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REVIEW ARTICLE

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Pulmonary hypertension in patients with multiple myeloma: A comprehensive review

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Abstract

Multiple myeloma (MM) is a common hematological malignancy resulting from clonal proliferation of plasma cells and is defined by criteria set forth by the international myeloma working group. Pulmonary hypertension (PH) is defined by an elevated mean pulmonary artery pressure >20 mmHg measured during right heart catheterization. Echocardiography-diagnosed PH is relatively common in patients with MM and has been associated with increased mortality, morbidity, and poor stem cell transplant outcomes. PH in patients with MM (PH-MM) is usually multifactorial in origin. MM disease-specific factors, host comorbidities, and treatment-related adverse effects are the key factors for the development of PH-MM. Pragmatically, patients with PH-MM can be grouped into either (i) PH in patients with a new diagnosis of MM or (ii) PH that develops or worsens along the way of MM treatment. In the latter group, drug-induced PH, venous thromboembolism, pulmonary veno occlusive disease, and cardiotoxicity should be considered as possible causes. PH-MM should be evaluated and managed in a multidisciplinary setting. Select individuals with PH-MM could be considered for pulmonary vasodilators at PH-specialized centers.

KEYWORDS

chemotherapy, drug induced, multiple myeloma, pulmonary hypertension, pulmonary vasodilators

INTRODUCTION, DEFINITIONS, AND TERMINOLOGY

Multiple myeloma (MM) is a cytogenetically heterogenous clonal plasma cell proliferative disorder and is the second most common hematological malignancy.[1,2] The International Myeloma Working Group defines MM as: Clonal bone marrow plasma cells (BMPC) ≥10% and any one of the myeloma-defining events. Myeloma-defining events are further defined as (I) *evidence of end-organ damage attributed to the plasma cell proliferation*, including hypercalcemia, renal insufficiency, anemia, lytic bone lesions (CRAB) or (ii) any one of the *biomarkers of malignancy* including clonal BMPCs ≥60% (or) involved/uninvolved serum free light chain ratio ≥100 (or) >1 focal lesion on MRI studies (≥5 mm).[3] Five-year survival for patients with MM has significantly improved from 27% (1987–1989) and 49% (2005–2011) to 58% (2012–2018) based on cancer statistics and SEER data.[4,5] Consequently, patients with MM are at an

increased risk of cardiovascular complications including PH, due to older age at disease onset, increased survival, and treatment-related adverse effects.[6–11]

Pulmonary hypertension (PH) is defined by elevated mean pulmonary arterial pressure (mPAP) >20 mmHg during right heart catheterization (RHC).[12] Systolic pulmonary artery pressure can be estimated noninvasively by echocardiography using the modified Bernoulli equation: $RVSP = 4 \times TR^2 + RAP$, where RVSP is right ventricular systolic pressure, TR is tricuspid valve regurgitant jet velocity, and RAP is estimated right atrial pressure. Since the estimation of right atrial pressure is fraught with errors, an approach to use the TR jet velocity as a key variable (to assign a probability of PH) has been recently recommended. A peak TR velocity >2.8 m/s may suggest PH, and based on the presence of additional echocardiographic parameters, the probability of PH and the need for further workup can be considered.[13] The gold standard test for diagnosis, quantification and classification of PH is RHC. The data obtained helps characterize PH into either precapillary PH, postcapillary PH or combined post and precapillary PH.[12] The World Health Organization (WHO) classification of PH categorizes PH into groups which share similar pathological and hemodynamic characteristics. *Group I PH* (Pulmonary arterial hypertension [PAH]) includes disorders with a proliferative arteriopathy and requires a pulmonary vascular resistance (PVR) ≥2 Woods units (WU) and pulmonary arterial wedge pressure (PAWP) <15 mmHg.[13] *Group II PH* is due to diseases of the left side of the heart, leading to elevated left atrial pressure, referred to as postcapillary PH or pulmonary venous hypertension (PH-LHD) where in the mPAP is >20 mmHg and PAWP is >15 mmHg. *Group III PH* results from disorders of the lung, hypoventilation, and/or hypoxia. *Group IV PH* includes PH due to chronic thromboembolic disease (CTEPH) and other pulmonary arterial obstructions. Groups III and IV also result in precapillary PH. *Group V PH* includes miscellaneous and systemic diseases associated with PH, often with unclear or multifactorial mechanisms.

If there is a single etiology to an individual's PH that can classify one's PH into either I, II, III or IV, then the presence of MM should not change the diagnosis. When multiple factors impact the pulmonary vasculature leading to PH, as can potentially occur in MM, the diagnosis of Group V PH is justifiable. Similarly, if the degree of PH is severe or felt to be inadequately explained by comorbidities other than MM, a diagnosis of Group V PH or PH-MM could be made.

We will discuss PH-MM in two pragmatic categories: (1) PH-MM-ND (newly diagnosed) and (2) PH-MM-TE (treatment emergent). *PH-MM-ND* is the presence of PH in a newly diagnosed patient with MM (before or within 30 days of a therapy targeting MM). *PH-MM-TE* is PH that is diagnosed after 30 days of the initiation of treatment for MM or pre-existing PH that is worsened by the treatment of MM. This time frame of 30 days was chosen based on the available data thus far but needs to be corroborated with further research. This distinction is crucial for understanding the true epidemiology, pathophysiology, management, and prognosis of PH-MM.

EPIDEMIOLOGY AND RISK FACTORS FOR PH IN MM

In patients with a new diagnosis of MM, the prevalence of PH (echocardiogram based) is 13%–34%.[6,8,9,14] However, the true epidemiology is unknown as most of the studies are limited by retrospective nature, referral bias, small samples, varying definitions of PH, and most importantly lack of invasive hemodynamic measurement. Risk factors for PH-MM-ND include older age (65–70 years), renal insufficiency, anemia, and elevated BNP/NT-pro-BNP levels.[8,9,14] Echocardiographic predictors include increased left atrial diameter, diastolic impairment, and atrial fibrillation.[8,14] Myeloma-specific features were not associated with a diagnosis of PH-MM in the above studies.

Data on PH-MM-TE is even more limited, although, from available studies, the incidence is about 1%–2% in patients treated with carfilzomib and 4.8% for those treated with thalidomide.[15–18]

CLINICAL SIGNIFICANCE OF PH IN PATIENTS WITH MM

Presence of echocardiography diagnosed PH-MM, is associated with an increase in all-cause and cardiovascular mortality.[14] As shown in Figure 1, echocardiography diagnosed PH-MM was associated with reduced progression-free survival (21 vs. 50 months) and reduced overall survival (45 vs. 90 months).[8] On the contrary, Sangani and colleagues did not find a significant difference in survival in relation to the presence or absence of PH-MM, but fewer patients with PH-MM are likely to undergo stem cell transplant (SCT).[9] In addition, patients with MM-PH that undergo autologous stem cell transplant are less likely to get a deeper response than those who do not have PH.[8]

ETIOLOGY AND PATHOPHYSIOLOGY OF PH-MM

PH in the context of MM is a very complex entity. If transition from MGUS to MM is considered as the "second hit," some of the factors below could potentially

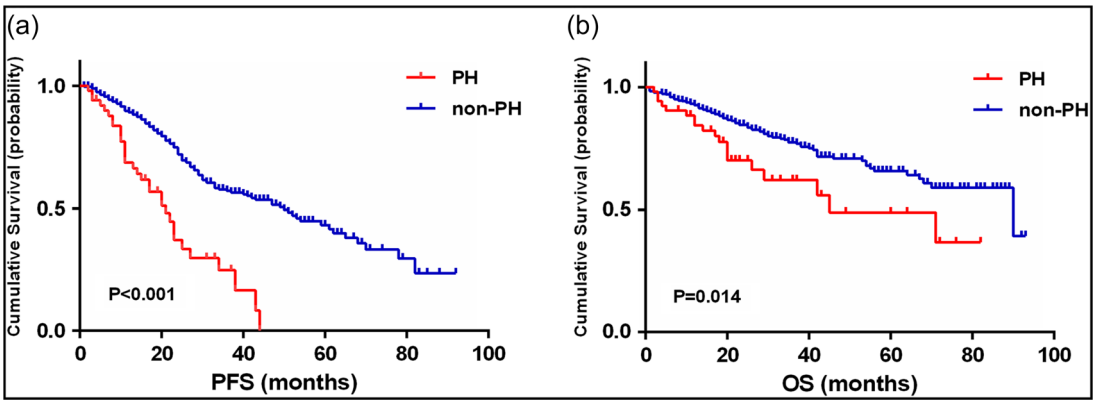

FIGURE 1 Effects of pulmonary hypertension (PH) on (a) progression-free survival (PFS) and (b) overall survival (OS) in patients with newly diagnosed multiple myeloma (MM). Reproduced under CC open access from Jian et al.[8]

be considered as a "third hit" resulting in PH in some patients with MM. Alternatively, the pulmonary circulation could be viewed as another "end organ" being affected by the systemic effects of MM. Pulmonary circulation is normally a very compliant and low resistance system. PVR can be calculated as shown below in the following equation, where PVR is pulmonary vascular resistance, mPAP is mean pulmonary artery pressure, PAWP is pulmonary arterial wedge pressure, and CO is cardiac output.

$$PVR = \frac{\text{mPAP} - \text{PAWP}}{\text{CO}}. \quad (1)$$

In patients with MM, when changes in CO, PVR or PAWP develop, the right ventricle (RV) "adapts" by generating more pressure (Equation 1 can be rearranged to Equation 2).

$$mPAP = CO \times PVR + PAWP. \quad (2)$$

(1) ***PH in patients with Newly Diagnosed MM (PH-MM-ND)***: In PH-MM-ND, the contributors leading to change in CO, PVR and PAWP are dependent on both MM disease-specific factors and patient-specific factors as discussed below.

(a) *Venous thromboembolism (VTE)*: MM and MGUS are both prothrombotic states. The highest risk is in the 1st year of diagnosis of MM and remains steadily increased thereafter. In a large Swedish study, after the diagnosis of MM, the hazard ratios for development of VTE were 7.5, 4.6, and 4.1 at 1, 5, and 10 years, respectively.[19] Similarly, in a large VA-based study, the RR of DVT was 3.3 with MGUS and 9.2 with MM.[20] VTE risk in patients with MM is multifactorial and can be grouped into three main categories: patient-related, disease-related, and treatment-related factors.[21] Traditional noncancer-related VTE risk factors are still pertinent. The precise mechanisms underpinning the prothrombotic nature of MM are not fully understood. The following factors could contribute: Increased thrombin concentrations, chromosome 11 abnormalities, higher P selectin, thrombin activatable fibrinolysis inhibitor, lupus-like anticoagulants, plasminogen activator inhibitor-1, and lower clot permeability and lysis among others.[22] Treatment-related factors contributing to VTE are reviewed in more detail later (see section on treatment-related VTE). Persistent pulmonary thrombosis can lead to CTEPH.

(b) *Pulmonary vasculopathy*: Several pathophysiologic mechanisms may adversely affect the pulmonary circulation and impair its adaptative mechanisms in MM, thus causing an increase in PVR (see Figure 2). Some examples include inflammation, endothelial dysfunction, smooth muscle proliferation, angiogenesis, and myeloma protein deposition.

There is a huge knowledge gap in our current understanding of MM-PH. However, there are several established biomarkers associated in the pathogenesis of both MM and PAH disease states. Here a select few of the overlapping biomarkers will be reviewed, making a case for the etiological plausibility of their role in PH-MM. Endothelin (ET) axis is known to be upregulated in MM, serving as a biomarker, and has been proposed as a treatment target in MM.[23,24] ET system has been well established in the pathogenesis of PAH and endothelin receptor antagonists (ETRA) are one of the cornerstones in the treatment in PAH.[25,26] Elevated levels of Osteopontin (OPN) have been known to be associated with tumor burden and bone destruction in MM.[27] OPN has also been identified as a critical mediator of pulmonary vascular remodeling

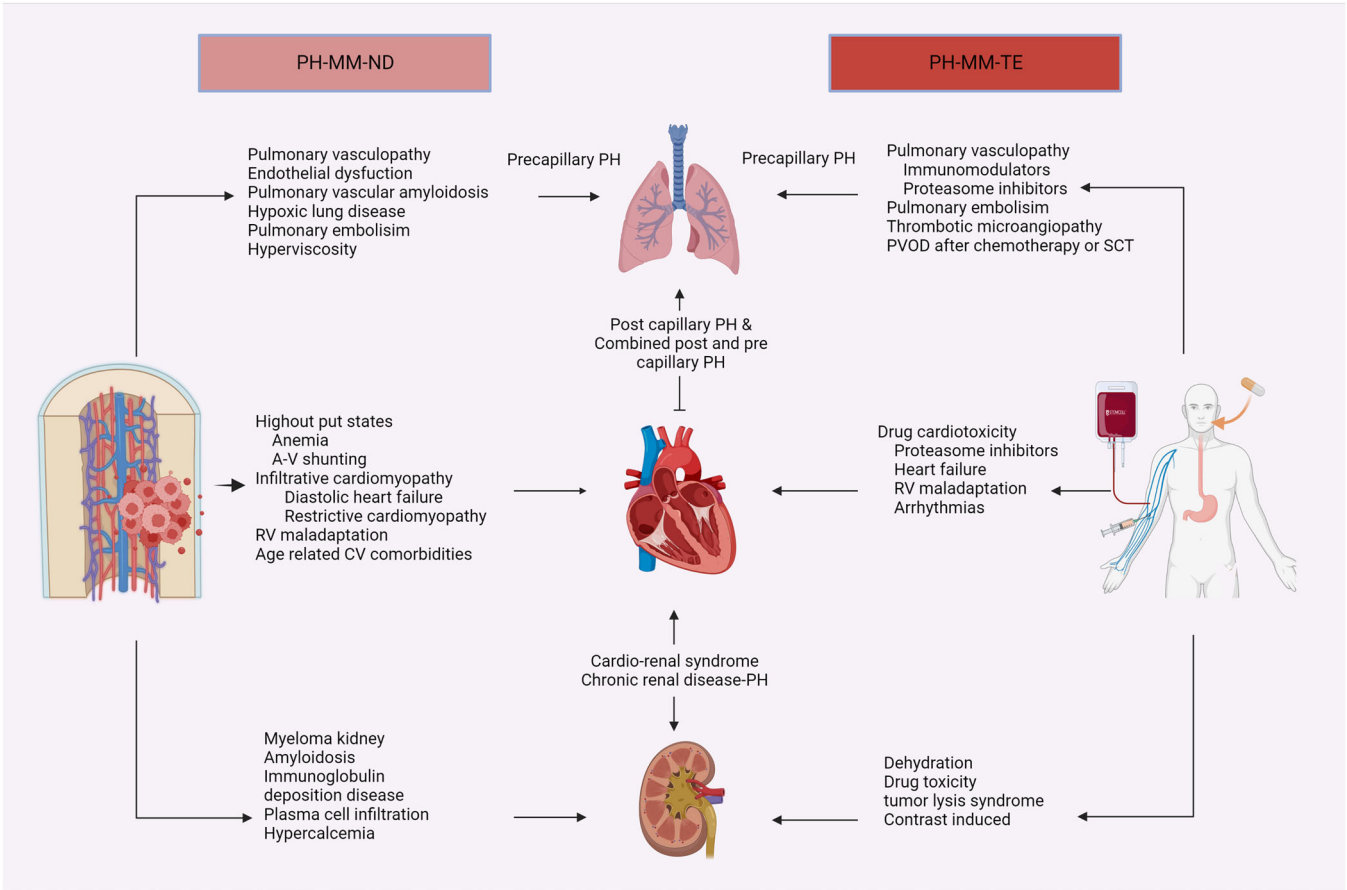

FIGURE 2 Etiology of PH in multiple myeloma. Several factors might contribute to PH in MM either by increasing cardiac output (CO) or increasing pulmonary vascular resistance (PVR) or left heart disease (by causing increase in pulmonary capillary wedge pressure). CV, cardiovascular; PH-MM-ND, pulmonary hypertension in patient newly diagnosed multiple myeloma; PH-MM-TE, pulmonary hypertension in patient with multiple myeloma after treatment initiation; PVOD, pulmonary veno occlusive disease; RV, right ventricle; SCT, stem cell transplant. See text for further details. Created with BioRender.com.

associated with pulmonary artery smooth muscle cell (PA-SMC) senescence by causing migration and proliferation of target cells.[28] Upregulated vascular endothelial growth factor (VEGF) and VEGF receptor has been associated with MM and has been implicated in pathogenesis of PAH in various disease states.[27,29] Both MM and PAH are known to have elevated levels of inflammatory cytokines such as IL6 and TNF-α.[29,30] For the interested reader, a more comprehensive and through review on current and emerging biomarkers for PH and MM can be found elsewhere.[29,31]

(c) *Left heart disease*: Patients with MM (most patients are >60 years age at diagnosis) are likely to have cardiovascular comorbidities such as coronary artery disease, hypertension (HTN), diastolic impairment, or heart failure with preserved ejection fraction, atrial fibrillation and valvular heart disease. All the above comorbidities are risk factors for PH-LHD.[32] In addition, patients with MM and amyloidosis can have infiltrative and restrictive cardiomyopathy (see sections on amyloidosis and diagnosis).

(d) *Renal disease*: Renal disease being a myeloma defining event, is present in over 50% of patients at the time of diagnosis. Renal disease in MM can be categorized into (i) immunoglobulin (Ig) mediated: cast nephropathy (aka myeloma kidney), monoclonal immunoglobulin deposition disease, light chain amyloidosis, (ii) non-Ig mediated disease due to hypercalcemia, hypovolemia, tumor lysis, or plasma cell infiltration, and (iii) glomerulonephritis.[33] A significant portion of patients with MM progress to chronic kidney disease (CKD) and consequently have increased morbidity and mortality.[34] CKD also causes PH through multiple or unexplained mechanisms and has been linked to poor outcomes.[35]

(e) *AL amyloidosis-related PH*: Amyloidosis is defined as the clinical syndrome associated with deposition of amyloid (a misfolded protein which is extremely insoluble and is resistant to proteolysis) in different

organs. In a study of 84 patients with newly diagnosed MM who underwent abdominal fat pad biopsy, 38% were found to have AL amyloid deposition.[36] Similarly, around 20% of patients with light-chain (AL) amyloidosis also had a concurrent diagnosis of MM.[37] As would be expected, patients with AL amyloidosis with MM (defined either by CRAB criteria or by more than 10% BMPCs) have a poor prognosis compared patients who have AL amyloidosis alone.[38] Amyloidosis can cause PH by several mechanisms based on the location of protein deposition. Deposition of amyloid in the elastic and muscular layers of the pulmonary artery has been reported (likely to be under-diagnosed) causing precapillary PH.[39] Light chain amyloidosis is the most commonly diagnosed type of cardiac amyloidosis, characterized by extracellular amyloid infiltration in the heart. Deposition in the ventricular walls causes concentric ventricular remodeling leading to HF, deposition in the intramyocardial vessels leads to decreased myocardial perfusion and deposition in the conduction system causes arrhythmias. Cardiac involvement is the leading cause of morbidity and mortality (1-year mortality of 40%), thus making cardiac biomarkers (troponin and NT-ProBNP) key in staging the disease.[40]

(f) *Anemia and high output states*: Anemia (hemoglobin <10 g/dL) is a MM-defining component. Although there are several possible mechanisms for the anemia in these patients a couple established possibilities include (a) marrow infiltration and (b) upregulation of hepcidin which then inhibits the absorption of iron and leads to anemia of chronic inflammation.[41,42] Anemia is associated with symptoms of fatigue and decreased exertional capacity. Cardiovascular system responds to anemia by increasing cardiac output (CO) to compensate for the reduced oxygen-carrying capacity.[43] With extensive bone involvement in MM, there can be arterio-venous shunting, contributing to the increased CO.[44] *To generate the extra CO might be challenging if the RV is already structurally and (or) functionally impaired, or the PVR is elevated due to factors listed above.*

(g) *Hyperviscosity*: Blood flow through the pulmonary circulation is impeded as the viscosity of blood is increased by paraproteins. Typical serum viscosity for a healthy person is 1.5 cP (centipoise) and relates primarily to its protein content. Immunoglobulins being relatively large and linear in shape, travel through the serum spinning around their longitudinal axis causing increase in serum viscous drag, and therefore viscosity.[45] Immunoglobulin M (IgM) is very large and travels as a pentamer adding on more to the viscosity compared with IgA which is smaller and IgG which is even smaller. Hyperviscosity is less frequent in MM than in Waldenström's macroglobulinemia, due to higher IgM levels in the latter.[37] In patients with echocardiogram diagnosed PH-MM, IgA levels were higher in patients with PH in one study[14] while another study did not find that association.[8] Symptoms of hyperviscosity include visual disturbances, central retinal vein occlusion, mucocutaneous bleeding, or neurological symptoms. *What could be viewed as trivial increase in protein level (and therefore blood viscosity) might have a great consequence on the pulmonary circulation and right heart especially when PVR is elevated due to factors listed above.*

(2) ***PH emerging in patients exposed to MM treatment (PH-MM-TE)***: In most patients with PH-MM-ND, treatment of MM alone or in combination with pulmonary vasodilators, PH resolves as MM improves (see section on treatment). On the other hand, some patients can have worsening PH, some develop PH during treatment of MM (treatment emergent, PH-MM-TE). Treatment-related factors contributing to development or worsening PH (by causing changes in CO, PVR and PAWP, see Equation 2 above) will be reviewed here (see Figure 2)

(a) *VTE associated with treatment of MM*: Use of erythropoietin and central venous catheters might contribute to elevated risk of VTE.[22] This risk is increased manifold by treatment regimens used to treat MM. Thalidomide and its derivative lenalidomide have been associated with a rise in VTE occurrence in the MM population. Thalidomide or lenalidomide monotherapy contribute to the baseline VTE risk (around 3%–4%) but can increase up to 26% with the addition of high-dose dexamethasone, multiagent chemotherapy, or anthracyclines.[21,22] While bortezomib is thought to be thromboprotective, induction with carfilzomib-based regimens was associated with higher VTE.[22,46] There are validated risk assessment models to help predict risk of VTE, and current treatment guidelines recommend incorporating prophylaxis in the treatment regimen.[21,22]

(b) *Endothelial dysfunction and pulmonary vasculopathy associated with MM treatment*: Both immunomodulatory drugs and proteasome inhibitors can cause endothelial dysfunction resulting in an imbalance between vasodilation and vasoconstriction, thus leading to development of PH. In a study evaluating the development of nonthromboembolic PH with thalidomide therapy, 4 of the 82 treated patients (4.8%) developed PH, which improved after

discontinuation of therapy.[16] A systematic review of literature also describes the clinical features of PH-MM associated with Thalidomide and its derivatives.[15] Bortezomib, is thought to alleviate experimental PH by regulating intra cellular calcium homeostasis in PA-SMCs.[47] However, clinically, PH has been reported after bortezomib and is also listed in the package insert.[48] Carfilzomib, another PI, has been associated with development of PH in about 1%–2% patients, between 1 and 3 months after treatment initiation (median of 46 days).[17,18] This may be due to inhibition of endothelial NO synthase, adverse effects on vascular smooth muscle cells or endothelial dysfunction.[49,50] Elderly patients, those with renal failure or prior anthracyclines exposure, and patients that had a prior adverse event might be at higher risk for PH.[51] Carfilzomib has been added to the list of drugs associated with development *PAH* in the most recent guidelines.[13]

(c) *Cardiac adverse events (CAEs) associated with MM treatment*: Cardiotoxicity is referred to as myocardial dysfunction, which may result in heart failure (HF, most frequent) and HTN, accelerated ischemic heart disease (IHD) and arrhythmias.[10] All of these can cause, or precipitate PH. Proteasome is an essential component of cellular homeostasis by degrading majority of regulatory proteins through the ubiquitin-proteasome system (UPS). Malignant myeloma cells produce large quantities of proteins (with higher error rate in folding and assembly) are also heavily saturated in UPS to prevent protein accumulation (causing cellular apoptosis) and, hence particularly sensitive to proteasome inhibition.[50] Meta analysis and pooled data suggest that bortezomib was not associated with incidence of arrhythmia, IHD, HF, and cardiac death. This decreased risk is probably due to recovery of proteasome activity 72 h after administration (reversible PI), reducing ischemia-reperfusion injury, and preventing left ventricular hypertrophy.[50] Carfilzomib (an irreversible PI) however is strongly associated with the development of HF and PH in both drug trials, and real-world data from the FDA adverse event reporting system.[10,18,50] A low incidence of cardiotoxicity has also been documented after Ixazomib probably because of the reversibility of proteasome inhibition with Ixazomib.[10] Immunomodulatory agents are associated with arrhythmias and cardiomyopathy probably to a lesser extent.[52] Similarly, other therapeutic agents in MM are also associated with cardiotoxicity to varying extent.[10]

(d) *Right Ventricular dysfunction and maladaptation*: The RV is normally a thin-walled and crescentic structure, and its function is highly sensitive to changes in afterload. When the RV is exposed to increasing afterload (PVR), it adapts by increasing contractility and undergoing hypertrophy. However, if the RV is challenged further (due to some or all the factors discussed in the preceding sections), it can maladapt (marked by decreased RV function and enlargement) and eventually progress to right HF (due to ventriculo-arterial uncoupling).[53]

(e) *Thrombotic microangiopathy associated with treatment of MM*: This more commonly presents as renal involvement (hemolytic uremic syndrome-thrombotic thrombocytopenia) and rarely as a pulmonary involvement, presenting as PAH. This presentation leads to occlusive microvascular thrombosis due to excessive platelet activation as well as endothelial injury by either impairment in VEGF versus direct endothelial damage because of the PI inhibitor bortezomib or carfilzomib.[49,54] Immunomodulators are also known to cause thrombotic microangiopathy.

(f) *PVOD (pulmonary veno occlusive disease)*: PVOD is a rare but devastating cause of PH characterized by preferential remodeling of the pulmonary venules and capillaries. RHC findings in patients with PVOD are similar to PAH and the PAWP is normal. Biopsy is hazardous and is not recommended to diagnose. Features such as severely reduced diffusion capacity on PFTs, and presence of subpleural thickened septal lines, centrilobular ground-glass opacities, and mediastinal lymphadenopathy on high resolution CT scan of chest will favor a diagnosis of PVOD. PVOD in the context of MM, can develop in patients treated with alkylating agents such as cyclophosphamide and as a complication of hematopoietic stem cell transplant, usually has a poor prognosis.[13,55,56]

POEMS syndrome

POEMS syndrome is a rare plasma cell disorder characterized by Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin changes.[57] Pulmonary manifestations of POEMS include PH, pleural effusions, restrictive lung disease, respiratory muscle weakness, and an isolated reduction in diffusing capacity.[58] Elevated VEGF levels (one of the diagnostic criteria for POEMS) is the main driver of the disease and there seems to be a correlation between PH and VEGF levels.[59] In patients with POEMS, the prevalence of echocardiogram-diagnosed PH is between 27% and 36% and is associated with decreased survival.[59,60] *Distinguishing POEMS syndrome from MM is very important*

since the treatment and expected toxicities are quite different.[57] Even PH associated with POEMS has distinctive features because patients are usually younger (thus eliminating the age-related CV comorbidities associated with MM), have a slightly higher preponderance for diastolic impairment and pericardial effusions, and the PH itself is responsive to treatment of POEMS.

SCREENING AND DIAGNOSIS

The symptoms and signs of PH are usually nonspecific, including dyspnea, fatigue, chest pain, palpitations, and in advanced disease, edema, and other signs of HF. In patients with MM, recognition of PH is more likely to be delayed as these symptoms are often attributed to malignancy itself, anemia, bone lesions, renal failure, and other comorbidities (see section on risk factors above). Pulmonary exam may reveal effusions that are refractory to diuresis (if associated with amyloid depositions). Signs of VTE include extremity erythema, warmth and swelling. Attention should be paid to sites of indwelling catheters/ports. Jugular venous distension, a loud S2, flow murmur or precordial heave may be present. Macroglossia and bilateral carpal tunnel syndrome can be signs of amyloidosis. Signs of hyperviscosity including mucocutaneous bleed, retinal hemorrhages, central retinal vein occlusions and neurological symptoms should prompt urgent evaluation and intervention. A high index of suspicion and early screening for PH is prudent, and should be contemplated by all providers involved in the care of patients with MM, including oncologists, cardiologists, pulmonologists and primary care physicians.

Laboratory tests that have been associated with PH in MM include anemia, decling renal function and sometimes IgA levels.[8,9,14] Elevated liver enzymes might reflect congestive hepatopathy. Elevation in BNP and NT Pro-BNP are very important for both diagnosis and prognostication in MM and amyloidosis.[50,61,62] These tests should be obtained at the time of diagnosis/staging of disease as well as monitored through therapy. Pulmonary function studies, chest imaging, assessment for sleep apnea and ambulatory oxygen saturations should be obtained in all patients to evaluate for underlying lung disease (Group III PH). A disproportionately low diffusion capacity is the hallmark of pulmonary vascular disease, especially in setting of clear lungs on imaging studies. Presence of subpleural thickened septal lines, centrilobular ground-glass opacities, and mediastinal lymphadenopathy might suggest a diagnosis of PVOD. VQ scan should be performed to rule out CTEPH. A thorough work up for MM is also crucial to appropriately differentiate it from other plasma cell disorders and staging the disease.[37,63,64]

Echocardiogram is easily available, noninvasive, and yields vital information about the size, function and nature of the myocardial wall (infiltrates if present). It can serve as a screening and monitoring tool, especially if able to evaluate with tissue doppler imaging and global longitudinal strain. Presence of tricuspid regurgitation, PASP >40 mmHg and right sided chamber enlargements predict PH in patients with MM.[8,9,14] Presence of TR jet velocity >2.8 m/s and/or other parameters suggestive of PH should suggest further evaluation for PH. Reduced Tricuspid annular plane systolic excursion (TAPSE), increased RV/LV basal diameter, flattening of interventricular septum, enlarged pulmonary artery or reduced RV out flow acceleration time and enlarged right atrium (RA) can all suggest presence of PH.[13] Moreover, echocardiogram can identify mitral valve disease, aortic valve disease, left atrial enlargement, LV enlargement or hypertrophy, impaired diastolic or systolic function, as well as infiltrative cardiomyopathy. Echocardiogram does have limitations including poor windows, erroneous estimation of PASP as well as being operator dependent. Cardiac MRI is also emerging as a modality of imaging for the RV in PH and also promising in evaluation in MM and cardiac amyloidosis.[61,65] A more thorough overview of cardiac imaging in the setting of MM has been recently reviewed.[10]

As already highlighted, RHC is of paramount importance in diagnosing and characterizing PH. RHC should ideally be performed by providers with experience in evaluating patients with PH as misclassification could have detrimental effects.

TREATMENT

After a comprehensive evaluation and work up by multidisciplinary group of providers with expertise in PH, oncology and cardio-oncology, risk assessment and treatment plan should be formulated for MM-PH.[62] The following structured approach would be helpful in managing patients with MM-PH.

(a) *General measures*: Counseling on salt and fluid restriction as well as smoking cessation is important and should be provided. Ambulatory oxygen saturation should be checked, and oxygen supplemented to keep saturations >90% with activity and rest recommended. Sleep apnea, if present, should be appropriately treated. Patients at increased risk of VTE must be on appropriate prophylaxis. Cardiopulmonary rehabilitation and exercise training has been shown to improve exercise capacity, muscular function,

quality of life in patients with PH and should be recommended as appropriate.[66]

(b) *Patient and disease-specific factors*: The nature of PH largely dictates the specific management. For example, if PH-LHD is identified, management should be geared towards optimizing volume status and antihypertensive medications should be tailored to address optimization of preload and afterload. In addition, heart rate and rhythm should be monitored and intervened appropriately. Patients with CTEPH should be referred to centers with experience in evaluating and treating CTEPH. PH severity, cardiac biomarkers, and RV function on imaging, and functional class (WHO FC) at the time of diagnosis could help determine if pulmonary vasodilators are indicated in patients with PAH or a significant precapillary disease. There is some literature supporting use of pulmonary vasodilators in PH-MM which is reviewed below and in Table 1. It should be emphasized that there is a wide knowledge gap in this area needing more research.

PH-MM-ND

To date, there are no randomized control studies directly assessing the role for PAH-specific medicines in MM. There have been several case reports and case series reported. In most instances of PH-MM-ND, the treatment of MM might improve PH and therefore, might be the preferred way in patients with minimal PH and WHO FC-I and II patients.[8,67,68] If possible, the selection of chemotherapy regimen should aim to minimize further "hits" on the cardiovascular system and pulmonary circulation. There is emerging literature that adding metformin or angiotension II receptor blockers might be cardioprotective in patients receiving carfilzomib.[69] In select PH-MM-ND patients who have a significant precapillary disease/PAH and poor functional status (WHO FC III or IV) pulmonary vasodilators could be initiated in tandem with MM treatment.

Currently approved medications for PAH can be grouped into 3 categories based on their mechanism of action: (i) Prostacyclin receptor agonists and Prostaglandin analogs, (ii) ETRA, and (iii) Phosphodiesterase 5 inhibitors/soluble guanylate cyclase stimulators. Yaqub et al describe a young patient with PH-MM-ND who was treated with IV Epoprostenol and coumadin along with chemotherapy leading to improvement in PAH.[70] Feyeresin et al. report the use of ambrisentan (an ETRA) in combination with sildenafil in one patient where MM and PH were treated simultaneously, and after remission was achieved in MM, PH also improved.[71]

PH-MM-TE

Thalidomide, cyclophosphamide, and carfilzomib are the MM-targeted chemotherapeutic agents that have been associated with PH the most, while other agents have

TABLE 1 Case reports of PH-MM treatment in literature.

Reference	Age, sex	Diagnosis	FC	PH-MM Type[a]	PAH specific treatments	Outcome
Yaqub et al.[70]	36, M	MM + DM	N/a	ND	IV Epoprostenol + coumadin	Improved
Rostagno and Ciolli[67]	31, M	MM	N/a	ND	None	Improved
Feyereisn et al.[71]	63, M	SMM, MM, MPGN, OSA	III	ND	Ambrisentan + sildenafil	Improved
	59, M	SM and SMM	III	TE (after SM treatment)	IV Epoprostenol + sildenafil	Improved
Krishnan et al.[78]	72, M	MM, A.fib, and severe AS	III	TE, post MM Rx and HSCT	Sildenafil and ambrisentan	improved
	69, F	MM, AL amyloidosis, CKD, Atrial tachycardia	III	TE, post MM Rx and HSCT	Sildenafil	Improved
	69, F	MM	IV	TE, post MM Rx and HSCT	Sildenafil and ambrisentan	Improved
Kreidy et al.[68]	77, M	MM, LHD, A.fib, SSS	n/a	TE (after SM treatment)	Tadalafil, ambrisentan, and inhaled treprostinil	Fatal

Abbreviations: AS, aortic stenosis; CKD, chronic kidney disease; DM, dermatomyositis; F, female; HSCT, hematopoietic stem cell transplant; LHD, left heart disease; M, male; MGPN, membranoproliferative glomerulonephritis; MM, multiple myeloma; OSA, obstructive sleep apnea; SM, scleromyxedema; SMM, smoldering multiple Myeloma; SSS, sick sinus syndrome.

[a]Assumed based on case description, not specifically categorized in the original articles and hence arbitrary.

also been reported to cause PH. In most reports, PH-MM-TE related to drug-induced PAH was reversible while in others both PH and MM were progressive and irreversible.[68,72–77] Feyereisn et al also report a case of likely, PH-MM-TE treated with Epoprostenol and calcium channel blocker in severe PAH that is vasodilator responsive.[71] Krishnan and colleagues report improvement in functional class and symptoms after institution of PAH treatment with sildenafil and ambrisentan in 3 patients PH-MM-TE that developed years after SCT.[78] Pharmacological basis for the use of ETRA in MM-PH is even more convincing because a recent study demonstrated that Macitentan (ETRA) curtailed tumor growth and angiogenesis in MM cells.[79]

In patients with PH-MM-TE, after systematic evaluation, either stopping the offending chemotherapeutic agent or choosing alternative chemotherapy should be thoughtfully considered with the addition of pulmonary vasodilators in patients with severe symptoms (a similar approach has been proposed for other cancer treatment related PH/PAH).[80] Some patients with PH may develop complications including pulmonary edema (suggesting presence of PVOD) after initiation of pulmonary vasodilators. Therefore, such decisions/treatments should be considered on a case-by-case basis by experts in oncology, cardio-oncology, PH and only after incorporating patient's preferences. Although exact frequency and methods of monitoring for PH-MM and interruption or changing treatments is not known, efforts are underway to provide further guidance.[62]

CONCLUSION

PH in MM is more prevalent than recognized and has been associated with increased morbidity and mortality. It can be related to patient-specific factors such as age, disease-specific factors, and treatment-related. Patient's symptoms of PH-MM are nonspecific and are likely to be attributed to other causes that are coexistent in patients with MM. High index of suspicion and screening will help recognize the disease early and intervene. Etiology and pathophysiology of PH-MM is complex and a detailed workup with a multidisciplinary approach between hematology-oncology, cardiologists, and PH specialists would help appropriate classification and management. Although evidence is limited to case series, it is either responsive to treatment of MM or with the addition of pulmonary vasodilators, and can be managed in parallel with MM.

AUTHOR CONTRIBUTIONS

Veeranna Maddipati conceptualized the idea and contributed to literature search and prepared the manuscript. Pratyaksha Sankhyan, Durga P. Goswami, and Akhilesh Mahajan have all contributed with literature review and drafting the manuscript. All authors have reviewed and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated.

ETHICS STATEMENT

Our manuscript is a review article of the existing literature on the topic. There is no research or direct use of any animal or human data or tissue.

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