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CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Cardiovascular Complications Associated with Multiple Myeloma Therapies: Incidence, Pathophysiology, and Management

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Abstract

Purpose of Review Multiple myeloma is a common hematologic malignancy characterized by recurrent relapsing disease course requiring use of various therapies. Over the past few decades, significant advancements in the treatment of myeloma have occurred including routine use of proteasome inhibitors and immunomodulatory drugs. These have effectively improved survival; however, some also have increased risk of cardiovascular toxicity. Here, we will review the incidence, pathophysiology, and management of cardiovascular complications associated with antimyeloma agents.

Recent Findings Cardiovascular complications associated with myeloma treatment are common. These cardiovascular complications include accelerated hypertension, ischemic heart disease, congestive heart failure, arrhythmia, pulmonary hypertension, venous thromboembolism, and arterial thromboembolism. Thromboprophylactic strategies during treatment with immunomodulatory agents and screening strategies to detect changes in myocardial function prior to the development of overt heart failure have occurred.

Summary Cardiovascular complications associated with proteasome inhibitors and immunomodulatory drugs are an important component in supportive care of patients with myeloma. The incidence of cardiotoxicity is high, and, as such, early intervention and collaborative efforts between cardiologists and oncologists to mitigate and effectively manage these complications are imperative. Additional studies are needed to clarify the underlying pathophysiology and evaluate effective strategies for prevention and treatment.

Keywords Cardiovascular complication · Multiple myeloma · Cardiotoxicity · Immunomodulatory drug · Proteasome inhibitor · Relapsed myeloma · Thrombotic complication · Venous thromboembolism · Heart failure · Thromboprophylaxis

Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the blood or urine, and associated organ dysfunction [1]. It is the second most common hematologic malignancy accounting for 1% of all cancers with approximately 86,000 new cases occurring annually worldwide. The median age of diagnosis is 70 years with 37% of patients being younger than 65 years of age [1, 2]. Survival in patients with MM has significantly improved over the past few decades with advancements in therapy. Based on the surveillance, epidemiology, and end results (SEER) data, the 5-year survival rates improved to 49% for the 2005–2011 year period compared to 27% from 1987 to 1990 [3]. This improvement in survival corresponds to the introduction and increased availability of modern therapies for MM including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies targeting CD38 (daratumumab) and SLAMF7 (elotuzumab), and autologous hematopoietic cell transplantation (AHCT) [4].

Although these new agents have led to improved survival outcomes, there has been a notable increase in serious therapy-related cardiovascular (CV) complications. These CV complications include accelerated hypertension, ischemic heart

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disease, congestive heart failure (CHF), arrhythmia, pulmonary hypertension, venous thromboembolism (VTE), and arterial thromboembolism (ATE) [5]. One study from a large US insurance database reported increased cardiac events in MM patients exposed to three or more types of therapy with a hazard ratio of 2.2 [6]. Increased vascular complications including VTE and ATE have been demonstrated in two large population-based studies. In a study of four million US veterans, patients with MM had a 9.2-fold increase in VTE risk compared with all other patients [7]. A second study including 18,627 Swedish patients showed 7.5-fold increase in VTE and 1.9-fold increase in ATE with associated decreased survival [8, 9].

Given the older age at diagnosis, it is important to note that there is a high baseline incidence of traditional CV risk factors and disease which likely enhances the treatment-related cardiotoxicities. A large retrospective study of 32,193 patients with MM showed that roughly 66% of patients had CV disease at baseline [10]. In addition, MM itself is also independently associated with the development of CV complications and thromboembolism regardless of treatment. A subset of these patients develops chronic kidney disease and concurrent amyloidosis potentially leading to a higher incidence of CV events [11–13].

Given these considerations, it is important to recognize baseline CV comorbidities in patients with MM and treat them effectively prior to treatment. Furthermore, a better understanding and early detection of MM-related CV issues and cardiotoxicity from MM therapies is essential to maximize benefits from modern therapies. This review will focus on the incidence and mechanisms of CV toxic effects of current MM therapies.

Proteosome Inhibitors and Cardiotoxicity

Proteasome Inhibitors: Mechanism of Action

Proteasome inhibitiors, along with IMiDs, are cornerstones of MM treatment regimens. The proteasome is an essential component of cellular homeostasis by degrading the majority of regulatory proteins through the ubiquitin-proteasome system (UPS). The UPS plays an important role in the pathophysiology of MM. In myeloma, plasma cells produce large quantities of immunoglobulins with a high error rate in protein folding and assembly. Malignant myeloma cells degrade these proteins via the UPS in order to prevent stress on the endoplasmic reticulum and subsequent cellular apoptosis. As a result, the proteasome capacity is at near saturation and MM cells are particularly sensitive to proteasome inhibition [14]. Three PIs have been approved for use in MM: bortezomib, carvlizomib, and ixazomib.

Bortezomib: Cardiovascular Implications and Mechanisms

Although there were initial reports of cardiotoxicity related to bortezomib including complete AV block and CHF, subsequent analyses showed no significant therapy-related CV outcomes [15, 16]. In a recent meta-analysis and retrospective pooled analysis of phase II and phase III studies, there was no difference in the incidence of arrhythmia, ischemic heart disease, heart failure, cardiac death, or VTE [17, 18]. More importantly, data suggests that bortezomib is not associated with thrombogenicity and may be thromoboprotective. Results from three trials (APEX, SUMMIT, and CREST) using bortezomib-based regimens showed that patients had a lower incidence of VTE independent of concomitant dexamethasone or erythropoietin use. In these trials, the bortezomib-only group had a 0.6–1.6% incidence of VTE compared to the dexamethasone-only group of 2.7% [19]. In addition, meta-analysis from several phase III trials showed that VTE risk is lowered when using bortezomib in conjunction with IMiDs compared to IMiDs alone [20]. One study reported a hazard ratio for VTE risk at 1.38 times higher for patients treated with thalidomide alone compared to thalidomide with bortezomib [21].

There are several proposed mechanisms for the cardioprotective and thromboprotective effects of bortezomib therapy. Bortezomib is a reversible PI with recovery of proteasome activity 72 h after administration which may lead to a lower risk of accumulation of misfolded proteins in cardiac myocytes [22]. In animal models, bortezomib has also been shown to reduce ischemia-perfusion injury and prevent left ventricular hypertrophy via the inhibition of NF-kappa B pathway [23–25]. Thromboembolism typically results from an alteration of the balance between procoagulant and anticoagulant proteins in addition to endothelial stress with activation of inflammatory pathways. Bortezomib has been shown to prevent VTE by both stimulating endothelial thrombomodulin which results in enhanced capacity to generate activated protein C and preventing downregulation of thrombomodulin through specific cytokine release [26, 27].

Carfilzomib: Cardiovascular Toxicity and Mechanisms

Carfilzomib is a second-generation irreversible PI with promising clinical trial data showing improved survival and overall response rates in pretreated patients' relapsed refractory multiple myeloma (RRMM) [28–30]. However, unlike the results for bortezomib, several of these trials have shown that carfilzomib has been associated with increased incidence of poor CV outcomes including CHF, accelerated hypertension resulting in hypertensive urgency or emergency, pulmonary hypertension, and symptomatic atrial fibrillation [31].

One of the most significant cardiotoxicities of carfilzomib is incident heart failure. In phase II studies with single-agent carfilzomib, the incidence of CHF was reported from 3.4 to 11% and varied depending on the infusion regimen. A meta-analysis of phase II studies showed that cardiotoxicities occurred in 22% of patients including hypertension (14.3%), arrhythmia (13.3%), CHF (7.2%), IHD (3.4%), and cardiomyopathy (1.7%) [32]. Of note, roughly 70% of the patients in the trials had reported history of baseline CV risk factors [33–35]. Interestingly, roughly half of these events (11.2%) occurred after the first infusion which was administered as a bolus infusion (2–10 min). In another analysis of 130 patients with RRMM treated with carfilzomib, 26 patients (20%) developed cardiotoxicities with 20 of the 26 cases occurring after the bolus infusion (2–10 min). As a result, the infusion time was extended to 30 min in some trials [33]. However, data supporting the role of infusion time is lacking. A phase I and phase II carfilzomib 30-min infusion study demonstrated that 20.8% and 25% of patients, respectively, experienced adverse cardiac events, which is similar to the reported data with the bolus infusion [36].

Although these early clinical trial data demonstrated cardiotoxicity associated with carfilzomib, the results were from single-arm studies in heavily pretreated patients with MM without a comparator arm. However, subsequent phase III data confirmed the cardiovascular toxic effects of the therapy. Results from the randomized phase III ASPIRE trial showed higher incidences of CV outcomes 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 [30]. Importantly, the high VTE incidence occurred despite protocol-mandated thromboprophylaxis. Similarly, a cardiac substudy from the phase III ENDEAVOR trial comparing carfilzomib to bortezomib-based regimens in RRMM showed increased CV outcomes including CHF (10.8% vs. 4.1%), hypertension (25.9% vs. 9.6%), and pulmonary hypertension (1.3% vs. 0%) [29]. The role of dose and infusion schedule was evaluated in the most recent phase III ARROW trial comparing once weekly (higher dose with 30-min infusion) vs. twice weekly (lower dose with 10-min infusion) carfilzomib in patients with RRMM. Interim analysis showed that there was little difference in cardiotoxicity comparing once weekly high-dose longer infusion to twice weekly low-dose shorter infusion including CHF (4% vs. 5%), hypertension (22% vs. 20%), and pulmonary hypertension (2% vs. 1%) [37•]. Recently, initial analysis from the prospective observational PROTECT trial comparing carfilzomib to bortezomib-based regimens in RRMM showed that there was a much higher incidence of CHF in the carfilzomib arm. In addition, the diagnosis of heart failure was seen in the first 3 months of therapy and incident events uncommon after that time period [38•].

The reported heterogeneous pattern of CV complications suggests that the mechanisms of cardiotoxicity associated with carfilzomib may be both vascular and myocardial in origin. However, the precise nature of carfilzomib-related cardiotoxicity is poorly understood. One proposed mechanism implicates long-term downregulation of the UPS which is essential to cardiomyocyte function. Because carfilzomib is an irreversible proteasome inhibitor, unlike bortezomib, the longer inhibition of the UPS may result in accumulation of misfolded proteins within cardiomyocytes resulting in adverse cardiac remodeling, which has been seen in pathology specimens in cases of hypertrophic and dilated cardiomyopathies [39–41]. Limited data suggests that there may be some affect on endothelial nitric oxide synthase activity and an adverse effect on vascular smooth muscle that could result in the associated vascular complications [42, 43]. Another theory suggests that these patients have "multiple hits" from prior cardiotoxic treatment regimens, most notably anthracyclines, that culminates in CV complications with PI therapy [44]. It is also unclear if a subgroup of these patients developed light chain cardiac amyloidosis prior to treatment [11]. Ultimately, further in vitro and in vivo experiments need to be conducted to test these hypotheses in order to better elucidate the mechanisms of cardiotoxicity.

Carfilzomib Cardiotoxicity: Monitoring and Prevention Strategies

Given the high incidence of CV complications associated with carfilzomib, monitoring and prevention strategies need to be developed. Currently, there is no consensus on ideal monitoring and management of therapy-related CV complications. Early identification of patients with cardiotoxicity is imperative as data suggest that CV complications are reversible with cessation of therapy and appropriate medical management [41]. Initial trial data suggested that bolus dose and infusion time may be implicated in carfilzomib cardiotoxicity. However, results from the ARROW trial clearly suggest that current bolus dose and infusion time have no significant effect on the development of CV complications [33, 37•]. Other trials have incorporated both serial laboratory data and transthoracic echocardiography (TTE) to allow for earlier identification of patients with cardiotoxicity. A cardiac subgroup study from the ENDEAVOR trial showed that serial TTE had no benefit in early detection or prevention of heart failure [45]. The PROTECT study demonstrated that use of naturetic peptides including BNP and NT-proBNP was effective to predict and monitor patients for development of CV events with carfilzomib-based therapy [38•]. With advancements in echocardiographic techniques, there may be a role in detection of subclinical changes in cardiac function to predict subsequent heart failure. Global longitudinal strain (GLS) measurement with Doppler echocardiography has been shown to predict

anthracycline-induced cardiotoxicity in patients with breast cancer [46]. Recently, cardiac MRI measurement of GLS was shown to correlate with changes in LVEF in a small observational cohort of patients receiving anthracycline-based chemotherapy regimens. There is currently no consensus on a superior modality for prediction of cardiotoxicity comparing Doppler echocardiography and cardiac MRI [47]. Further studies incorporating measurements of subclinical cardiac dysfunction including GLS are needed for early detection and prevention of CV complications, which may include treatment regimen adjustment with the development of subclinical myocardial dysfunction.

Immunomodulatory Drugs and Thromboembolism

Immunomodulatory Drugs: Mechanism of Action

IMiDs have shown remarkable efficacy in the treatment of MM through modulation of the tumor microenvironment, angiogenesis, and direct inhibition of tumor cell proliferation [48, 49]. Unlike PIs, the mechanism of IMiDs involves utilizing the UPS to degrade lymphoid transcription factors that are essential to B and T cell function. IMiDs bind cereblon, a component of E3 ubiquitin ligase, causing selective ubiquitination and proteasome degradation of two lymphoid transcription factors: Ikaros family zinc finger protein (IKZF) 1 and 3. IZKF3 is critical to plasma cell development and is an essential component to myeloma pathogenesis [50, 51]. As a result, IMiDs function to inhibit proliferation of malignant myeloma plasma cells. In T cells, studies have shown that IMiDs increase degradation rates of IKZF1 and IZKF3 resulting in altered cytokine production, which may explain their potential immunomodulatory effect [52]. Additionally, they were shown to inhibit fibroblast growth factor–induced angiogenesis [53]. Three generations of IMiDs have been approved for use in MM: thalidomide, lenalidomide, and more recently pomalidomide.

Thromboembolism Associated with IMiDs

MM itself has intrinsic prothrombotic effects with a reported cumulative DVT risk of 0.6–4.7% depending on patient age [7]. Prior to the introduction of IMiDS, approximately 10% of MM treated with conventional chemotherapy experienced VTE complications [54]. Early clinical trials with single-agent thalidomide and lenalidomide did not show increased VTE risk [55–57]. However, further studies involving combination therapy with dexamethasone and/or cytotoxic chemotherapy showed that patients in the IMiD arms had significantly increased VTE and ATE complications.

For patients with newly diagnosed MM, two phase II trials involving thalidomide-dexamethasone and thalidomide-dexamethasone-doxorubicin showed 7% and 27% incidence of DVT, which led to early trial suspension in the latter study [58]. In subsequent studies, the increased VTE risk with thalidomide combination therapy was confirmed. A meta-analysis showed that combination therapy with thalidomide-dexamethasone increased VTE risk by 8-fold [59]. The more potent newer generation IMiDs, lenalidomide and pomalidomide, also increase VTE risk. A randomized control trial comparing lenalidomide with high-dose dexamethasone and lenalidomide with low-dose dexamethasone in patients with newly diagnosed MM was conducted. VTE incidences were reported at 26% with high-dose dexamethasone vs. 12% in the comparator arm, which confirmed the role of high-dose dexamethasone as an important component to the pathophysiology of thromboembolic complications [60]. This led to the routine use of mandated thromboprophylaxis in future study protocols [61]. More recently, two randomized phase III trials in patients with RRMM receiving pomalidomide combination therapy and thromboprophylaxis showed VTE incidence < 1% [62•, 63]. Moreover, it appears that VTE risk may be greater in patients with newly diagnosed MM compared to RRMM [61].

Both thalidomide and lenalidomide have been implicated with ATE complications. In a phase III trial with thalidomide combination therapy, the incidence of arterial thrombosis was 5.6% with the highest incidence within the first year of induction therapy (HR 1.9, 95% CI 1.8–2.1) [64]. In the long-term follow-up of 704 patients with MM in two large randomized phase III trials comparing lenalidomide-dexamethasone with placebo-dexamethasone in patients with RRMM, there was higher incidence of ATE complications in the lenalidomide arm. Complications included MI (1.98 vs. 0.57%) and cerebrovascular accident (3.4 vs. 1.7%), which led to an FDA black box warning for increased ATE events with lenalidomide [65].

Mechanisms for Thromboembolism Associated with IMiDs

While the exact mechanism by which IMiDs contribute to thrombosis is not known, several mechanisms have been proposed. In a small observational cohort study, patients receiving thalidomide combination therapy had transiently lower serum levels of thrombomodulin, which is an anticoagulant pathway cofactor [66]. Other association studies suggest a link between IMiDs, increased cytokine levels, and increased activity of endothelial tissue factor, which likely contributes to thrombosis (Fig. 1). Resistance to activated protein C in the absence of factor V Leiden has also been associated to IMiD treatment [67, 68]. Recently, genetic analysis of single nucleotide polymorphisms (SNPs) showed that a SNP in nuclear

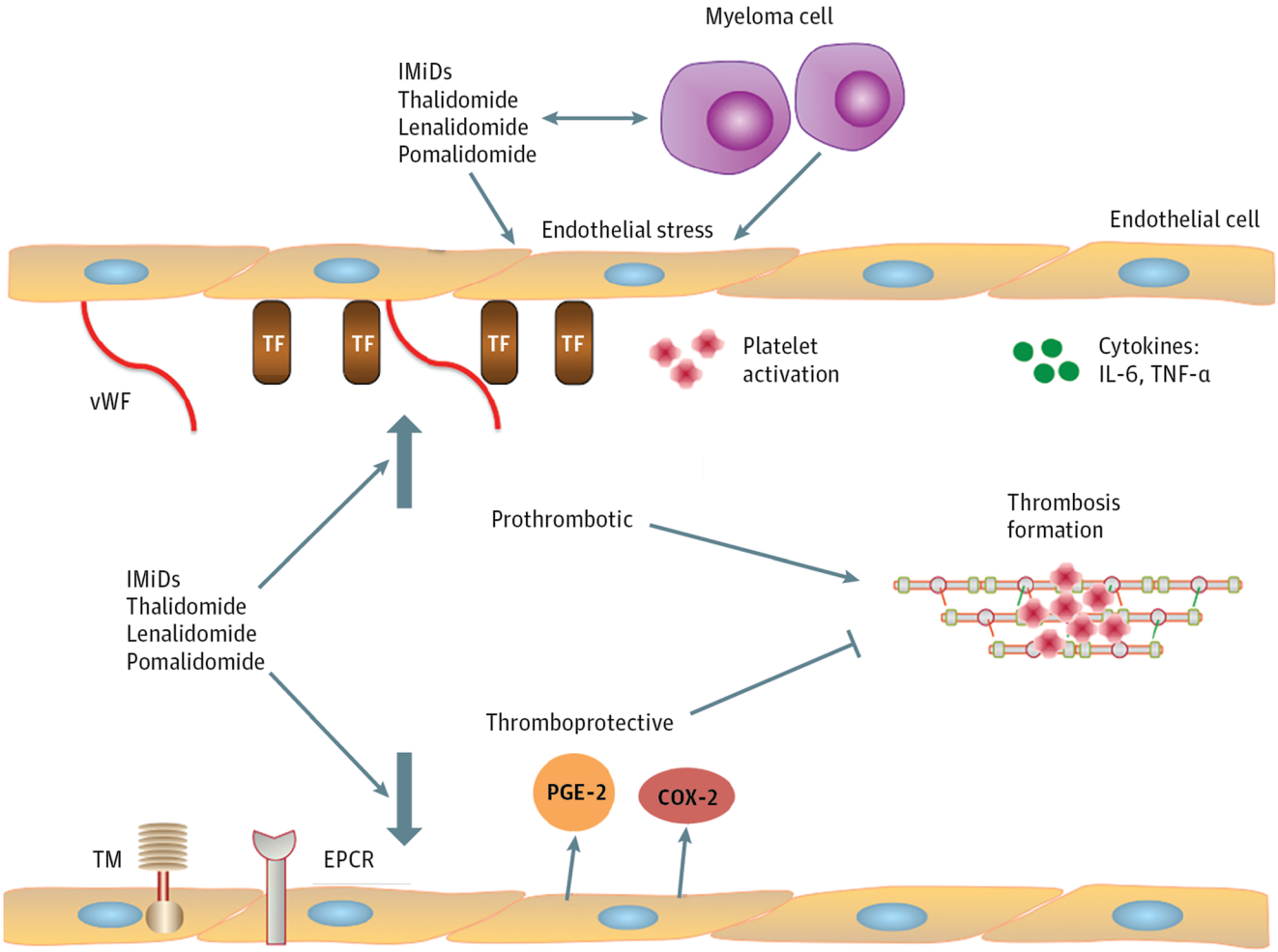

Fig. 1 Underlying mechanisms of immunomodulatory drugs (IMiDs) and increased venous thromboembolic event (VTE) risks. Reproduced from Li W, Garcia D, Cornell RF, et al. Cardiovascular and thrombotic complications of novel multiple myeloma therapies: a review. *JAMA Oncol*. 2017; 3:7, 980–8, with permission from the American Medical Association. Immunomodulatory drugs can cause an alteration of the balance between procoagulant and anticoagulant proteins on the surface of endothelial cells, including enhancing expression of phosphatidylserine (PS) and tissue factor (TF), activated glycoprotein GPIIb/IIIa (PAC-1), inhibiting expression of endothelial protein C receptor (EPCR) and thrombomodulin (TM). Immunomodulatory drugs can also upregulate the potent platelet activator cathepsin G both in vitro and in vivo, increase factor VIII and von Willebrand factor levels, inhibit the production of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE_2) synthesis, and increase endothelial cell stress and injury

factor-kB was associated with increased risk of VTE in patients treated with lenalidomide-based regimens [69]. The role of endothelial stress, particularly with high-dose steroids, requires further investigation in future studies [70].

Thromboprophylactic Strategies with IMiDs

The first thromboprophylactic regimen utilized fixed low-dose warfarin (1–1.25 mg daily), which was largely ineffective [57, 71, 72]. As a result, later trials incorporated aspirin (81–325 mg), therapeutic warfarin (INR 2–3), and low-molecular-weight heparin (LMWH) and were more effective (Table 1). The first phase III trial of 667 patients with newly diagnosed MM treated with thalidomide-based regimens suggested that aspirin (100 mg daily) or low-dose warfarin (1.25 mg daily) were non-inferior to LMWH (enoxaparin 40 mg daily) in reducing VTE. Of note, patients who were at high risk of VTE were excluded from the study [21]. Another randomized prospective study of 342 patients treated with lenalidomide followed by cyclophosphamide for stem cell mobilization showed that aspirin (100 mg daily) was non-inferior to LMWH (enoxaparin 40 mg daily). However, patients included in the study were young (< 65 years old), had no CV or thrombosis risk factors, and had no history of VTE or ATE [73]. Therefore, aspirin should be considered only for low VTE risk patients in lenalidomide-based regimens [74]. The efficacy of direct oral anticoagulants (DOACs) for thromboprophylaxis was investigated until recently. In a pilot observational cohort of 50 patients with MM receiving IMiDs, low-dose apixaban was well tolerated

Table 1 Incidence of VTE in trials of immunomodulatory agents with thromboprophylaxis in MM [5]

Therapy	Aspirin (100–325 mg)	Fixed low-dose heparin	Full-dose heparin	LMWH
Thalidomide				
Plus dexamethasone	NA	13–25%	8%	NA
Plus melphalan	14%	NA	NA	3%
Plus doxorubicin	7%	12–14%	NA	8–10%
Plus multiagent chemotherapy	14–25%	8%	NA	5–24%
Lenalidomide				
Plus dexamethasone	3–19%	NA	NA	NA
Plus melphalan	0–6%	NA	NA	NA
Plus doxorubicin	4%	NA	NA	NA
Pomalidomide				
Plus dexamethasone	0–5%	NA	NA	NA

LMWH low-molecular-weight heparin, *NA* not applicable, *VTE* venous thrombolytic event

without any VTE or ATE complications in an interim analysis [75•].

Overall, there have been limited well-powered prospective, randomized studies evaluating the efficacy of thromboprophylactic regimens. Despite routine use of thromboprophylaxis, a meta-analysis of 1051 patients showed that the relative risk of VTE in patients with MM treated with IMiDs and LMWH thromboprophylaxis was 1.54 times higher than patients not receiving IMiD therapy [76]. It is imperative that future studies evaluate the efficacy of DOACs as patients may be more compliant with oral regimens as opposed to daily injections with LMWH, which could be a possible component to the ongoing elevated relative risk.

Novel Agents and Cardiotoxicity

Several novel agents have recently been approved or under development for potential treatment of RRMM including bruton tyrosine kinase inhibitor (ibrutinib), newer generation proteasome inhibitor (ixazomib), monoclonal antibodies targeting CD38 (daratumumab) and SLAMF7 (elotuzumab), and chimeric antigen receptor (CAR) T cell therapy. In a phase I study with ibrutinib and carfilzomib combination therapy, there was no significant increase in treatment-related cardiotoxicities [77]. Similarly, a phase II trial of ibrutinib with dexamethasone showed no major increase in cardiotoxicities [78]. However, it is important to consider the proarrhythmic potential of ibrutinib in future studies as it has been associated with atrial fibrillation with a relative risk of 3.9 determined from a pooled analysis of four randomized control trials and in rare cases sudden cardiac death from ventricular arrhythmia [79]. A review of clinical trials for ixazomib, daratumumab, elotuzumab shows no significant signal in increased cardiovascular risk associated with these drugs.

CAR T cell therapy has shown promising results for the treatment of leukemia and lymphoma. Of the trials involving CAR T cells targeting CD 19, cardiotoxicities typically resulted as a complication of cytokine release syndrome including arrhythmia and decreased LVEF. The pathophysiology remains unknown and is thought to be related to a stress cardiomyopathy. Direct cardiac infiltration of CAR T cells has been reported in a few cases as an off-target effect for T cells engineered to target a testis antigen. It is thought that there was cross-reactivity with antigens expressed by cardiac tissue [80–82]. Trials involving CAR T cells against B cell maturation antigen (BCMA) for multiple myeloma are ongoing. As CAR T cell is implemented in multiple myeloma, it is imperative to detect cardiovascular toxic effects associated with therapy and further elucidate the role of cytokine release syndrome in cardiotoxicity.

Conclusions

Advancements in the treatment of multiple myeloma have significantly increased survival and quality of life, but have also been implicated in the development of cardiovascular disease. Proteasome inhibitors, immunomodulatory drugs, and high-dose steroids each have unique cardiotoxicity profiles in patients with MM. In addition, multiple myeloma itself is intrinsically associated with cardiovascular disease, and many of the treated patients have a high baseline prevalence of CV risk factors and disease, which likely potentiates the effect of the cardiotoxicity. As a result, it is imperative to optimize CV risk prior to and during treatment. Oncologists also need to recognize the prevalence and early clinical presentations of cardiotoxicities. A subset of these patients have concurrent cardiac AL amyloid causing heart failure and dysautonomia which may warrant consideration of cardiac MRI and endomyocardial biopsy to differentiate from drug-

related cardiotoxicities. Screening strategies need to be developed to allow for the early detection of subclinical changes in myocardial function prior to the development of overt heart failure in patients treated with PIs. Moreover, further studies are needed to understand the underlying pathophysiology of cardiotoxicity and develop more effective prophylactic and treatment strategies for the sequelae associated with treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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