

Cardiovascular Considerations in Multiple Myeloma

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Background

Multiple myeloma (MM) is the second most common hematologic malignancy, with an estimated incidence rate of 6.5 per 100,000 men and women annually in the United States [1]. MM rarely presents before age 40, with a median age at diagnosis of 70 years [2, 3]. The prevalence is expected to increase in developed countries in concert with increasing life expectancy [4].

With the introduction of new therapeutics in recent years, both progression free, and overall survival have improved substantially [5, 6]. Despite significant improvement in the overall outcome, some patients only survive a few months [2]. Consequently, cardiovascular (CV) events are increasingly common in patients with MM [7]. The etiologies of CV disease in these patients are a result of the presence of pre-existing age related CV comorbidities, the direct effect of the malignancy on the CV system, and cardio-toxic effects of anti-MM therapies. We present a

review of the CV considerations patients with MM, as well as describe some potential CV toxicities in these patients.

Age-Related Comorbidities

The peak incidence of MM is in the 6th and 7th decades of life. This combined with the high prevalence of CV disease in this elderly population, results in a high proportion of patients with MM having significant CV comorbidities and associated adverse outcomes [8, 9]. Men have higher rates of both MM and CV risk factors [2, 10, 11]. Notably, in the study by Kistler et al, [7] in 52,000 patients with newly diagnosed and relapsed MM, CV events (arrhythmias, ischemic heart disease, and congestive heart failure) occurred in nearly three-quarters of patients with MM during the 11 months of follow-up. Older age and baseline CV comorbidities were strongly associated with occurrence of subsequent CV events [7].

Multiple Myeloma Related Cardiovascular Toxicity

Multiple myeloma is characterized by uncontrolled clonal proliferation of plasma cells and accumulation in the bone marrow compartment. Serum and/or urinary monoclonal immunoglobulins and protein fragments are markedly elevated, except the patients with non-secretory MM. The spectrum of clinical manifestations in patients with symptomatic MM includes skeletal lesions, symptoms of impaired hemopoiesis and hyperviscosity, renal dysfunction, neuropathy, systemic symptoms, and infections [12]. Furthermore, in addition to hematologic abnormalities (notably anemia, hyperviscosity syndrome, bleeding), renal insufficiency, hypercalcemia, and light chain (AL) amyloidosis, MM can independently lead to a number of cardiovascular adverse effects [13].

AL Amyloidosis

AL amyloidosis represents a spectrum of several clinical conditions caused by extracellular deposition of insoluble fibrillar amyloid protein in various organs, particularly in the heart. AL amyloidosis affects up to 30% of patients with MM. Most patients have evidence of isolated monoclonal gammopathy or smoldering myeloma. AL deposition may result in damage of the vasculature, heart valves and myocardium. This manifests clinically as cardiomyopathy, congestive heart failure (CHF), arrhythmias, thromboembolism and pulmonary hypertension [14]. Patients with amyloid cardiomyopathy typically have heart failure syndrome in the setting of a normal or mildly decreased left ventricular ejection fraction [15]. The development of cardiomyopathy is a result of amyloid accumulation in myocardial interstitium, as well as direct cardiomyocyte toxicity [13, 16]. Though the precise molecular mechanisms of the direct cardiotoxic effect of amyloid protein is still being investigated, it is thought that the isolated light chains in patients with AL amyloidosis induce oxidative stress, cell dysfunction and apoptosis of isolated mature cardiomyocytes [17]. Amyloid also infiltrates vessel walls causing impairment of coronary autoregulation, and can subsequently lead to myocardial ischemia. The intramyocardial vessels are affected in 90% of patients with AL amyloidosis [18]. Cytotoxic effects of amyloid are also demonstrated in blood vessels, thought to be a result of light chain mediated endothelial dysfunction and apoptosis [19]. Even though cardiac valves are commonly noted to have amyloid depositions by histology, clinical symptoms and hemodynamic dysfunction are rare [14]. Amyloid deposits in the cardiac conduction system result in an increased incidence of arrhythmias. Atrial fibrillation is the most common, affecting 10–15% of patients and is associated with significant morbidity related to thromboembolism and heart failure [14]. Early diagnosis

Hyperviscosity syndrome is the direct result of both increased plasma viscosity and increased erythrocyte

of cardiac amyloidosis is imperative and can be accomplished through aggressive screening with serum biomarkers, cardiac imaging and appropriate target organ biopsies [20]. Detecting and grading the presence and severity of cardiac involvement has profound implications on the overall treatment strategy and prognosis for patients [21, 22]. Moreover, patients diagnosed with congestive heart failure as a result of amyloid cardiomyopathy are treated differently, with traditional heart failure therapies being poorly tolerated or even contraindicated [23, 24]. Importantly, patients with proven cardiac amyloidosis should not be treated with calcium channel blockers or digoxin. Furthermore, beta-blockers, renin-angiotensin receptor blockers and nitrates often result in profound fatigue and hypotension [25–29]. Loop diuretics alone or in combination with thiazide diuretics are an important therapy for patients with congestive symptoms, but care must be taken to avoid nephrotoxicity [25].

Multiple Myeloma

A common physiologic consideration in MM is anemia that is seen in more than two thirds of patients [30]. While there are several mechanisms responsible for the development of anemia (low erythropoietin levels, erythropoietin resistance, bone marrow infiltration, pancytopenia, toxic effects of chemotherapy, etc.) [31], the impact on the cardiovascular system is uniform. Severe and prolonged anemia may cause high-output cardiac failure [32, 33] and in those patients with coexistent CAD, myocardial ischemia and infarction [34].

Renal dysfunction commonly presents during evaluation or treatment of MM. Kidney damage may be multifactorial (myeloma kidney, amyloidosis, light chain deposition disease, hypercalcemia and dehydration, hyperuricemia, urinary tract infections, or acute tubular necrosis caused by nephrotoxic agents) [35] and occur in 20–50% of patients [36]. Volume overload and electrolyte imbalances result in pulmonary congestion, and atrial and ventricular arrhythmias [37]. Disruption of the cardio-renal axis can decrease cardiac output and further worsen renal function [38].

Hypercalcemia as a result of excessive osteolysis, is a frequent electrolyte disturbance in MM, and is seen in approximately one-third of patients [39]. Both acute and chronic hypercalcemia, have important and potentially life-threatening CV implications. Acute hypercalcemia is associated with shortening of the QT interval, predisposing to arrhythmias. Chronic hypercalcemia is associated with the accelerated calcification of cardiac valves and coronary arteries [40]. Conversely, hypocalcemia secondary to bisphosphonate therapy may also potentially cause cardiac arrhythmias [41].

The molecular size of the paraprotein is related to the threshold for its development - with IgM requiring

lower paraprotein concentrations than IgG. Consequently, the incidence of symptomatic hyperviscosity in Waldenström's macroglobulinemia is 10-30%, while with IgG myeloma it is 2-6%. The CV manifestations include heart failure, angina, and myocardial infarction[42].

Therapy Related Cardiotoxicity

Therapeutic advances over the past decade have improved the median overall survival of patients newly diagnosed with MM from 4.6 years during 2001-2005, to 6.1 years during 2006-2010[6]. Despite these encouraging findings, MM remains largely incurable as patients will

inevitably relapse multiple times, resulting in exposure to a variety of therapeutic agents with differencing off-target effects and complications. In this section we focus on corticosteroids, proteasome inhibitors, immunomodulatory agents, cyclophosphamide, histone deacetylase inhibitors, and autologous stem cell transplant (Auto-HCT). While these effects tend to be class- and dose-dependent, it is conceivable (albeit very rare in the non-immunotherapy-based agents) that patients may incur idiosyncratic reactions that have cardiovascular effects[43]. Table 1 shows the spectrum of CV complications caused by commonly used anti-MM drugs.

Table 1: The spectrum of CVS toxicity of agents commonly used for treatment of MM

Cardiovascular complications of pharmacology MM therapies	
AGENT	CARDIOVASCULAR MANIFESTATION
CARFILZOMIB	LV dysfunction, CHF, myocardial ischemia, pulmonary hypertension
BORTEZOMIB	LV dysfunction, CHF, myocardial ischemia, pulmonary hypertension, autonomic dysfunction, hypotension, AVt blocks, prolonged QTc
LENALIDOMIDE	Thromboembolism, arrhythmias
POMALIDOMIDE	Thromboembolism, arrhythmias, autonomic dysfunction, hypotension
CYCLOPHOSPHAMIDE	LV dysfunction, CHF, pericardial effusions, hemorrhagic myopericarditis* *high dose
DEXAMETHASONE	CHF, arterial hypertension
PANOBINOSTAT	Prolonged QTc, ventricular arrhythmias
MELPHALAN	LV dysfunction, arrhythmias

Corticosteroids

Corticosteroids have been the backbone of therapy for treatment for MM, either in combination with other drugs or as monotherapy in palliative cases [44-46]. Corticosteroids are associated with a wide range of side effects including sodium and water retention that result in hypertension and CHF. This is particularly important as patients with MM have increased prevalence of CHF, especially heart failure with preserved ejection fraction.

These side effects can be minimized through dose reduction or treatment with diuretics, as needed [47, 48]. On a practical level, serial measurement of serum NTproBNP, renal function and electrolytes, as well as advising patients to weigh themselves daily are important management tools. Patients should expect a significant increase in weight after a steroid pulse, and treating with as-needed diuretics in this situation, often mitigates the development of severe symptomatic heart failure [49].

Proteasome Inhibitors

The newer chemotherapeutic agents used to treat MM also seem to be associated with an increased rate of CV

events and morbidity[50]. Proteasome inhibitors, bortezomib, ixasomib and carfilzomib, are currently approved for the treatment of MM in all stages of the disease, and have proven to be very effective[51]. Traditionally, bortezomib was thought to have only limited cardio-toxic potential. However, recent studies and case reports suggest proteasome inhibitors are associated independently with increased risk of CV events[50, 52-55]; seen in approximately in 15% patients with bortezomib- [56], and 22.1% patients with carfilzomib-containing regimens[57]. The most commonly reported cardiac adverse events in clinical trials were decreased left ventricular ejection fraction, CHF, arrhythmias, and ischemic heart disease[53, 57-60]. The mechanism of injury is likely due to disruption of the ubiquitin-proteasome pathway – a pathway that is crucial for proteolytic degradation [Figure 1]. Proteasome inhibitors exhibit antitumor activity via disrupted protein repair mechanisms and an overwhelmed

autophagy pathway, ultimately leading to proteotoxicity and apoptosis [61]. The CV system, particularly cardiomyocytes and endothelial cells, are highly metabolically and mechanically active, and subsequently rely heavily on an efficient ubiquitin-proteasome system (UPS). It is plausible that myocardial ischemia may occur as a result of decreased endothelial nitric oxide synthase activity. Furthermore, the cardiomyocyte mitochondria and contractile apparatus are exposed to constant biochemical and mechanical stress – ordinarily dealt with effectively by the UPS. Disruption of this pathway can also cause systolic dysfunction – particularly when under additional hemodynamic stress (e.g. sepsis)[62].

Bortezomib therapy also results in peripheral neuropathy in 37-44% of patients. This can manifest as autonomic dysfunction and cause orthostatic hypotension and conduction abnormalities [63-65].

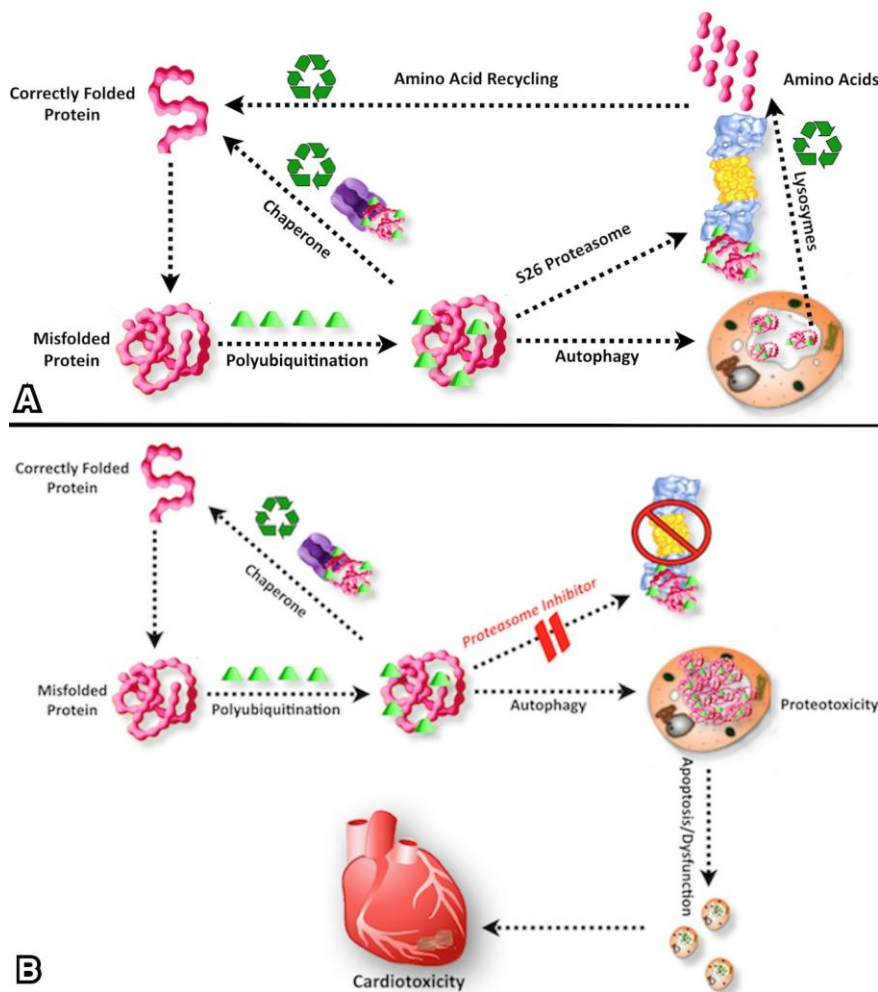


Figure 1: Ubiquitin Proteasome System (UPS) and Proposed Mechanism of Proteasome Inhibitor Mediated Cardiotoxicity.

(A) Normal protein quality maintenance is governed by either labeling-refolding by ATP-dependent chaperone proteins (“foldase”) or through degradation to constituent amino acids by the UPS. The UPS constitutes 2 main phases - tagging of the substrate protein by the covalent attachment of multiple ubiquitin molecules; and subsequently degradation 26S proteasome. A third, but less efficient pathway, is through the development of autophagic vesicles, lysosomal degradation, and recycling of constituent amino acids.

(B) In the setting of Proteasome Inhibitors, both the chaperone- and autophagy pathways become overwhelmed. Misfolded proteins then accumulate within autophagic vesicles, which accumulate and subsequently trigger apoptosis (proteotoxicity).

Immunomodulatory Agents

Immunomodulatory agents (IMiDs), thalidomide, lenalidomide and pomalidomide, are drugs that have improved outcomes in the treatment of MM. Thalidomide

strongly increased the risk of venous thrombosis. IMiDs inhibit the secretion of pro-angiogenic cytokines resulting in alteration of endothelial homeostasis and can explain the vascular toxicity seen in clinical practice [66, 67].

Several studies have been reports of IMiD-related deep vein thrombosis and pulmonary embolism[68-71].

IMiD-Dexamethasone regimes can risk raise up to 26%[72].Peripheral neuropathy from IMiDs can also cause autonomic dysfunction resulting in tachycardia and orthostatic hypotension [73, 74]. Pomalidomide is frequently associated with anemia and thrombocytopenia[75].

Cyclophosphamide

Cyclophosphamide, used in combination with chemotherapy for treatment of MM[76, 77]is also associated with an increased risk of cardiotoxicity[78]. Though systolic dysfunction and overt heart failure are most commonly seen,hemorrhagic pericardial effusion and severe myopericarditis can rarely occur[79 - 82]. The risk of cardiac complications appears to be dose related (doses more than 150 mg/kg during 2-4 days or $>1.5 \text{ g/m}^2/\text{day}$)and occurs within 10 days of administration of the first dose [78].The precise mechanism of cardiotoxicity is unknown, though it is hypothesized that cyclophosphamide causes direct endothelial injury followed by extravasation of toxic metabolites that results in cardiomyocyte damage [76].

Histone Deacetylase Inhibitors

Histone deacetylase inhibitors (vorinostat and panobinostat) have demonstrated activity against MM, with panobinostat recently being approved for the treatment of relapsed and refractory MM. Panobinostat has been reported to cause hypokalemia and hypocalcemia, QTc prolongation, and subsequent ventricular arrhythmias. This has resulted in a black box warning for CV ischemic, arrhythmias and ECG changes. Subsequently panobinostat should not be initiated in patients who have a baseline QTc of greater than 450 msec, a history of recent myocardial infarction, or unstable angina. Concomitant QTc-prolonging agents should also be avoided[83, 84].

Hematopoietic Stem Cell Transplantation

While chemotherapy and hematopoietic stem cell transplant (HSCT) are the therapies of choice for the majority of patients [109], radiation therapy (RT) is also used as an

High dose melphalan (HDT) followed by autologous hematopoietic stem cell transplant (auto-HCT) improves survival in myeloma patients has been the standard of care for eligible patients for many decades [85, 86]. Eligibility criteria vary among countries and centers but typically includes an ejection fraction of $>50\%$, no medically uncontrolled systemic illness, and physiologic age of <65 . Auto-HCT is also a good treatment option for patients with AL amyloidosis, though only 20-25% of patients are eligible due to advanced disease at the time of diagnosis [85].

In the modern era, treatment related mortality associated with HDT plus auto-HCT is approximately 1-2% for myeloma patients [87] and 4 - 7% for AL amyloid patients [88, 89], and may be associated with acute complications that can affect the CV system. Patients are subjected to large intravenous volume, electrolyte shifts, melphalan-induced arrhythmias, immunosuppression and sepsis, anemia, thrombocytopenia, and bleeding[90-92]. Careful patient selection and vigilant monitoring in the peri-transplant period are associated with improved outcomes. To reduce morbidity and mortality in AL amyloidosis,risk-adapted dose reduction strategies have been used[93].

Both early and late left ventricular systolic dysfunction and CHF have been well described in patients undergoing auto-HCT for lymphoma [94-96].Allogeneic HCT (Allo-HCT) is used less commonly for the treatment of MM; however patients are at higherrisk for developing acute and late cardiac complications [97, 98]. This risk is dependent on the intensity and type of conditioning. A recent study found that while Allo-HCT survivors have a higher burden of CV morbidity, the risk for life-threatening conditions in auto-HCT recipients remains substantial[99].Patients undergoing Allo-HCT are at risk of developing valvular heart disease, arrhythmias, serositis, pericarditis, and CHF [100, 101]. As a direct result of the chronic inflammation and endothelial damage, patients are prone to accelerated atherosclerosis and may develop coronary artery disease (angina and myocardial infarction), cerebrovascular disease (cerebrovascular accident), and peripheral artery disease (claudication and limb ischemia)[102,103].Direct cardiac damage by lymphocytic infiltration,prolonged and intensified immunosuppressive treatment, endocrine dysfunctions, growth hormone insufficiency, hypothyroidism, and gonadal dysfunction may all be also involved in this process[104].The treatment of GVHD (with glucocorticoids, calcineurin inhibitors, and sirolimus) often has CV side effects[105].Lastly, Allo-HCT recipients have an increased risk of development of late CV complications (hypertension, diabetes, dyslipidemia and renal insufficiency), further increasing the global CV risk[106-108].

effective adjunct or as a palliative measure. RT is effective in reducing bone pain and in treatment of pathological fractures, and spinal cord compression [110, 111].

Irradiation to the thorax (sternum or thoracic spine in this indication), can lead to cardiac damage, with the pericardium, myocardium, valves, and coronary vessels most commonly involved [112]. Pericardial effusion typically manifests early after radiation exposure [113, 114]. The remaining complications tend to be seen several years after a treatment course[114-117]. Given the median age of MM patients, and that the overall prognosis is currently <10 years [6], many of the cardio-toxic effects of RT are not encountered as frequently in MM. Moreover, radiation doses encountered in MM are much lower than other cancers (<25 Gy)[118].

Conclusion

Patients suffering from MM present an opportunity in the field of cardio-oncology for improved management of acute and chronic CV conditions that may independently impact mortality. Advances in research and development of novel agents have clearly resulted in improved responses and survival with maintenance of excellent functional capacity in many patients, but has also highlighted the need for greater understanding of the mechanisms responsible for cardiotoxicity, and for the development of cardio-protective approaches. As we continue to make strides toward transforming MM from a lethal cancer into a chronic condition, we must do so with vigilant off-target cardiovascular toxicity.

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