

Assessment and monitoring of patients receiving chemotherapy for multiple myeloma: strategies to improve outcomes

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Abstract: Improved understanding as to the biology of multiple myeloma (MM) and the bone marrow microenvironment has led to the development of new drugs to treat MM. This explosion of new and highly effective drugs has led to dramatic advances in the management of MM and underscores the need for supportive care. Impressive and deep response rates to chemotherapy, monoclonal antibodies, and small molecule drugs provide hope of a cure or prolonged remission for the majority of individuals. For most patients, long-term, continuous therapy is often required to suppress the malignant plasma cell clone, thus requiring clinicians to become more astute in assessment, monitoring, and intervention of side effects as well as monitoring response to therapy. Appropriate diagnosis and monitoring strategies are essential to ensure that patients receive the appropriate chemotherapy and supportive therapy at relapse, and that side effects are appropriately managed to allow for continued therapy and adherence to the regimen. Multiple drugs with complex regimens are currently available with varying side effect profiles. Knowledge of the drugs used to treat MM and the common adverse events will allow for preventative strategies to mitigate adverse events and prompt intervention. The purpose of this paper is to review updates in the diagnosis and management of MM, and to provide strategies for assessment and monitoring of patients receiving chemotherapy for MM.

Keywords: multiple myeloma, treatment, symptoms, assessment, monitoring, symptom management, targeted therapies

Introduction

Multiple myeloma (MM) is an incurable, but highly treatable cancer characterized by an overproliferation of bone marrow plasma cells, which leads to the production of a monoclonal protein. Through a series of genetic changes, genetic mutations, and cellular alterations, the normal plasma cell turns malignant. Cancerous plasma cells overproduce clonal immunoglobulin (Ig) proteins which cause organ destruction. Although the genetic makeup of the tumor itself and patient symptoms at presentation are heterogeneous, common signs and symptoms of MM exist at diagnosis. Known as “CRAB” criteria, the pneumonic stands for hyperCalcemia, Renal insufficiency, Anemia, and Bone damage. The incidence of these at diagnosis is as follows: anemia 73%, bone pain 68%, renal insufficiency 19%, and hypercalcemia 13%.¹ To delay worsening of existing organ damage, or to prevent future organ damage, prompt treatment of the malignant plasma cells with chemotherapy is warranted.

As of 2012, it is estimated that 65,000 individuals are living with MM globally and comprise ~2% of all cancer types.² The incidence of MM is expected to increase over the next decade. The etiology of MM is unknown, but the risk is associated with

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increasing age, obesity, and race. MM is more prevalent in individuals over the age of 65 and is nearly two times higher in African–American individuals and men. Obesity and high body mass index further increases the risk to develop monoclonal gammopathy of undetermined significance (MGUS) and potential MM.³

Initial evaluation

All patients who present with an abnormal paraprotein should undergo a thorough laboratory, radiologic, and physical assessment, as multiple factors are considered to make the correct diagnosis. In addition to usual tests such as a complete blood count with differential count and complete metabolic panel testing, common biomarkers to assess MM disease include serum protein electrophoresis with quantification of monoclonal protein, urine protein electrophoresis, and kappa/lambda serum free light chain (FLC). Beta-2 microglobulin and lactate dehydrogenase (LDH) also assess the burden of disease.⁴

Genetic changes and aberrations to the plasma cell clone and within the bone marrow microenvironment can lead to myeloma cell development and breed resistant disease over time. Three main ways to identify genetic aberrations in MM patients on clonal plasma cells include: 1) karyotype chromosome analysis, 2) fluorescence in situ hybridization, and 3) gene expression profiling.^{5,6} Traditional MM-specific tests (such as serum protein electrophoresis, urine protein electrophoresis, kappa/lambda FLCs, and LDH) are combined with these methods to estimate prognosis. Clinicians should have knowledge of biomarker and genomic results which are essential when stratifying patients into appropriate risk categories, as the results guide treatment selection.^{7–10}

In addition to laboratory testing and bone marrow evaluation with biopsy, radiologic testing at diagnosis is important to determine if bone disease is present. Back or bone pain is a common presenting symptom of MM, as destructive, painful osteolytic lesions are common at diagnosis. Pain can be a result of increased osteoclastic activity, skeletal fractures, bone marrow plasmacytosis, or can be due to a plasmacytoma.¹¹ Not all lesions are painful; however, assessment of MM bone disease is critical to delineate one's diagnosis and should continue periodically with disease monitoring. At baseline, conventional plain radiography with a metastatic skeletal survey should be performed and include the axial skeleton, skull, and large cortical bones. An abnormal survey will reveal osteolytic lesions, osteopenia, or fractures in ~80% of patients with MM at diagnosis. However, ~30% bone loss should have occurred before bone lesions are detected.^{12–14}

For patients with a high suspicion of extramedullary disease or occult bone disease not seen on conventional radiology, 18-F-fluorodeoxyglucose positron emission tomography–computed tomography, positron emission tomography–magnetic resonance imaging (MRI), or MRI of spine or suspicious lesions should be considered.¹⁵

Diagnosis and differential diagnosis of MM

The diagnosis of MM continues to evolve as new drugs that effectively treat MM are available. In previous years, the diagnosis of MM was made if patients had experienced a myeloma-defining event, or “CRAB” criteria were achieved. MM occurs along a spectrum of plasma cell disorders that range from an asymptomatic and often benign condition called MGUS, smoldering MM (SMM), and symptomatic MM. It is currently recommended that patients with MGUS or SMM be only treated within the context of a well-designed clinical trial. Currently, only symptomatic MM requires immediate treatment (Table 1). Thus, it is essential that an accurate diagnosis of MM be confirmed prior to initiating plasma cell directed therapy.^{4,16}

MGUS is present in ~3%–4% of the US population in individuals over the age of 50 years and often precedes the diagnosis of MM and other plasma cell disorders.^{1,17} Patients qualify for an MGUS diagnosis if they lack CRAB criteria and have no evidence of organ damage related to the monoclonal protein.⁹ There are three types of paraproteinemia: IgG, IgA, and IgM. Individuals with non-IgM MGUS carry a relatively low risk of progression to MM, lymphoma, amyloidosis, or other plasma cell dyscrasias at a rate of <1% per year. One's individual risk of progression, however, is based on the level of monoclonal protein concentration in the blood or urine, serum FLC burden, and percentage of bone marrow plasmacytosis.^{16,18–20} Patients with SMM have a higher burden of disease, but remain without CRAB criteria or evidence of organ damage. While some patients with SMM behave more like MGUS, meaning a low risk of progression and quiescent disease course, a majority of patients will progress within 2 years if bone marrow plasma cells are >10% and there is elevated serum FLC ratio, and t(4:14), gain 1q, or other genetic abnormalities are present.^{21,22} It is important to consider that ~7% of newly diagnosed MGUS or MM patients will have a concurrent diagnosis of amyloidosis. Close attention to renal, cardiac, or other abnormalities should alert the clinician to assess for the presence of amyloid, which would require emergent treatment.

Table 1 Diagnostic criteria for multiple myeloma and differential diagnosis

Condition	MGUS	SMM	Active multiple myeloma
% of clonal plasma cells in bone marrow	<10%	10%–60%	≥10%
Myeloma-defining events: hypercalcemia, anemia <10 g/dL or 2 g below normal, renal insufficiency with creatinine >2 g/dL, bone disease (more than one focal lesion on MRI or widespread lytic lesions)	None	None; however, patients are at a high risk for progression if diffuse abnormalities or one focal lesion on MRI	Yes, or any one: 1) clonal BMPCs ≥60%, or 2) serum FLC ratio ≥100 (plus measurable involved FLC level ≥100 mg/L), or 3) more than one focal lesion on MRI scan
Likelihood of progression	~1% per year	~10% per year; higher if serum involved/uninvolved FLC ratio ≥8 (but <100), IgA isotype and immunoparesis	Not applicable
Treatment	No, watchful waiting	Yes for high risk (especially in the context of clinical trial) No for others	Yes

Note: Data from Durie et al,¹⁶ Rajkumar et al.⁴

Abbreviations: BMPC, bone marrow plasma cell percentage; FLC, free light chain; IgA, immunoglobulin A; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; SMM, smoldering multiple myeloma.

In 2014, the International Myeloma Working Group revised the criteria for diagnosis of MM to include clonal bone marrow plasma cell percentage ≥60%, an involved to uninvolved serum FLC ratio ≥100, and >1 focal lesions on MRI.^{4,14,16} The update was based on prior studies which supported an increased risk of progression to MM based on these three aforementioned factors. The presence of greater than one lesion on MRI was associated with a median time to progression of 13 months, and 70% of individuals had progressed at 2 years. In a study of patients with SMM, those with clonal bone marrow plasma cell percentage of 60% or greater had all progressed to symptomatic MM within 2 years.²³ Elevated serum FLC ratios >100 and involved FLC >100 mg/L have been linked to an increased risk of MM disease progression in as less as 18 months.^{24–26} The recommendation to include the presence of more than one focal lesion was based on a study which evaluated the use of whole-body MRI in MM. The presence of a single lesion on MRI was associated with a median time to progression of 13 months, and 70% of individuals in the study progressed at 2 years.²⁷

Prognosis and risk stratification is based on the revised international staging system (ISS), Durie–Salmon staging system, and genetic classification with chromosomal abnormalities.^{5,28–32} Host factors and genetic factors are two criteria which influence prognosis. Host factors affect prognosis and include increased age and comorbid illnesses. Genetic factors include IgH translocations and high LDH levels. A majority of patients will have trisomy or hyperdiploid MM with t (11; 14) or t (6; 14), which confers a favorable prognosis. Approximately 10% will have intermediate-risk disease

with fluorescent in situ hybridization t (4; 14). The remainder of patients are categorized as high risk with t (14; 16), t (14; 20), 17p deletion, or a high-risk gene expression profiling signature.^{5,9}

Treatment of MM

Just as the diagnosis of MM continues to evolve, so do its treatment goals. While a cure may be possible for a small percentage of patients, usually those with standard- or low-risk disease, the primary goal of treatment is disease control and improvement of symptoms. Prompt initiation of chemotherapy to prevent worsening of symptoms or organ damage is recommended. Despite the availability of methods to assess the risk status and disease burden, there is no clear consensus as to the best treatment for newly diagnosed MM patients, but it is clear that the newer drugs are superior to older drugs and should be included in treatment.

With four new drug approvals by the US Food and Drug Administration (FDA) in 2015, there are now seven therapeutic classes of drugs approved for use in the US to treat myeloma. Examples include: 1) alkylating agents (melphalan, cyclophosphamide); 2) other chemotherapy (doxorubicin, vincristine, etoposide); 3) corticosteroids (dexamethasone, prednisone); 4) histone deacetylase inhibitors (panobinostat); 5) immunomodulatory agents (lenalidomide, pomalidomide, thalidomide); 6) monoclonal antibodies (daratumumab and elotuzumab [ELO]); and 7) proteasome inhibitors (bortezomib, carfilzomib, and ixazomib).³³ The survival of patients with MM has increased over the past decade as new classes of drugs with novel mechanisms of action have been added to the treatment armamentarium, although it

remains unclear which drug or drug combination should be given sequentially.³⁴ Most will agree that combination therapies, given at diagnosis or relapse, have provided improved response rates and progression-free survival (PFS), compared to standard chemotherapy alone.^{35–46} Current guidelines suggest every patient with MM should be evaluated for hematopoietic stem cell transplantation at the time of diagnosis. Regardless of transplant eligibility, prolonged doses of melphalan should be avoided in transplant-eligible patients as melphalan can impair the ability to collect stem cells. For most, combination therapy with two drugs or three drugs upfront remains common practice. Table 2 highlights the common side effects of treatment categorized by body system and general recommendations, as the clinicians have to be aware of them for health promotion.

Bortezomib

Bortezomib is a proteasome inhibitor that has been extensively studied and shown to improve PFS and overall survival (OS) in several studies on newly diagnosed or relapsed MM.^{35,38,39} In a trial of 682 patients with newly diagnosed MM (NDMM) and ineligible for autologous stem cell transplant, each of them was randomly assigned to receive nine 6-week cycles of melphalan (9 mg/m²) and prednisone (60 mg/m²) on days 1–4. Melphalan and prednisone (MP) was given to patients either alone or in combination with bortezomib (1.3 mg/m²) on days 1, 4, 8, 11, 22, 25, 29, and 32 for four cycles. This was followed by a maintenance phase for responding patients (cycles 5–9). The combination of bortezomib + MP was superior to MP alone, as 71% of patients had achieved at least a partial response versus 35% of patients receiving MP alone.³⁹ Side effects of peripheral neuropathy and diarrhea were greater in the bortezomib, melphalan, and prednisone (VMP) versus MP groups, thus close attention to peripheral neuropathy symptoms and diarrhea is warranted.

Bortezomib has been studied in combination with lenalidomide and dexamethasone in newly diagnosed and relapsed MM.^{47–49} Recent results of a large cooperative group study showed a clinically meaningful and statistically significant improvement in PFS among groups. In this Phase III, multicenter Southwest Oncology Group study, bortezomib, lenalidomide, and dexamethasone (VRd) was compared to standard therapy with lenalidomide and dexamethasone (Rd). The primary end point was PFS. Of 474 patients evaluable for response, median PFS was 43 months (VRd) versus 31 months (Rd). Median OS was not reached in the VRd group versus 63 months in the Rd group. The most common

hematologic adverse events (AEs) were low hemoglobin (VRd = 13% vs Rd = 16%), leukopenia (VRd = 14% vs Rd = 16%), lymphopenia (VRd = 23% vs Rd = 18%), neutropenia (VRd = 19% vs Rd = 21%), and low platelets (VRd = 18% vs Rd = 14%). Side effects such as hypokalemia, muscle weakness, diarrhea, and dehydration were more common in the VRd versus Rd groups, although the incidence of thromboembolic events was similar (VRd = 8% vs Rd = 9%). Sensory neuropathy was more common in the VRd versus Rd groups (23% vs 3%), with greater severity in the VRd versus Rd groups (24% vs 5%). It is important to note, however, that administering bortezomib by the subcutaneous (SC) route will minimize the incidence and severity of peripheral neuropathy.^{50,51} The impressive PFS data in this Southwest Oncology Group study support the use of a three-drug combination upfront; however, the improved survival is counterbalanced by increased risk of neurotoxicity. Thus, for individuals who receive this regimen, zoster prophylaxis, neuropathy surveillance, SC bortezomib administration, dose adjustments, and education are essential to minimize the risk of AEs. Appropriate laboratory and disease monitoring is also recommended.⁹

Lenalidomide

Lenalidomide and dexamethasone have proved to be superior to dexamethasone alone in randomized clinical trials in patients with newly diagnosed and relapsed MM, and can be given to patients who are transplant eligible and ineligible.^{52–54} In the Frontline Investigation of Revlimid (lenalidomide) and dexamethasone versus Standard Thalidomide study, 1,623 NDMM patients were randomized to one of three treatment arms. These included: 1) standard Rd in 28-day cycles until disease progression (n=535), 2) Rd for 72 weeks (18 cycles; n=541; Rd18), and 3) melphalan, prednisone, and thalidomide (MPT) for 72 weeks (n=547). The median PFS was 25.5 months in the continuous Rd arm, 20.7 months in the Rd18 arm, and 21.2 months in the MPT arm. The 4-year OS rate in the Rd continuous group was 59% compared to 51% among patients who received MPT.⁴⁵ The incidence of grade 3 side effects was lower in the continuous Rd group versus MPT group (85% vs 89%), primarily because of the higher incidence of neuropathy in the MPT versus Rd groups (9% vs 1% respectively).

The Rd combination is generally well tolerated and effective in transplant-eligible and -ineligible patients. The most common starting dose for patients with a creatinine clearance >60 mL/min/1.73m² is 25 mg orally on days 1–21 of a 28-day cycle in combination with dexamethasone

Table 2 Common adverse events and survivorship considerations in patients with MM

Toxicity	Signs and symptoms	Associated drugs	Patient education/intervention
Cardiovascular Bradycardia	Fatigue, low heart rate	Thalidomide	<ul style="list-style-type: none"> Educate patient as to the risk of fatigue and importance of managing activities Evaluate for hypothyroidism, ECG if moderate to severe, or if patient is symptomatic
Deep vein thrombosis, pulmonary embolism	Pain in leg or arm, unilateral swelling of extremity; shortness of breath and/or tachycardia	IMiDs High-dose carfilzomib Erythropoietin Dexamethasone	<ul style="list-style-type: none"> Patients with MM are at increased risk for VTEs. All patients must be screened for the risk and educated on the signs and symptoms of VTE. Daily ASA 81–325 mg PO. Anticoagulation with LMWH, direct thrombin inhibitor, or therapeutic warfarin is recommended if more than two risk factors are present <p>Educate patients regarding signs, symptoms, and prophylactic strategies (such as ambulation)</p>
Heart failure	Shortness of breath, edema	Proteasome inhibitors (bortezomib, carfilzomib) Alkylating agents (melphalan, cyclophosphamide) Anthracyclines (adriamycin, doxorubicin) corticosteroids (especially if severe low left ventricular ejection fraction) Dexamethasone, carfilzomib	<ul style="list-style-type: none"> Evaluate for swelling of extremities Titrate diuretics according to chemotherapy Minimize the use of pre-/posthydration for proteasome inhibitors
Hypertension	Headache		Educate patient as to the risk of increased blood pressure and to report prolonged headaches
Hypotension	Dizziness, fatigue	Bortezomib (more common with IV than SC)	<ul style="list-style-type: none"> Educate patient on adequate hydration, careful position changes, and to report worsening of the symptom
Prolonged QT-c interval	Palpitations; or may be asymptomatic	HDAC-i panobinostat, vorinostat	<ul style="list-style-type: none"> Avoid medications (such as levofloxacin, ondansetron) that prolong QT-c interval
Endocrine Diabetes	Polyuria, polydipsia, polyphagia	Dexamethasone, prednisone	<ul style="list-style-type: none"> Patients may develop steroid-induced hyperglycemia or diabetes; glucose monitoring, insulin-sensitizing agents, or insulin may be necessary Educate patients on the increased risk of diabetes with steroids. Exercise and low-carbohydrate diet, especially around the dates of steroids, can decrease the risk of high blood sugars
Hypothyroidism	Anemia, fatigue	Immunomodulatory drugs	<ul style="list-style-type: none"> Hypothyroidism can occur with lenalidomide or thalidomide Routine screening of TSH levels should be conducted, especially if there is anemia, fatigue
Gastrointestinal Constipation	Abdominal pain, bloating, lack of bowel movements	Immunomodulatory drugs, anthracyclines, bortezomib, and corticosteroids	<ul style="list-style-type: none"> Inquire about bowel habits at each visit Educate patients on the benefits of increased fluid and dietary fiber intake, and encourage exercise Initiate a bowel regimen: Stool softeners are indicated for patients taking opiate analgesic agents. Laxatives should be prescribed if no bowel movement within 24 hours

(Continued)

Table 2 (Continued)

Toxicity	Signs and symptoms	Associated drugs	Patient education/intervention
Diarrhea	Increase in loose or watery stools, or ostomy output from baseline	Lenalidomide (long term) Bortezomib	<ul style="list-style-type: none"> First institute dietary modifications (avoid bulk fiber, spicy, fried, salty foods) and increase fluid intake <p>Recommend loperamide if associated with chemotherapy for mild-to-moderate diarrhea. Hospitalization will be required for severe diarrhea. A stool sample may be indicated to rule out <i>Clostridium difficile</i> or other infection, if change in character of diarrhea, abdominal cramping, fever, or chills</p>
Myelosuppression Anemia	Fatigue and shortness of breath which can be mild to severe, depending on the degree of anemia	Most chemotherapy agents can cause mild-to-moderate anemia	<ul style="list-style-type: none"> Encourage adequate rest and hydration Treat anemia with RBC transfusion or ESAs. ESAs must be used with caution as can increase the risk of VTE Ensure patients are not bleeding <p>Check intermittently for secondary causes of anemia (such as vitamin B12 or iron deficiency, or progressive MM disease)</p>
Neutropenia, infection risk	Fever > 100.4°F (38°C), chills, sweats (signs of infection) Neutropenia may not have associated signs or symptoms	Most agents can cause, specifically chemotherapy	<ul style="list-style-type: none"> Avoid patient contact with individuals with known infection. Administer hematopoietic growth factors, if indicated Administer antibiotic prophylaxis if at high risk for neutropenic fever Administer acyclovir for HSV prophylaxis (if on proteasome inhibitor, posttransplant) Give influenza vaccine yearly Give pneumonia vaccine (PCV-13 and PPSV23) every 5 years Wash hands and avoid people with colds <p>Patients must seek emergent care if fever is present with ANC <500 mm/mL</p>
Neurologic Peripheral neuropathy (sensory or motor)	Numbness or pain, dysesthesia, hyperesthesia, ataxia, and imbalance if severe	Common drugs: proteasome inhibitors thalidomide, vincristine, and cisplatin	<ul style="list-style-type: none"> Monitor for symptoms of sensory or motor neuropathy. Educate the patient to report promptly as dose reductions may be necessary, especially with proteasome inhibitors Follow safety precautions due to decreased sensation and/or muscle strength For mild neuropathy, no adjustment to the chemotherapy agents is necessary For moderate loss of sensation, weakness, or pain, chemotherapy must be held and decreased once acute symptoms resolve Secondary causes of neuropathy, such as vitamin B deficiency, are common and must be ruled out <p>Pain medications, anticonvulsives agents (gabapentin, pregabalin), antidepressants (duloxetine), and vitamins (B vitamins, alpha-lipoic acid) can mitigate symptoms in some patients. For severe neuropathy, a neurology referral may be necessary</p>
Disease-related considerations Disease monitoring	-	-	<ul style="list-style-type: none"> Obtain SPEP, UPEP, 24-hour urine, and serum free light chains (if indicated) monthly during treatment <p>Obtain skeletal survey every year or when there is new-onset bone pain or suspicion for relapse</p>

<p>Fatigue</p>	<p>Lack of energy, excessive sleep (or too little)</p>	<p>Many drugs to treat MM cause fatigue. Additional agents such as gabapentin and opioids may worsen fatigue. Insomnia may result from steroids.</p>	<ul style="list-style-type: none"> • Encourage patient to remain active and balance activities • Educate patient about the need for adequate rest, nutrition, and hydration • Review medication list to see if any can be eliminated if contributing to fatigue • Consider the timing of when the patient takes medications. For example, immunomodulatory drugs should be taken at bedtime • Administer bisphosphonates to all with MM diagnosis for at least 12–24 months, then intermittently or stop, according to disease status and extent of bone damage • All patients should maintain some form of exercise with weight/lifting restrictions
<p>Osteoporosis, weakened bone structure, lytic lesions, or plasmacytoma</p>	<p>Pain</p>	<p>Pamidronate 90 mg IVPB or zoledronic acid 4 mg intravenously should be given monthly to prevent skeletal-related events</p>	<p>Surveillance skeletal imaging with skeletal survey should be performed at least annually. Orthopedic intervention may be warranted (prophylactic rodding or pinning of extremity), with or without radiotherapy, if large lesions and cortical disruption are present</p>
<p>Renal</p>	<p>Low urinary output, dysuria, or none</p>	<p>Dose reduction with lenalidomide, melphalan, ixazomib, and cisplatin. Refer to package insert for dosing instructions for patients on dialysis</p>	<ul style="list-style-type: none"> • Patients can develop renal insufficiency at diagnosis or throughout • Avoid NSAIDs, IV contrast dyes, and aminoglycoside antibiotics • Encourage hydration • Monitor serum creatinine at least monthly during active treatment and every 3 months when in remission • Work with the patient and primary care provider to ensure adequate blood pressure control if hypertensive and control of diabetes if diabetic <p>Dose adjustment of antibiotics, antiviral agents, or chemotherapy may be necessary</p>
<p>Survivorship Psychosocial</p>			<ul style="list-style-type: none"> • Screen patients for depression or anxiety <p>Refer to support groups and counselors when necessary</p>
<p>Safety</p>			<ul style="list-style-type: none"> • Watch for risk of falls if older age or on multiple medications or mood altering drugs • Instruct patients to remove throw rugs, increase physical activity, and use assistive devices <p>Refer to physical therapy for balance, gait training</p> <p>Evaluate financial and social support available</p> <ul style="list-style-type: none"> • Emphasize the importance of maintaining a well-balanced diet, mild-to-moderate exercise (based on the level of physical fitness) • Routine health screening for hypertension, hyperlipidemia, correct modifiable risk factors (obesity, smoking, excessive alcohol intake) <p>Disease monitoring for MM, surveillance of secondary cancers</p>
<p>Financial Health maintenance, disease monitoring</p>			

Notes: Based on information from: Faiman et al.¹²; Bilotti et al.²⁹; Faiman et al.²⁹; Miceli et al.³⁶; Rome et al.¹²⁴; Rome et al.¹²⁴; Colson.⁷⁵; Richards and Brigle.¹⁵ and product prescribing information.
Abbreviations: ANC, absolute neutrophil count; ASA, acetylsalicylic acid; ECG, electrocardiogram; ESAs, erythropoiesis stimulating agents; HDAC-I, histone deacetylase inhibitor; HSV, herpes shingles virus; IMiDs, immunomodulatory drugs; IV, intravenous; LMWH, low-molecular-weight heparin; MM, multiple myeloma; NSAIDs, nonsteroidal anti-inflammatory drugs; PCV, pneumococcal polyvalent vaccine; PPSV, pneumococcal polysaccharide vaccine; RBC, red blood cell; SC, subcutaneous; SPEP, serum protein electrophoresis; TSH, thyroid stimulating hormone; UPEP, urine protein electrophoresis; VTE, venous thromboembolic events.

40 mg orally weekly. However, the dose of lenalidomide and dexamethasone should be carefully considered. Recent studies suggest that patients do better with reduced doses of lenalidomide and dexamethasone, which is especially found in patients of older age (>75) or in those with decreased renal function.⁵⁵⁻⁵⁸

Carfilzomib

Carfilzomib, an epoxyketone proteasome inhibitor, differs from bortezomib in that it binds selectively and irreversibly to the proteasome.⁴⁴ Carfilzomib has demonstrated activity as a single agent and in combination with other drugs. The combination of carfilzomib, lenalidomide, and dexamethasone is approved by the FDA, in combination with Rd, based on the results of a large, Phase III study called the ASPIRE trial. In this trial, 792 patients with relapsed MM were randomized to receive intravenous (IV) carfilzomib + Rd (KRd) or Rd.⁴⁴ A higher overall response rate (ORR) was observed in the KRd versus Rd groups (87.1% vs 66.7%), and was accompanied by a 31% decrease in the risk of progressive disease (PD) or death. The most common side effect in both groups was myelosuppression. The study supports the use of a three-drug regimen (proteasome inhibitor, immunomodulatory drug, and corticosteroid) to treat relapsed and refractory MM.⁴⁴

In patients with relapsed and refractory MM, carfilzomib is effective when administered IV in doses from 27 to 56 mg/m² IV twice weekly.⁵⁹⁻⁶⁴ In the Phase III ENDEAVOR trial, 929 patients were randomized to receive carfilzomib + dexamethasone (Kd) or bortezomib and dexamethasone (Vd). In the study, treatment with Kd doubled the PFS, compared to Vd (18.7 months compared with 9.4 months, respectively).⁵⁹ Carfilzomib is also being investigated in combination with cyclophosphamide and dexamethasone in patients with an average age of 74 years, and in doses as high as 56 mg/m².⁶⁵⁻⁶⁷ Additional studies have reported promising results with carfilzomib in combination with pomalidomide. In a trial of patients with relapsed and refractory MM, an ORR of 50% with carfilzomib and pomalidomide was observed.⁶⁸ Preliminary results of this and other studies demonstrate promising response rates with a tolerable safety profile, no unexpected toxicities, and merit the investigation of higher doses and in combination with other agents.⁶⁹⁻⁷¹

Common hematologic toxicities are thrombocytopenia, lymphopenia, and anemia. Nonhematologic toxicities include hypokalemia, cough, respiratory tract infections, and diarrhea. It is interesting that although venous thromboembolic event (VTE) prophylaxis is generally not recommended for proteasome inhibitors, there was an increase in VTE among patients who received Kd versus Vd in the ENDEAVOR trial, and

therefore, VTE prophylaxis is recommended.⁵⁹ Since cardiac events such as congestive heart failure and cardiac arrest can occur, echocardiogram and electrocardiogram should be performed at baseline and periodically, as warranted. A longer infusion time of carfilzomib to be given over 30 minutes may also effectively reduce shortness of breath or symptoms and is currently recommended for all doses.^{72,73}

Pomalidomide

Pomalidomide is an oral immunomodulatory agent that was approved for use by the FDA in 2013 for treatment of relapsed and refractory MM based on a Phase II randomized study of pomalidomide alone or in combination with dexamethasone.⁷⁴ An ORR of 33% was observed in the pomalidomide and dexamethasone group, with median PFS of 4.2 months. The combination was well tolerated in heavily pretreated patients who are refractory to bortezomib and lenalidomide. Neutropenia was mild and the most notable AE in the study.⁴² Results of ongoing studies of pomalidomide in combination with bortezomib, ixazomib, cyclophosphamide, daratumumab, and pembrolizumab will undoubtedly further support the use of pomalidomide in MM, as preliminary results show high response rates in these combination regimens.⁷⁵⁻⁷⁸

Panobinostat

Panobinostat is pan-deacetylase (histone deacetylase) inhibitor that, through epigenetic alterations, impairs the growth and survival of MM cells. This is an oral agent which is currently indicated for relapsed and refractory MM based on the results of a Phase II randomized study in which patients received bortezomib, panobinostat, and dexamethasone (PAN-BTZ-Dex) or BTZ-Dex alone. Patients who received PAN-BTZ-Dex experienced a PFS advantage of 10.6 months versus 5.8 months in patients who received BTZ-Dex alone.⁷⁹ A recent analysis showed a PFS benefit of 7.8 months for the PAN-BTZ-Dex group among those who received more than two regimens.⁸⁰ Common AEs in the PAN-BTZ-Dex versus BTZ-Dex group included thrombocytopenia (67% vs 31%), diarrhea (26% vs 8%), asthenia or fatigue (24% vs 12%), and peripheral neuropathy (18% vs 15%).

Based on common side effects in the study, patients should be closely monitored for diarrhea, electrolyte imbalance, and peripheral neuropathy. In the study, there was a high incidence of diarrhea, and 25% was severe. Therefore, loperamide is recommended to ameliorate diarrhea symptoms in patients who receive this three-drug regimen. Also, assessment and correction of blood electrolyte abnormalities is critical to prevent fatigue, muscle cramping, and potential

electrocardiogram changes. Baseline and ongoing electrolyte monitoring should be employed on at least a monthly basis and include a complete metabolic panel + magnesium. Electrocardiogram monitoring to assess for prolongation of the QT-c interval should be performed at baseline and periodically in all patients and more often in those with known cardiac dysfunction. In the study, a high incidence of neuropathy was reported, likely due to IV administration of bortezomib. Thus, bortezomib should be given SC to minimize the onset of neuropathy, and all patients should be monitored closely for the onset of peripheral neuropathy symptoms.^{73,79}

Ixazomib

Ixazomib is an oral proteasome inhibitor approved in the US for treatment of MM in patients who received one prior therapy. In the TOURMALINE MM-1 study, 722 patients who received one to three prior lines of therapy and were not refractory to prior lenalidomide or proteasome inhibitor based therapy were randomized to receive oral ixazomib 4 mg on days 1, 8, 15 every 28 days; oral lenalidomide 25 mg on days 1–21 q 28 days; and dexamethasone 40 mg on days 1, 8, 15, 22 (IRd), or lenalidomide and dexamethasone (Rd) for up to twelve 28-day induction cycles. At interim analysis, an increased median PFS in the IRd versus Rd groups (20.6 vs 14.7 months) without a substantial increase in overall toxicity was observed.⁸¹ Fairly common but mild side effects in patients who received IRd included peripheral neuropathy, diarrhea, constipation, rash, and myelosuppression. Therefore, education and assessment of these side effects is highly important.

Daratumumab

Daratumumab is a human, IgG1 kappa monoclonal antibody against CD38 with single agent activity, and is also effective in combination with other therapies. Daratumumab is approved for use in relapsed and refractory MM in patients who have received more than three prior therapies.^{82,83} A recent analysis of two key studies demonstrated exciting results and single agent activity. Among 148 heavily pretreated patients with MM, double-refractory to a proteasome inhibitor and immunomodulatory drug, a group that generally confers a poor prognosis, a combined ORR of 31% was observed.

Daratumumab is generally well tolerated; yet, there is a high incidence of infusion reactions with daratumumab, particularly with the first dose. Thus, it is recommended to give an IV corticosteroid (methylprednisolone 100 mg or equivalent dose), oral antipyretics (acetaminophen 650–1,000 mg PO), plus an antihistamine (such as diphenhydramine 25–50 mg PO/IV or equivalent) prior to each

infusion. Postinfusion medications with an oral corticosteroid (such as methylprednisone 20 mg) should also be given on the first and second days after all infusions, and especially for the first four infusions.⁸⁴ Anecdotal evidence supports the use of montelukast and loratadine the day before daratumumab infusion and for the first and second days after the first three infusions.

Red blood cell (RBC) transfusions are often necessary in this heavily pretreated MM population. In an ongoing study, 40% of patients receiving daratumumab at a dose of 16 mg/kg as a monotherapy required blood transfusions. Blood typing for compatibility may be an issue, as daratumumab binds to CD38, a protein that is ubiquitously expressed on myeloma cells, but also expressed, to a lesser extent, on RBCs. As daratumumab interferes with antibody testing by binding to endogenous CD38 on RBCs, resulting in pan-agglutination, blood banks should be informed of patients receiving daratumumab to allow for the identification of safe blood products in these patients. Baseline compatibility typing should be performed before daratumumab treatment is started. Results should be recorded and referenced for all transfusions. For emergency transfusions, non-cross-matched, ABO–RhD-compatible RBCs can be given.

Elotuzumab

Elotuzumab (ELO) is an IV monoclonal antibody which targets the myeloma cells expressing signaling lymphocyte activation family 7 (SLAMF-7), which leads to cell death through promoting natural killer-mediated myeloma cell death.^{43,85} In a Phase III study, 321 patients were assigned to receive ELO and Rd, with 325 patients assigned to receive Rd alone. At 1 year, there was an improved PFS in the ELO and Rd group versus Rd alone (68% vs 57%), and at 2 years, the rates were 41% and 27%, respectively. The ORR in the ELO group was 79% versus 66% in the Rd group ($P < 0.001$). A 30% relative reduction in PD or death was observed. Common grade 3 or 4 AEs in the two groups were lymphocytopenia, neutropenia, fatigue, and pneumonia. Infusion reactions were generally mild, but occurred in 33 patients (10%) in the ELO group and were grade 1 or 2 in 29 patients. Based on these side effects, regular complete blood count monitoring and premedication of ELO with corticosteroids is recommended.

Response monitoring and clonal evolution

Most patients will achieve a remission and then ultimately relapse. Remissions and relapses can occur over time and lead to clonal evolution, drug resistance, and ultimately drug-resistant disease.^{86–88} Close monitoring of response to

therapy and evaluation for biochemical and symptomatic disease progression are vital to prevent disease-related complications.

Supportive care

Patients are living longer than ever, in part, due to advances in supportive care within the last 20 years. Attention must be given to prevent and intervene on common myeloma-related complications. These include prevention of skeletal-related events with bisphosphonates, avoidance of nephrotoxic agents such as nonsteroidal anti-inflammatory agents or contrast dyes, immunization, and use of appropriate anti-infective and antiviral agents to treat infections.

Bone

Bone complications are common at diagnosis and throughout. Multiple cytokines and mechanisms are responsible for bone loss in MM, yet an age- or disease-related imbalance in osteoblast and osteoclast system occurs. Accelerated osteoclast activity without osteoblastic stimulation leads to bone turnover.^{13,14,89,90} Therefore, all patients with MM should receive bisphosphonates on a monthly basis for at least 12 months to prevent skeletal-related events, and possible antimyeloma benefit.^{14,91–95} A baseline dental evaluation and ongoing surveillance of complications such as osteonecrosis of the jaw and renal toxicity should be employed.⁹⁶ Regular physical activity such as walking, swimming, or light weight-bearing exercise should be encouraged to maintain mobility, decrease the risk of falls, and for overall health.⁹⁷ Regular monitoring of vitamin D levels and routine calcium and vitamin D intake are also recommended.^{96,98}

Renal

The etiology of renal impairment in patients with MGUS or MM can be due to the disease itself or multifactorial. Patients with older age, long-standing comorbid illnesses such as hypertension or diabetes, hydronephrosis, renal obstruction, acute tubular injury, or concurrent amyloidosis are at a higher risk for renal insufficiency.⁹⁹ In patients with active MM, excess urinary light chains can overwhelm the proximal tubules as the level of light chain burden increases, hindering the kidneys' ability to compensate, and combine with Tamm–Horsfall mucoprotein at the level of the nephrons, leading to cast nephropathy.⁹⁹

As a result of these MM-related and other factors, ~50% of patients with MM will experience renal insufficiency throughout the course of their disease.⁹⁹ Medications such as nonsteroidal anti-inflammatory drugs, IV dyes,

aminoglycoside antibiotics, and loop diuretics should thus be avoided, unless patients are closely monitored. Avoidance of dehydration with adequate fluid intake, especially if patients are experiencing diarrhea, which can occur with bortezomib, panobinostat, or long-term lenalidomide use, is recommended.¹⁰⁰ In patients with renal failure, aggressive oral or IV hydration and treatment of the disease or underlying cause is warranted.

Infections

Infections remain a common cause of early MM mortality, whether from neutropenia secondary to chemotherapy or from the disease itself. Bacterial and/or viral infections are common in MM and a leading cause of death.^{101,102} Functional impaired immunoglobulin synthesis, altered antibody formation after antigenic stimulation, and treatment-related myelosuppression from chemotherapy or steroid therapy place patients at risk to develop life-threatening infections.

The most common types of infections at diagnosis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and herpes shingles virus, although other types have been reported.¹⁰³ Seasonal inactivated influenza vaccination and immunization with polyvalent pneumococcal vaccines every 5 years (pneumococcal conjugate vaccine-13 and pneumococcal polysaccharide vaccine 23) are recommended for all patients.¹⁰⁴ Attention to common causative organisms and appropriate and prompt antibiotic selection to treat these organisms are essential. For life-threatening or recurrent infections, IV immunoglobulin (IVIg) should be considered.³³

Peripheral neuropathy

Peripheral neuropathy can occur at diagnosis in a majority of individuals (20%), and in up to 75%, it occurs throughout the course of one's illness. Improved survival and a longer lifespan for patients with MM are counterbalanced by these common and deleterious side effects of treatment. Peripheral neuropathy is commonly cited as a main side effect of MM therapy that affects one's quality of life in a negative fashion.^{105–107} Moderate-to-severe peripheral neuropathy secondary to bortezomib generally occurs within 4–6 months and can limit one's ability to receive effective antimyeloma therapy with new and yet undiscovered agents.¹⁰⁸ Ixazomib, carfilzomib, vincristine, and thalidomide are agents which can cause neurotoxicity to a lesser extent than bortezomib.¹⁰⁹

No gold standard for the diagnosis of peripheral neuropathy exists. Electromyography, nerve conduction studies, and quantitative sensory testing are methods to quantify

the extent of muscular or sensory nerve impairment. These techniques can be painful and often fail to capture the extent of the symptoms.^{110,111} Patients' self-report of numbness, muscle weakness, tingling or paresthesias, combined with an astute physical examination are the two most reliable methods to report new-onset or worsening symptoms.¹¹² Since self-report is of high importance, the patient and caregiver must be educated on signs and symptoms of peripheral neuropathy, and advised to alert the providers of these symptoms. Prompt intervention of symptoms with holding, dose reduction, or discontinuation of the offending agent can lead to improvement of neuropathy symptoms.¹⁰⁶ Investigation into secondary causes of neuropathy, such as vitamin B6, B12 deficiencies, should be explored, as vitamin B deficiencies and diabetes are fairly common in MM.^{106,113,114}

Deep vein thrombosis (DVT) and VTEs

VTEs encompass DVT, which occurs in an extremity, and pulmonary embolism (PE). Patients with MM are at risk for life-threatening VTEs, as a result of their disease as well as individual and inherited risk factors. Immunomodulatory drugs, anthracyclines, carfilzomib (at a dose of 56 mg/m² IV twice weekly), and erythropoiesis stimulating agents further contribute to the risk.¹¹⁵ For all patients on IMiDs and carfilzomib, VTE risk stratification is imperative. Factors such as surgery, previous DVT or PE, obesity, history of cardiac or renal disease, and combination chemotherapy should be considered. If patients have nil or one risk factor, aspirin is recommended to further reduce the risk.^{42,59,115,116}

Ongoing patient education should be targeted toward signs and symptoms of DVT or PE with prompt reporting of unilateral edema and coolness or pain in an extremity. Severe symptoms of PE with acute shortness of breath, anxiety, and tachycardia require emergent management. Ambulation and adequate hydration is recommended for all patients. Prophylactic anticoagulation with low-molecular-weight heparin in patients while being hospitalized, or full anticoagulation with warfarin, enoxaparin, or direct oral anticoagulants (in patients with glomerular filtration rate >30) in patients at a high risk for thrombosis is recommended.^{117,118}

Survivorship in MM

Survivorship was once considered as the time period after the individual successfully completed cancer treatment. Since treatment is often ongoing in MM, survivorship in MM begins at diagnosis and continues through the balance of the individual's life.¹¹⁹ The importance of survivorship in

cancer and the generation of a survivorship care plan (SCP) emerged following the release of an Institute of Medicine report that focused on the importance of health prevention and promotion models of care for cancer survivors.¹²⁰ To guide patients and primary providers on personalized screening recommendations based on prior chemotherapy, age, and other risk factors, an SCP is recommended for each individual with cancer. The provision of a care plan should be twofold and include: 1) a treatment summary and 2) essential components of a healthy lifestyle which include coordination of care among primary and other providers, health maintenance recommendations, early detection and screening, and psychosocial welfare.^{119,121}

Until the last decade, patients with MM were not considered cancer survivors due to lack of effective treatment options. Patients with MM are living longer than ever, and health promotion and disease prevention are as important among this group as in others with a chronic illness.¹²² Due to the complexity of current regimens to treat MM, a multidisciplinary team of physicians, advanced practice providers (such as nurse practitioners or physician assistants), nurses, pharmacists, and social workers is essential to enhance outcomes. Each member can take on a different role to educate patients on the complex treatment regimens, review and recommend supportive therapies (such as bisphosphonates, immunizations, and blood transfusions), and attend to symptom management (constipation, diarrhea, and other complications). Clinicians should consider the use of a treatment summary and/or provide an SCP to each patient to promote one's understanding of the disease and enhance adherence.¹²¹ The SCP can be as simple as a calendar list of appointments, printout, and review of current medications with recommended dose, duration, and rationale, and assessment and intervention of side effects. The importance of health maintenance with routine cancer and cardiovascular screening and partnership with a primary care provider should be emphasized for all.

Conclusion

MM is a heterogeneous disorder of the plasma cell, which remains incurable, but highly treatable. Advances in the understanding of plasma cell development within the bone marrow milieu have led to newer therapies with sophisticated mechanisms of action. It is essential for clinicians to be aware of the new drugs and common side effects for effective patient management. The provision of care plans, calendars, or other tools can help patients understand and adhere to treatment, and allow the patient to participate in one's care.

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