethasone-doxorubicin reported 7% and 27% incidence of VTE respectively, with the latter leading to trial suspension.10 The increased VTE risk associated with IMiDs was later confirmed in many other studies. A meta-analysis of 3322 patients with MM showed that thalidomide increased VTE risk by 2.6-fold; when thalidomide was combined with dexamethasone, VTE risk increased by 8-fold.11 Lenalidomide and pomalidomide, structurally related to thalidomide but more potent, also increase VTE risk. In a large randomized trial of lenalidomide plus high-dose dexamethasone vs lenalidomide plus low-dose dexamethasone in patients with NDMM, the VTE incidences were 26% and 12%, respectively, which also confirmed the critical role of high-dose dexamethasone as a cofactor. Owing to the high VTE incidence, the study protocol was amended, requiring mandatory thromboprophylaxis in high-risk patients.12 Moreover, this risk appears greater in patients with NDMM compared with those who have RRMM, although the effect of concomitant therapy is important. Owing to these early reports of VTE risk associated with IMiDs, thromboprophylaxis is now widely used.13,14

Immunomodulatory drugs are also associated with higher risks of ATE. In the long-term follow-up of 704 patients with MM recruited in 2 large randomized phase III trials comparing lenalidomide plus dexamethasone with placebo plus dexamethasone in patients with RRMM, the incidences of MI and cerebrovascular events were 1.98% and 3.4%, respectively, in patients treated with lenalidomide and dexamethasone, compared with 0.57% and 1.7% in patients treated with dexamethasone alone.15 For this reason, lenalidomide carries a black box warning for increased MI and stroke risks in patients with MM receiving lenalidomide and dexamethasone treatment.16

IMiDs: Mechanisms of Action

Immunomodulatory drugs have shown remarkable anti-MM effects through the direct inhibition of tumor cell proliferation as well as modulation of the immune system and the tumor microenvironment, including effects on angiogenesis.17,18 The precise mechanism of IMiDs has been elucidated more recently; IMiDs bind cereblon, a component of a E3 ubiquitin ligase, causing selective ubiquitination and proteasome-mediated degradation of 2 key lymphoid transcription factors, Ikaros family zinc finger protein (IKZF) 1 and 3, which play central roles in the biology of B and T cells. In particular, IKZF3 is critical for plasma cell development and essential in multiple myeloma pathogenesis.19,20 In T cells, IMiDs increase degradation rates of IKZF1 and IKZF3, resulting in enhanced production of interleukin-2 and other cytokines known to regulate T cell function, which may explain their potential immunomodulatory effects.21

Mechanisms Underlying Increased VTE and ATE Risks Associated With IMiDs

The mechanisms underlying IMiD-associated thromboembolism are not known. Association studies suggest a link between IMiDs and increased cytokine levels and increased activity of endothelial tissue factor, which may contribute to thrombosis (Figure 1). Genetic factors may also play a role; single-nucleotide polymorphisms (SNPs) are associated with thalidomide-related VTE.22 An SNP (rs3774968) in nuclear factor-κB was associated with increased risk of VTE in patients treated with lenalidomide-based regimens.23 However, these are merely association studies and only hypothesis generating. Critical roles of other agents in increasing endothelial stress when used in combination (such as steroids) need to be considered.24 The recent findings that IMiDs work by modulating protein ubiquitination

Table 1. Incidences of VTE in Trials of Thalidomide, Lenalidomide, or Pomalidomide Without Thromboprophylaxis

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>VTE Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDMM</td>
<td>RRMM</td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>4%</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>12-26%</td>
</tr>
<tr>
<td>Plus melphalan</td>
<td>18-20%</td>
</tr>
<tr>
<td>Plus doxorubicin</td>
<td>26-27%</td>
</tr>
<tr>
<td>Plus multiagent chemotherapy</td>
<td>26%</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>NA</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>19-75%</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed or refractory multiple myeloma; VTE, venous thromboembolic events.

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and degradation may generate testable hypotheses regarding their potential thromboembolic effects.

Thromboprophylactic Strategies

Fixed low-dose warfarin (1-1.25 mg daily) was the first thromboprophylactic regimen used; this proved largely ineffective. Aspirin (81-325 mg daily), therapeutic warfarin (INR 2-3), and low-molecular-weight heparin (LMWH) were used in later trials and decreased VTE risk (Table 2). However, large, prospective, randomized comparisons have been limited, and the optimal thromboprophylactic regimen remains an important question. A phase III trial of 667 patients with NDMM treated with thalidomide-based regimens indicated that aspirin (100 mg daily) or low-dose warfarin (1.25 mg daily) had similar efficacy in reducing VTE as LMWH (enoxaparin 40 mg daily). However, patients with high risk of VTE were excluded from this study. In another prospective study of 342 patients with NDMM treated with lenalidomide and low-dose dexamethasone for 4 cycles, followed by cyclophosphamide for stem cell mobilization and collection, patients were randomized to either low-dose aspirin (100 mg daily) or LMWH (enoxaparin 40 mg daily). Aspirin was as effective as LMWH. In this study, patients were relatively young (<65 years), without CV or thrombosis risk factors and no history of VTE or ATE. Therefore, aspirin should only be considered in patients with NDMM treated with lenalidomide plus low-dose dexamethasone who are at low VTE risk. Despite thromboprophylaxis, IMiDs can still be associated with increased risk of thrombosis. A meta-analysis of 1051 patients showed that the relative risk of VTE in patients with MM who were treated with a

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Table 2. Incidences of VTE in Trials of Thalidomide, Lenalidomide, or Pomalidomide With Thromboprophylaxis

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Aspirin</th>
<th>Fixed Low-Dose Warfarin</th>
<th>Full-Dose Warfarin</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>NA</td>
<td>13-25&lt;sup&gt;51,65&lt;/sup&gt;</td>
<td>8&lt;sup&gt;63&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>Plus melphalan</td>
<td>14&lt;sup&gt;64&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>3&lt;sup&gt;70&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plus doxorubicin</td>
<td>7&lt;sup&gt;65&lt;/sup&gt;</td>
<td>12-14&lt;sup&gt;56,87&lt;/sup&gt;</td>
<td>NA</td>
<td>8&lt;sup&gt;-10&lt;/sup&gt;&lt;sup&gt;88,89&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plus multiagent chemotherapy</td>
<td>14-25&lt;sup&gt;50,91&lt;/sup&gt;</td>
<td>8&lt;sup&gt;92&lt;/sup&gt;</td>
<td>NA</td>
<td>5-24&lt;sup&gt;91,93&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>3-19&lt;sup&gt;94,95&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Plus melphalan</td>
<td>0-6&lt;sup&gt;96,97&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Plus doxorubicin</td>
<td>4&lt;sup&gt;98&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>0-5&lt;sup&gt;99,100&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, low-molecular-weight heparin; NA, not applicable; VTE, venous thromboembolic events.
Cardiovascular and Thrombotic Complications of Multiple Myeloma Therapies

A  Venous thromboembolic events (VTE) risk assessment and recommendations

Pretreatment VTE risk assessment

- Individual risk factors: obesity (body mass index ≥30); previous VTE; central venous catheter; inherited thrombophilia; immobilization; surgery; cigarette smoking; comorbidities (cardiac disease, DM, CKD, acute infection, etc)
- Myeloma-related risk factors: disease status; hyperviscosity
- Therapy-related risk factors: high-dose dexamethasone (≥480 mg/month), concomitant use of erythropoietin; combination IMiDs with high-dose dexamethasone or doxorubicin or multiagent chemotherapy

Recommendations

- Aspirin 81-325 mg once daily should only be recommended for low-risk patients (≤1 individual or myeloma-related risk factor)
- LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2-3) should be recommended in the presence of ≥2 individual or myeloma-related risk factors
- LMWH or full-dose warfarin should be considered in all patients who receive high-dose dexamethasone or doxorubicin or multiagent chemotherapy, independent of the presence of additional risk factors
- The dose of LMWH should be adjusted according to renal function. LMWH is generally not recommended for patients with creatinine clearance <30 mL/minute

B  Cardiovascular (CV) risk assessment and recommendations

Pretreatment CV risk assessment

- A thorough history: DM, cigarette smoking, preexisting HTN, HLD, CAD, CHF
- A thorough physical examination: repeat BP measurements, volume status
- Lab and other tests: kidney function, baseline EKG, consider baseline echocardiogram in high-risk patients

Low CV risk regimen

- Regimens do not contain anthracycline, carfilzomib, or IMiD plus carfilzomib

High CV risk regimen

- Regimens contain anthracycline, carfilzomib, or IMiD plus carfilzomib

- Standard CV primary and secondary prevention
- Thromboprophylaxis as recommended in 3A
- Early involvement of cardiologist to manage CV comorbidities

- Standard CV primary and secondary prevention
- LMWH should be considered in patients on carfilzomib plus IMiD
- Early involvement of cardiologist to manage CV comorbidities
- Close monitoring CV complications during treatment

A, Modified recommendations from International Myeloma Working Group regarding VTE risk assessment and prevention in multiple myeloma (MM) patients treated with IMiDs-containing regimens. B, Proposed CV risk assessment and monitoring during MM treatment. BP indicates blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; HTN, hypertension; HLD, hyperlipidemia; IMiD, immunomodulatory drugs; and LMWH, low-molecular-weight heparin.

Thalidomide-based regimen and LWMH thromboprophylaxis was 1.54 times higher than patients not receiving thalidomide.28

The International Myeloma Working Group has made an effort to make recommendations regarding VTE risk assessment and prevention of IMiD-associated thrombosis in patients with MM (Figure 2, A). Given the relatively limited existing evidence, these recommendations are also based on expert opinion and consensus.29,30 The choice of thromboprophylaxis is deferred to treating physician's best clinical judgment based on a patient's individual risk factors, disease status, and treatment regimen, with important associations of certain combinatorial agents reducing thrombotic risk (eg, bortezomib), and others (such as steroids and cytotoxic chemotherapy) increasing VTE risk.30

Proteasome Inhibitors (PIs) and Cardiovascular Implications

Ubiquitin-Proteasome System (UPS) and PIs

Proteasome inhibitors (PIs), along with IMiDs are cornerstones of MM treatment regimens. The proteasome is an essential member of the ubiquitin-proteasome system (UPS), where proteins are tagged with ubiquitin leading to proteasome-mediated degradation. The UPS degrades the majority of regulatory proteins in eukaryocytes and plays a critical role in maintaining normal cellular homeostasis. The UPS also plays an important role in the pathophysiology of MM. The malignant plasma cells produce large quantities of immunoglobulins with an appreciable error rate in protein folding and assembly. The misfolded or unassembled proteins need to be degraded by the proteasome to prevent endoplasmic reticulum stress and apoptosis. In myeloma plasma cells, the proteasome capacity is near saturation.31 Therefore, MM cells are very sensitive to proteasome inhibition, making the UPS an ideal target for drug development. Three PIs are approved by the US Food and Drug Administration (FDA): bortezomib, carfilzomib, and ixazomib (Figure 3).

Bortezomib: Cardiovascular Implications

Although there were case reports on cardiotoxic effects associated with bortezomib,32,33 a recent meta-analysis did not show significant cardiotoxic effects of bortezomib.34 Moreover, bortezomib has been shown to have several cardioprotective roles in animal models, such as in reducing ischemia-perfusion injury,35 preventing left ventricle hypertrophy,36 and suppressing cardiac hypertrophy.37

Importantly, bortezomib is not associated with thrombogenicity. When used alone or in combination with IMiDs, bortezomib does not result in an increased VTE risk, with low rates of 0% to 5%, and may in fact have some thromboprotective properties.38 In an analysis of 3 trials (APEX, SUMMIT, CREST) using bortezomib-based regimens, patients had a low VTE risk (≤3.1%), independent from concomitant dexamethasone or erythropoietin use.39 A comprehensive review of the available data from phase III studies indicates that VTE risk is lower when bortezomib is used in combination with regimens that have thrombogenic potential, including IMiDs.38 In another study, the HR for VTE risk was 1.38 times higher in patients treated with thalidomide without bortezomib than those treated with both agents.25 There have been several proposed mechanisms that may explain the decreased VTE risk associated with bortezomib. Bortezomib can stimulate endothelial thrombomodulin expression via induction of Kruppel-like transcription factor, resulting in enhanced capacity of endothelial cells to generate activated protein C, and bortezomib can also prevent down-regulation of thrombomodulin by inflammatory cytokines.40,41

Carfilzomib: Emerging Evidence of Cardiovascular and Endothelial Toxic Effects

Early clinical trials with carfilzomib involved patients with MM who had been heavily pretreated and had advanced disease, and carfilzomib was used as monotherapy. In this setting, carfilzomib was
The UPS is constituted by 6 components, including ubiquitin, ubiquitin-activating enzymes (UbA, E1), ubiquitin-conjugating enzymes (UBC, E2), ubiquitin ligase (E3), proteasomes, and deubiquitinases (Dub). Ubiquitin is activated by ubiquitin activating enzyme, E1. Activated ubiquitin is transferred to ubiquitin conjugating enzyme E2 and subsequently conjugated to target proteins in a process mediated by E3 ubiquitin ligase. The polyubiquitinated substrate protein is degraded by the 26S proteasome into peptides. The immunomodulatory drugs (IMiDs) including thalidomide, lenalidomide, and pomalidomide, bind to E3 ubiquitin ligase and enhance the degradation of 2 specific B cell transcription factors, IKZF1 and IKZF3. There are 3 proteasome inhibitors, bortezomib, carfilzomib, and ixazomib, which are approved by the US Food and Drug Administration. The 26S proteasome consists of the 20S proteasome core and 2 19S regulatory complexes, which recognize the ubiquitinated substrates, assemble the Ub chains, unfold the target proteins, and translocate them to the 20S proteasome chamber. The 20S proteasome chamber comprises 3 types of proteolytic subunits, β1, β2, and β5, which are responsible for caspase-like, trypsin-like, and chymotrypsin-like proteolytic activity. On stimulation with interferon-γ (INF-γ), the production of immunoproteasome is stimulated, in which the active subunits are replaced by β1i, β2i, and β5i subunits. Bortezomib, carfilzomib, and ixazomib bind to and inhibit the chymotrypsin-activity of both constitutive 20S proteasome and immunoproteasome.

Clearly an effective cancer therapy but also showed significant cardiotoxic effects (eTable in the Supplement). In an integrated safety analysis of all pivotal phase II trials in which carfilzomib was used as monotherapy in patients with RRRM, 22.1% of patients experienced cardiotoxic effects, including arrhythmia (13.3%), heart failure (7.2%), and cardiovascular-related deaths (1.5%). When carfilzomib was used in combination with IMiDs in clinical trial settings, the reported cardiac and vascular adverse events were also high (16%-19%) (eTable in the Supplement).

Several retrospective case series also suggest an increased risk of cardiotoxic effects with carfilzomib. In a cohort study of 22 patients from Germany, 23% of patients experienced heart failure with significantly increased b-type natriuretic peptide (BNP) and cardiomyopathy, despite preserved cardiac function prior to carfilzomib treatment. All patients required hospitalization and intravenous diuretics; some patients required isotropic support and intensive care. Pulmonary hypertension and newly developed symptomatic atrial fibrillation were also reported in this analysis. In another analysis of 130 patients with RRM treated with carfilzomib, 26 (20%) experienced considerable cardiac adverse events during the first 2 cycles of therapy, 46% of whom did not have known cardiac diseases prior to treatment. The median left ventricular ejection fraction (LVEF) dropped significantly from 55% to 33% in these patients. The initial carfilzomib clinical trials were designed with carfilzomib administered as a bolus infusion (2-10 minutes). Owing to the observed increasing cardiac events, the infusion time was extended to 30 minutes based on the observation that 20 of the 26 cases of serious cardiac events occurred in patients receiving the 2 to 10 minute infusion. However, in a phase I carfilzomib 30-minute infusion study, 20.8% of the patients experienced cardiac adverse events. In a phase II study of carfilzomib 56 mg/m², 30-minute infusion, with or without low-dose dexamethasone, high-grade hypertension and heart failure occurred in 25% and 11% of patients, respectively, with 5 patients discontinuing treatment owing to decline in LVEF. Dyspnea is another common adverse effect associated with carfilzomib, which occurred in one-third of the patients without detectable lung injury. Dyspnea may be exacerbated by required hydration (250-1000 mL intravenous hydration given during the first cycle) and/or from cardiac dysfunction. For this reason, overly aggressive hydration in elderly and vulnerable patients should be avoided.

An important caveat with the previously-mentioned reports is that they represent single-arm studies without a comparator arm in heavily treated patients with MM; the baseline CV risk and the relative risk of CV toxic effects are unknown. On the other hand, results from the randomized, phase III trial (ASPIRE) comparing the efficacy of carfilzomib-lenalidomide-dexamethasone with lenalidomide-dexamethasone showed higher incidences of various cardiovascular toxic effects, including CHF (6.4% vs 4.1%), IHD (5.9% vs 4.6%), VTE (10.2% vs 6.2%), and hypertension (14.3% vs 6.9%) in the carfilzomib arm. The heterogeneous pattern observed suggests that carfilzomib cardiovascular toxic effects are likely more "vascular" than "myocardial" in origin, which is supported by a recent case series that carfilzomib treatment was associated with hypertensive urgency, pulmonary hypertension, acute renal insufficiency with hypertensive emergency, and acute CHF. It is important to note that in ASPIRE and earlier studies, treatment with carfilzomib was highly effective. In ASPIRE, the addition of carfilzomib significantly
prolonged progression-free survival and as a result, on July 24, 2015, the FDA approved carfilzomib in combination with lenalidomide and dexamethasone for the treatment of RRMM. The FDA statement suggests an even higher rate of CV events. The incidence of VTE in the first 12 cycles was 13% in the carfilzomib arm vs 6% in the control arm, despite protocol-mandated use of thromboprophylaxis. The revised labeling includes new warnings and precautions of VTE, cardiac toxic effects, and hypertension. The phase III ENDEAVOR trial, which compared carfilzomib-dexamethasone with bortezomib-dexamethasone in patients with RRMM, showed carfilzomib was superior to bortezomib, with a 2-fold improvement in median progression-free survival and significantly fewer neurotoxic effects. However, carfilzomib was again associated with a higher CV toxic effects profile. The incidences of hypertension, dyspnea, and heart failure were significantly higher in the carfilzomib arm in both the high-risk and standard-risk groups. A subgroup study conducted within ENDEAVOR to evaluate the left and right ventricular function via echocardiogram showed that HF incidence was higher in the carfilzomib arm (10.8% vs 4.1%). Carfilzomib was also associated with a significantly higher risk of hypertension (20.3% vs 8.1%). Close postmarketing surveillance of carfilzomib associated CV toxic effects are therefore warranted. Given these data, we also propose an algorithm of cardiovascular risk assessment and monitoring of patients with MM during treatment (Figure 2, B).

The precise nature of carfilzomib-associated CV toxic effects is incompletely understood, although underlying endothelial toxicity is suspected given the spectrum of clinically observed vascular toxic effects ranging from hypertension to VTE; however, better phenotyping of CV toxic effects in carfilzomib-treated patients is needed to inform preventive and treatment algorithms. In this regard, several studies have shown carfilzomib can impair vascular relaxation, and potentiate vasospasm. Further in vitro and in vivo experiments are needed to expand on this hypothesis to better elucidate mechanisms of endothelial injury. Existing trials involving carfilzomib will need to have comprehensive CV toxic effect end points as well as vascular markers and other surrogates evaluated.

Effect of Proteasome Inhibitors on the Cardiovascular System

It is important to note that UPS plays an essential and complicated role in the cardiovascular system. A large body of evidence shows that both the inhibition and the activation of proteasome function in the heart can confer cardiotoxic effects. The mechanisms underlying the distinct clinical effects of bortezomib and carfilzomib on the cardiovascular system are unclear. Bortezomib, as a reversible PI that binds and forms a complex with the active site of β5 subunit, blocks the chymotrypsin-like activity of the proteasome. Bortezomib becomes undetectable 72 hours after administration and the inhibited proteasome activity recovers. In contrast, carfilzomib inhibits the β5 proteasome subunit by forming an irreversible adduct through 2 covalent bonds. As an irreversible PI, carfilzomib produces more sustained inhibition of the proteasome because synthesis of new proteasome complexes is required to reverse its effects. The effects of PIs on endothelial function and the CV system have been tested in various in vitro, ex vivo, and in vivo models. Although only reversible PIs (specifically bortezomib, MG132, and MLN-273) were used in these model systems, chronic inhibition of the proteasome appears to have a harmful effect on the CV system, whereas low-dose PI has a protective role (especially in cardiac injury models).

Ixazomib, as a reversible inhibitor that primarily targets the chymotrypsin-like activity of the 20S proteasome, was recently approved by the FDA for the treatment of patients with RRMM. There has not been a CV toxic effects signal with ixazomib in early studies. These studies and the larger clinical trial data now available, suggest the possibility that the extent of proteasome inhibition may determine the extent and frequency of CV toxic effects. Alternatively, the differential toxic effects profiles observed clinically between bortezomib and carfilzomib may be owing to their different substrate specificities. For example, bortezomib has multiple nonproteasome targets; it reacts with active-site serine residues found in serine proteases including chymotrypsin, cathepsins A and G, elastase, and chymase. Neurotoxic effects, which are more pronounced with bortezomib, are likely through a proteasome-independent mechanism and owing to inhibition of HtrA1/Omi, a stress-induced protease involved in neuronal cell survival. Although carfilzomib shows minimal activity against off-target enzymes, it is still possible that some unidentified nonproteasome targets are responsible for the CV toxic effects. More mechanistic studies using carfilzomib are needed to better understand the underlying mechanisms of toxicity, and to elucidate the complicated roles of proteasome in the CV system and vascular endothelium in general.

Other Recently Approved Agents in MM

In 2015, other than ixazomib, the FDA granted approval for panobinostat (a nonselective histone deacetylase inhibitor), daratumumab (a CD38 monoclonal antibody), and elotuzumab (a SLAMF7 monoclonal antibody) for treatment of RRMM. These newer agents target MM through distinct mechanisms. A review of the clinical trials reporting the efficacy of these novel therapies for patients with MM shows no significant signal of increased cardiovascular risk associated with these drugs, although in a phase III trial comparing panobinostat-bortezomib-dexamethasone with placebo-bortezomib-dexamethasone, slightly more patients in panobinostat group had QTc interval increase and T-wave/ST-T segment changes. Postmarketing surveillance is therefore important to detect the cardiovascular toxic effects associated with these agents, if any.

Cardio-oncology Considerations

Cardio-oncology has emerged as a new clinical field because of the increased incidences of adverse cardiovascular sequelae associated with cancer treatment and because of the need for better cardiovascular care for cancer patients during their treatment and survivorship. Despite the high prevalence of baseline CV risk factors in patients with MM, optimization of CV comorbidities may be overlooked when a diagnosis of malignant abnormality is made. Furthermore, because cardiovascular risk factors can further increase the rate of complications from MM and its treatment, the role of cardiology input is important. Therefore, it is necessary for oncologists to recognize the prevalence, risk factors, and early clinical presentations of these cardiovascular toxic effects. Moreover, further preclinical and clinical studies are required to comprehensively address treatment strategies to reduce the extent, frequency, and sequelae associated with CV toxic effects, and so improve patient outcome.
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Author Contributions: Drs Li and Moslehi had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of data analysis. Concept and design: Li, Cornell, Gailani, Moslehi. Acquisition, analysis, or interpretation of data: Li, Garcia, Laubach, Maglio, Richardson. Drafting of the manuscript: Li, Cornell, Maglio, Richardson, Moslehi. Critical revision of the manuscript for important intellectual content: Garcia, Cornell, Gailani, Laubach, Maglio, Richardson, Moslehi. Statistical analysis: Li, Moslehi. Administrative, technical, or material support: Laubach, Moslehi. Study supervision: Cornell, Gailani, Moslehi. No additional contributions: Garcia, Maglio, Richardson.

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REFERENCE


