Multiple Myeloma

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LEARNING OBJECTIVES

1. Assess the epidemiology, pathophysiology, molecular biology, and disease course for patients with a diagnosis of multiple myeloma (MM).
2. Develop an induction treatment strategy for initial treatment of MM on the basis of a patient's candidacy for a stem cell transplant, cytogenetics, comorbidities, and patient preference.
3. Evaluate initial response to induction treatment for newly diagnosed MM, and convert a patient to an appropriate maintenance regimen, as applicable.
4. Design a plan of care and salvage regimen for relapsed, refractory MM for a patient on the basis of treatment history, medical comorbidities, and toxicity profile.
5. Evaluate patients for potential toxicities from MM treatment regimens, and recommend appropriate therapy-specific supportive care.

ABBREVIATIONS IN THIS CHAPTER

ESA	Erythropoiesis-stimulating agent
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
NCCN	National Comprehensive Cancer Network
ONJ	Osteonecrosis of the jaw
RANKL	Receptor activator of nuclear factor kappa-B ligand
REMS	Risk Evaluation and Mitigation Strategies
SRE	Skeletal-related event
VTE	Venous thromboembolism

Table of other common abbreviations.

INTRODUCTION

Multiple myeloma (MM) is a malignant clonal plasma cell dyscrasia characterized by the clinical constellation of infection, nephropathy, and bone disease. Multiple myeloma is not curable with currently available therapies; however, overall survival and quality of life have dramatically improved with the advent of modern antimyeloma treatment regimens and improvements in supportive care. This chapter highlights a basic overview of the MM disease process, standard treatment approaches, and supportive care measures that guide a pharmacist in optimizing pharmacotherapy for this patient group.

EPIDEMIOLOGY

Multiple myeloma is a relatively uncommon cancer, with an estimated 32,270 new cases diagnosed and 12,830 deaths in the United States in 2020, accounting for less than 2% of all new cancer cases diagnosed per year (NCI 2021; Siegel 2020). As of 2017, 140,779 people were living with MM in the United States (NCI 2021). With the advent of modern therapies, the 5-year relative survival rate increased from 32.1% in 2000 to 55.6% in 2017 (NCI 2021). Multiple myeloma is most common in older adults age 65–74, with a median age of diagnosis of 69 years (NCI 2021). Multiple myeloma is more common in males than in females (about 1.5:1), and the incidence in African Americans is 2–3 times that in whites (NCI 2021). The cause of MM is largely unknown, with no established lifestyle, occupational, or environmental risk factors, though some studies have shown a direct relationship between MM and obesity (Alexander 2007).

RISK FACTORS

Age is a significant risk factor for MM, with over 30% of newly diagnosed cases in patients 65–74 years of age and less than 3% of patients being given a diagnosis when younger than 44 (NCI 2021). Risk is also higher in both male and African American patients (NCI 2021). Patients with a family history of MM or a personal history of monoclonal gammopathy of undetermined significance (MGUS) are at increased risk of being given a diagnosis of symptomatic MM, with a rate of progression from MGUS to an active myeloma at about 1% per year.

PATHOPHYSIOLOGY

Multiple myeloma is an incurable malignant disease of plasma cells, or mature B cells. Myeloma cells typically overproduce both free light chain (kappa and lambda) and heavy chain monoclonal immunoglobulins (antibodies), or M proteins (Rajkumar 2014). These B cells typically mature in the bone marrow and are involved in the adaptive immune response (Warrington 2011). Normally, healthy B cells become plasma cells, which produce and secrete antibodies after antigen exposure (Warrington 2011). However, MM is typically characterized by an overproduction of plasma cells within the bone marrow, osteolytic bone lesions, renal insufficiency, hypercalcemia, and immunodeficiency (Rajkumar 2014). Typically, symptomatic MM is preceded by an asymptomatic period diagnosed as either MGUS or smoldering MM, depending on the extent of bone marrow involvement. Smoldering MM is an intermediate stage between MGUS and symptomatic MM that progresses to symptomatic MM at a much higher rate than MGUS, at about 10% of cases annually. The basic premise underlying the progression of MM is that several genetic mutations occur, which leads to a dysregulation in the normal differentiation of the plasma cell, changing it in ways that progress to the symptomatic presentation of MM and eventually lead to the development of treatment resistance.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General baseline knowledge of hematopoiesis and immunology
- Understanding of the mechanism of oral and intravenous anticancer agents and the pharmacology of monoclonal antibodies
- Baseline understanding of the importance of and accountability needed for a pharmacy REMS program

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Warrington R, Watson W, Kim HL, et al. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol 2011;7(suppl 1):S1.
- Lee YT, Yi JT, Chern EO. Molecular targeted therapy; treating cancer with specificity. Eur J Pharmacol 2018;834:188-96.
- Shane R. Risk evaluation and mitigation strategies: impact on patients, healthcare providers, and health systems. Am J Health Syst Pharm 2009; 66(24 suppl 7):S6-S12.

CLINICAL PRESENTATION

Patients with MM usually present with symptoms related to the infiltration of plasma cells within the bone marrow or immunoglobulin deposition within an organ. The diagnosis of MM requires identification of abnormal monoclonal plasma cells in the bone marrow, M protein in the urine or serum, osteolytic lesions, and end-organ damage. The acronym "CRAB" is used to define end-organ events that lead to the diagnosis of MM (Box 1). In a review of over 1000 patients with newly diagnosed MM, the following signs and symptoms were observed: hypercalcemia (28%), elevated creatinine (48%), anemia (73%), bone pain (58%), fatigue/weakness (32%), and weight loss (24%) (Kyle 2003).

In addition, malignant plasma cells secrete large proteins, which can be responsible for a spectrum of other manifestations, including symptomatic hyperviscosity syndrome (headache, blurred vision, altered mental status, oral bleeding), cord compression, amyloidosis, recurrent infections, peripheral neuropathy, and extramedullary plasmacytomas. A distinguishing point between patients with MGUS or smoldering myeloma and those with symptomatic MM is that patients with MGUS or smoldering MM have none of the CRAB criteria discussed earlier. However, patients with MGUS and smoldering myeloma should be followed closely for transformation to active symptomatic disease and need for prompt treatment initiation.

MOLECULAR BIOLOGY

In MM, malignant plasma cells produce both heavy and light chain M proteins. The most common subtype of MM is immunoglobulin (Ig) G myeloma, occurring in almost 55% of patients (Sirohi 2004). Immunoglobulin A myeloma occurs in 25% of patients and IgD and IgM in 1%, and 20% of patients produce light chains only. Cytogenetic abnormalities are prognostic factors in MM, and up to 65% of cases present with a translocation present on chromosome 14. Differences in genetic abnormalities are most likely one of the main reasons for the heterogeneity of myeloma with respect to presentation, treatment response, and survival. Deletion 17p, translocation

Box 1. CRAB Acronym for Diagnosis of Multiple Myeloma

- **C - Hypercalcemia:** Hypercalcemia (corrected serum calcium concentrations of 11 mg/dL or greater) occurs in MM as a direct result of bone destruction. Signs and symptoms of hypercalcemia can include altered mental status, muscle weakness, thirst, shortened QT interval, constipation, and acute renal insufficiency. Active treatment of hypercalcemia should be initiated to minimize long-term renal damage.
- **R - Renal Insufficiency:** Almost one-half of patients with MM have an increased creatinine at diagnosis. The two primary causes of renal insufficiency, defined as a CrCl of less than 40 mL/minute or an SCr of greater than 2 mg/dL, are concomitant hypercalcemia and the deposition of calcium phosphate crystals within the renal tubules and light chain cast nephropathy. When MM cells secrete high concentrations of light chains, the kidneys become overloaded with proteins that cannot be filtered or reabsorbed, leading to tubular damage and eventual kidney failure. Other issues common in patients with MM such as dehydration and infection can contribute to and exacerbate renal impairment.
- **A – Anemia:** Anemia, defined as an Hgb of 10 g/dL or less or as 2 g/dL less than the lower limit of normal, occurs in 97% of patients at some point during their disease (Bird 2011; Kyle 2003). At presentation, patients often have symptoms of anemia, including weakness, dyspnea, fatigue, and dizziness. Several factors contribute to the development of anemia in MM: bone marrow replacement by immature plasma cells, reduction in the number of erythroid precursors, erythropoietin deficiency as a result of kidney damage, and impaired iron use as a result of the increased production of hepcidin caused by the chronic inflammation often seen in MM. In addition, iron deficiency, vitamin B_{12} deficiency, or antimyeloma therapies can induce or exacerbate preexisting anemia.
- **B - Bone Disease:** Malignant plasma cells produce osteoclast-activating factors such as tumor necrosis factor, interleukin-1, and interleukin-6, which enhance bone destruction and inhibit osteoblast activity. Osteolytic bone disease can result in both severe bone pain and pathologic fractures. Bone pain typically involves the central skeleton (back, neck, shoulders, pelvis, hip) rather than the extremities, and this pain is often exacerbated by movement. Bone pain can also be the result of expanding plasma cell tumors within the bone as a soft tissue mass. Bone disease can compromise patient mobility, affect activities of daily living, and adversely affect patient quality of life.

Information from Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33.

(4;14), translocation (14;16), and deletion 13q are considered high-risk cytogenetics (Sirohi 2004) with a poor prognosis. The National Comprehensive Cancer Network (NCCN) guidelines recommend that cytogenetics at least examine for t(4;14), t(14;16), del(17p13), and chromosome 1 amplification for prognostic purposes (NCCN 2021). Today, use of cytogenetics to determine prognosis and select initial therapy has become common practice.

DIAGNOSIS

A diagnostic workup for MM includes a detailed history and physical examination, a laboratory workup, a bone marrow biopsy, a cytogenetic analysis, and various radiographic tests. Diagnostic criteria and staging symptoms for MM are based on the 2014 guidance from the International Myeloma Working Group (IMWG), a collaboration of researchers and practitioners that sets consensus definitions for staging and response criteria for MM (Rajkumar 2014). Traditionally, an MM diagnosis was based on the presence of 10% or more clonal plasma cells in the bone marrow in addition to a myeloma-defining event, defined as one of the CRAB criteria. In 2014, three new biomarkers for patients without CRAB features were added: clonal bone marrow plasma cell percentage 60% or greater, serum free light chain ratio 100 mg/mL or higher, and one or more focal lesions 5 mm or greater on MRI. The intent of the revised guidelines was to identify patients at high risk of disease progression and hopefully prevent end-organ damage.

STAGING AND RISK STRATIFICATION

In 2015, the IMWG published a Revised International Staging System that added Lactate Dehydrogenase (LDH) and cytogenetic features to the original staging definitions, which included serum albumin and β_2-microglobulin (Palumbo 2015). Patients with stage I or stage III disease must fit all defined criteria within that category. Patients who do not fit the criteria of either stage fall into the stage II definition (Table 1). Previously, the most common way to stage patients with MM was using the Durie-Salmon Staging System. This

Table 1. R-ISS for Multiple Myeloma

Stage	Criteria
I	• β_2-microglubulin < 3.5 mg/L *and* • Albumin ≥ 3.5 g/dL *and* • Standard-risk chromosomal abnormalities *and* • Normal LDH (defined as less than ULN)
II	• Not R-ISS stage I or III
III	• β_2-microglobulin ≥ 5.5 mg/L regardless of albumin concentrations *and* • High-risk chromosomal abnormalities: del(17p), t(4;14) or t(14;16) *or* • High LDH (defined as higher than ULN)

LDH = lactate dehydrogenase; R-ISS - Revised International Staging System; ULN = upper limit of normal.

Information from: Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 2015;33:2863-9.

Table 2. mSMART Stratification by Cytogenetic Risk

Risk Category	Cytogenetics	Incidence
High	Presence of any of the following: • FISH ◦ del(17p) ◦ t(4;14)[a] ◦ t(14;16) ◦ t(14;20) ◦ p53 ◦ gain (1q) • Cytogenetic deletion 13 • Cytogenetic hypodiploidy • Plasma cell labeling index ≥ 3%	25% of patients
Standard	All others including: • Hyperdiploid • t(11;14) • t(6;14)	75% of patients

[a]Patients with t(4;14), β_2-microglobulin < 4 mg/L, and Hgb ≥ 10 g/dL may have intermediate-risk disease. This is included for completeness and was not included as a separate category because patients are typically treated on the basis of either the standard- or the high-risk category.

FISH = fluorescence in situ hybridization.

Information from: Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc 2009;84:1095-110.

system analyzed the amount of myeloma present (M protein) together with the damage it caused, such as bone disease or anemia.

In addition, the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) classifies a patient's risk according to the patient's cytogenetic abnormalities and can support clinicians in individualized treatment decisions on the basis of the patient's initial prognosis and risk of disease progression (Table 2). For example, deletion of 17p results in mutations in the tumor-suppressor protein 53 and is associated with a worse prognosis and outcome.

RESPONSE CRITERIA

The ability to assess the quality of a clinical response for MM is more complex than for solid tumor malignancies. In solid tumor malignancies, the standard response paradigm of complete response, partial response, stable disease, and progressive disease is outlined in much greater detail in MM. Table 3 outlines these response criteria.

Table 3. Multiple Myeloma Treatment Response Criteria

Stringent complete response (sCR)	CR as defined in the columns that follow plus: • Normal free light chain (FLC) ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Complete response (CR)	• Negative serum and urine immunofixation • Disappearance of soft tissue plasmacytomas • ≤ 5% plasma cells in bone marrow • Normal FLC ratio if disease only measurable that way
Very good partial response (VGPR)	• Serum and urine M protein detectable by immunofixation but not electrophoresis *or* • ≥ 90% reduction in serum M protein plus urine M protein < 100 mg per 24 hr
Partial response (PR)	• ≥ 50% reduction in serum M protein and ≥ 90% reduction in 24-hr urine M protein or to < 200 mg per 24 hr
Minimal response (MR)	• ≥ 25% but ≤ 49% reduction in serum M protein and reduction in 24-hr urine M protein by 50%–89% • If present at baseline, ≥ 50% reduction in soft tissue plasmacytomas • No increase in size or quantity of lytic bone lesions (development of compression fractures in existing lesions OK)
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Clinical relapse	Requires at least one of the following: • Development of new bone lesions or soft tissue plasmacytoma • Increase in existing plasmacytomas or bone lesions (50% increase or > 1 cm) Any of the following attributable to myeloma: a. Development of hypercalcemia (> 11 mg/dL) b. Development of anemia (drop in Hgb ≥ 2 g/dL) c. Rise in SCr (by > 2 mg/dL)

Information from: Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328-46.

TREATMENT STRATEGIES

Because no therapies for MM are available that can achieve cure, the overarching goal in MM treatment is to obtain the highest degree of remission possible for an individual patient and to maintain that remission for as long as possible. Historically, the approach was to combine cytotoxic chemotherapy such as the agent melphalan with a corticosteroid such as prednisone, which could achieve some degree of clinical response in about 50% of patients, with a median survival of 3 years. Intensifying the treatment regimen(s) by adding more alkylating agents or other cytotoxic agents had only marginal benefit. Not until high-dose chemotherapy with melphalan with autologous stem cell rescue was validated in randomized clinical trials in the 1990s did the overall survival in MM begin to improve relative to the 3-year overall survival baseline.

The modern approach to treat MM seeks to use combination therapy with targeted anticancer agents such as immunomodulatory drugs (IMiDs), proteasome inhibitors, and/or monoclonal antibody therapy directed at plasma cell surface antigens (e.g., CD38). Given the success in extending overall survival for high-dose chemotherapy with autologous stem cell transplantation in treating MM, a critical question upon diagnosis is whether the patient is a reasonable candidate for transplantation on the basis of age, medical comorbidities, and performance status. The answer to that fundamental question directs patients to be treated with a regimen tailored to their transplant eligibility with respect to establishing a risk-adapted strategy for treatment. Table 4 lists the currently approved agents for MM treatment, their therapeutic class, and their major toxicities.

Induction Treatment Strategies

For patients considered transplant eligible, initial or induction therapy is composed of combination therapy with a proteasome inhibitor, an IMiD, and a steroid, as outlined in Table 5. The goal of induction therapy is to induce a remission by elimination of the M protein clone or to reduce the disease burden substantially. Typically, induction therapy is administered over several months, with subsequent collection of peripheral blood stem cells to be used for autologous stem cell transplantation. Choice of induction regimen can be individualized according to the risk conferred by the cytogenetic abnormalities identified in individual patients, as outlined in Table 6.

For patients with significant medical comorbidities such as cardiac, pulmonary, hepatic, or irreversible renal disease that make them too frail to consider for treatment with high-dose chemotherapy with autologous stem cell transplantation, induction therapy is administered over several months and then followed by a single agent in the maintenance phase.

Role of Transplantation

Transplantation often follows induction therapy within several months, though prescribers may opt to delay transplantation further for selected patients. Transplantation for MM typically consists of using a single agent for conditioning – melphalan at 200 mg/m^2 followed by an infusion of autologous hematopoietic stem cells within 24–48 hours. Patients typically have aplasia for about 14 days, during which there is a high likelihood of infection as a result of neutropenia. Profound thrombocytopenia increases the risk of bleeding and severe mucositis, secondary to the high-dose melphalan conditioning chemotherapy, and often requires intravenous opioid pain medication. However, after engraftment of the stem cell aliquot, the acute toxicities soon resolve. Unlike in allogeneic hematopoietic stem cell transplantation, where the transplanted cells are from an external donor, there is no risk of graft-vs.-host disease from an autologous stem cell source, and the risk of acute infection diminishes within 1 month after transplantation. For up to 1 year after transplantation, patients are at risk of reactivation with herpes simplex virus, for which most transplant centers provide acyclovir prophylaxis.

Clinical trial data suggest that a "tandem" autologous hematopoietic stem cell transplant (two unique transplant procedures) confers incremental benefit above a single transplant with respect to the quality of remission achieved after transplantation. However, in the era of several target therapies, most centers perform a single transplant after induction therapy and reserve consideration for a second transplant with a later relapse.

Maintenance Therapy

The concept of maintenance therapy has been used in the treatment of hematologic disorders such as acute lymphocytic leukemia to either prevent or delay relapse. In MM, maintenance therapy has been evaluated with several older agents (e.g., interferon) with minimal to no benefit.

In the era of modern therapy, agents such as thalidomide, lenalidomide, and bortezomib have been evaluated to determine whether clinical benefit could outweigh the potential for long-term toxicity with the drugs. Each agent has shown a significant benefit in progression-free survival compared with no maintenance therapy. This benefit has been shown in patients who have received high-dose chemotherapy with autologous stem cell transplantation and those who have just received standard-dose chemotherapy. Of these agents, bortezomib and lenalidomide are favored because the significant toxicity associated with thalidomide does not lend itself to long-term administration in many patients, particularly older patients with comorbid illnesses.

Relapsed Disease

All patients with MM have disease relapse regardless of whether they received high-dose chemotherapy with autologous stem cell transplantation or any of the available induction therapy regimens available for use. Thus, therapy options for relapsed disease are an essential treatment consideration for all patients with MM. The goal of a therapy

Table 4. Agents Used to Treat Multiple Myeloma

Agent	Mechanism of Action	Toxicity
Belantamab mafodotin-blmf	Antibody drug conjugate directed at B-cell maturation antigen with a microtubule inhibitor payload	IRR; thrombocytopenia, visual disturbances/loss induced by corneal ulceration
Bortezomib	Proteasome inhibition	Peripheral neuropathy, thrombocytopenia, cardiomyopathy
Carfilzomib	Proteasome inhibition	Cardiac ischemia, CHF, pulmonary toxicity, pulmonary hypertension, hemorrhage, thrombocytopenia, hepatotoxicity, thrombotic microangiopathy, progressive multifocal leukoencephalopathy
Daratumumab	Monoclonal antibody directed at CD38	IRR, interference with cross-matching for blood transfusions, neutropenia, thrombocytopenia
Elotuzumab	Monoclonal antibody directed at SLAMF7	IRR, infection, second primary malignancy, hepatotoxicity, interference with assays used to monitor M protein
Idecabtagene vicleucel	CAR T-cell therapy directed at B-cell maturation antigen	CRS, HLH/MAS, fever, infection, prolonged cytopenias
Isatuximab	Monoclonal antibody directed at CD38	IRR, neutropenia, interference with cross-matching for blood transfusions; assays used to monitor M protein
Ixazomib	Proteasome inhibition	Thrombocytopenia, diarrhea, peripheral neuropathy, peripheral edema, rash, thrombotic microangiopathy, hepatotoxicity
Lenalidomide	Immunomodulatory drug	Rash, tumor flare reaction, hepatotoxicity, second primary malignancies, diarrhea, thrombocytopenia, neutropenia, thromboembolism, teratogenicity
Melphalan flufenamide	Peptide-drug conjugate targeting aminopeptidases	Anemia, diarrhea, fatigue, infection, nausea, neutropenia, thrombocytopenia
Panobinostat	Histone deacetylase inhibitor	Hemorrhage, hepatotoxicity, diarrhea, fatigue, peripheral edema, cardiac ischemia and arrhythmias, QT interval prolongation
Pomalidomide	Immunomodulatory drug	Neutropenia, anemia, nausea, diarrhea, thromboembolism, teratogenicity
Selinexor	Nuclear export inhibitor	Hyponatremia, infection, neutropenia, chemotherapy-induced nausea/vomiting, dizziness/confusion, thrombocytopenia
Thalidomide	Immunomodulatory drug	Somnolence, neutropenia, orthostatic hypertension, peripheral neuropathy, thromboembolism, teratogenicity

CHF = chronic heart failure; CRS = cytokine release syndrome; HLH/MAS = lymphohistiocytosis/macrophage activation syndrome; IRR = infusion-related reaction.

Information from: Goldschmidt H, Ashcroft J, Szabo Z, et al. Navigating the treatment landscape of multiple myeloma: which combinations to use and when? Ann Hematol 2019;98:1-18; Mikhael J, Ismaila N, Cheumg MC, et al. Treatment of multiple myeloma: ASCO and CCO Joint Clinical Practice Guideline. J Clin Oncol 2019;37:1228-63.

option for relapsed disease is to reestablish remission to the highest degree possible and minimize the cumulative toxicities associated with all of the patient's prior lines of treatment. With the advent of all the agents now available for the treatment of MM (see Table 4), it is possible to provide treatment options for patients with defined clinical benefit after at least five lines of prior therapy. Table 7 and Table 8 present stratified treatment algorithms for patients with relapsed disease on the basis of prior treatment exposure.

Table 5. Transplant-Eligible Regimens for Induction Therapy

Cytogenetic Risk Groups	Treatment Regimen
t(11;14), t(6;14), trisomies	VRd (bortezomib/lenalidomide/dexamethasone) × 4 cycles; then stem cell collection ↓ Autologous stem cell transplantation ↓ Lenalidomide maintenance OR Repeat VRd × 4 cycles, followed by lenalidomide until progression, then delayed autologous stem cell transplantation
t(4;14), t(14;16), t(14;20), gain (1q), del(17p)	VRd + daratumumab × 4 ↓ Autologous stem cell transplantation (may consider tandem transplantation) ↓ Bortezomib-based maintenance until progression
Double (any two high-risk cytogenetic abnormalities) or triple hit myeloma (three or more high-risk cytogenetic abnormalities)	VRd + daratumumab × 4 ↓ Autologous stem cell transplantation (may consider tandem transplantation) ↓ Bortezomib-based maintenance until progression

Information from: Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol 2020;95:548-67.

Table 7. Regimens for First Multiple Myeloma Relapse

Patient Profile	Regimen
Post-maintenance therapy – fit patients	KPd – carfilzomib/pomalidomide/dexamethasone or DVd – daratumumab/bortezomib/dexamethasone if relapsed while on lenalidomide maintenance therapy DRd – daratumumab/lenalidomide/dexamethasone if relapsed while on bortezomib maintenance therapy
Post-maintenance therapy – frail patients	DVd or ICd – ixazomib/cyclophosphamide/dexamethasone for patients receiving lenalidomide maintenance IRd – ixazomib/lenalidomide/dexamethasone or DRd – daratumumab/lenalidomide/dexamethasone if bortezomib maintenance
Off therapy/no maintenance – fit patients	KRd – carfilzomib/lenalidomide/dexamethasone or DRd – daratumumab/lenalidomide/dexamethasone
Off therapy/no maintenance – frail patients	IRd – ixazomib/lenalidomide/dexamethasone or ERd – elotuzumab/lenalidomide/dexamethasone

Information from: Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol 2020;95:548-67.

Table 6. Treatment Regimens for Patients Who Are Transplant Ineligible

Cytogenetic Risk Groups	Treatment Regimen
t(11;14), t(6;14), trisomies	VRd – (bortezomib/lenalidomide,/dexamethasone) followed by lenalidomide maintenance OR DRd – daratumumab/lenalidomide,/dexamethasone
t(4;14), t(14;16), t(14;20), del(17p)	VRd – (bortezomib/lenalidomide/dexamethasone) followed by bortezomib-based maintenance until progression

Information from: Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol 2020;95:548-67.

Table 8. Regimens for Second or Later Multiple Myeloma Relapse

Patient Profile	Regimen
Single Refractory: Refractory or IMiD or proteasome inhibitor but not both	DVd – daratumumab/bortezomib/dexamethasone if refractory to IMiD DRd – daratumumab/lenalidomide/dexamethasone if refractory to proteasome inhibitor
Dual Refractory: Bortezomib and/or ixazomib with lenalidomide	Pomalidomide/dexamethasone + daratumumab or isatuximab or KPd – carfilzomib/pomalidomide/dexamethasone or KRd – carfilzomib/lenalidomide/dexamethasone
Triple Refractory: Bortezomib and/or ixazomib with lenalidomide and carfilzomib	Pomalidomide/dexamethasone + daratumumab or isatuximab or Pomalidomide/cyclophosphamide/dexamethasone
Triple Refractory: Bortezomib and/or ixazomib with lenalidomide and pomalidomide	Daratumumab- or alkylator-based regimen if alkylator naive or proteosome inhibitor + panobinostat
Quadruple-refractory: Lenalidomide, pomalidomide, bortezomib, and carfilzomib; secondary plasma cell leukemia or extensive extramedullary disease	VDT-PACE (bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cytarabine/etoposide) × 2 cycles

IMiD = immunomodulatory drug.

Information from: Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol 2020;95:548-67.

SUPPORTIVE CARE

Although MM is not currently curative, patients with the disease are now living longer. Supportive care for these patients has become increasingly important as providers try to improve the patient's quality of life throughout treatment. Most modern combination regimens for MM use targeted agents, have low or moderate emetic potential, and do not require intensive antiemetic prophylaxis. Prophylactic antiemetic regimens should follow the current ASCO guidelines for antinausea prophylaxis (Hesketh 2020).

Hypercalcemia

Multiple myeloma is associated with excessive tumor-induced, osteoclast-mediated bone destruction. Hypercalcemia is the most common metabolic complication of myeloma, occurring in up to 28% of patients (Oyajobi 2008). Cytokines released from the primary tumor stimulate the production of parathyroid hormone–related protein, which induces the receptor activator of nuclear factor kappa-B ligand (RANKL/RANK) interaction in the bone. This results in excessive osteoclast activation, bone resorption, and hypercalcemia. Renal dysfunction is also common in patients with MM, reducing the ability of the renal tubules to clear the excess calcium load from circulation. Depending on serum calcium concentrations, hypercalcemia can be categorized as mild (10.5–11.9 mg/dL), moderate (12–13.9 mg/dL), or severe (14 mg/dL or greater) (Asonitis 2019). The clinical presentation of hypercalcemia can vary depending on calcium concentration and can be life threatening, as in hypercalcemic crisis, which requires immediate medical treatment. Use of several therapies can rapidly correct serum calcium concentrations as well as improve patient symptoms (Oyajobi 2008).

Treatment of hypercalcemia depends on clinical presentation and is consistent with treatment of hypercalcemia of malignancy in other solid and hematologic malignancies. Because many patients with myeloma are dehydrated at presentation, normal saline is the initial treatment of choice to restore renal perfusion and increase calcium excretion. The rate of hydration depends on the severity of hypercalcemia and the patient's comorbid conditions, but typically, a bolus of 1–2 L of normal saline followed by maintenance fluids at 100–150 mL/hour suffices. After a patient has reestablished euvolemia, oral or maintenance intravenous fluids can be continued to maintain adequate urine output until other anti-hypercalcemic agents are fully effective. A loop diuretic such as furosemide can be added for patients with congestive heart failure or volume overload, if needed. Thiazide diuretics, such as hydrochlorothiazide, should be avoided because they can exacerbate hypercalcemia through reabsorption of calcium in the distal tubules.

For patients who need a rapid decrease in serum calcium, calcitonin can be used. Calcitonin is a fast-acting peptide

Table 9. Treatments for Hypercalcemia

Treatment	Dosing	Onset	Duration of Action	Other Considerations
Normal saline	1- to 2-L NS bolus followed by 100–150 mL/hr maintenance	Immediate	2–3 days	Watch for fluid overload
Calcitonin	4–8 units/kg subcutaneously every 6–12 hr	4–6 hr	Up to 3 days	Tachyphylaxis develops after 72 hr; AEs include nausea/vomiting, pain at injection site
Zoledronic acid	4 mg IV over 15–30 min	48 hr	3–4 wk	AEs: Nephrotoxicity, bone pain, flu-like symptoms, ONJ. May repeat dose after 7 days
Pamidronate	60–90 mg IV over 2–24 hr	48 hr	3–4 wk	AEs: Nephrotoxicity, bone pain, flu-like symptoms, ONJ. May repeat dose after 7 days
Denosumab	120 mg subcutaneously weekly for 4 wk and then monthly	7–10 days	3–4 mo	Approved for hypercalcemia refractory to bisphosphonate therapy AEs: Arthralgias, hypocalcemia, ONJ

AE = adverse effect; IV = intravenous(ly); NS = normal saline; ONJ = osteonecrosis of the jaw.

Information from: Asonitis N, Angelousi A, Zafeiris C, et al. Diagnosis, pathophysiology and management of hypercalcemia in malignancy: a review of the literature. Horm Metab Res 2019;51:770-8.

secreted by the thyroid gland that inhibits osteoclast activity and promotes renal calcium excretion, typically lowering serum calcium concentrations by 1–2 mg/dL over 2–3 days (Asonitis 2019). Subcutaneous calcitonin is dosed at 4–8 international units/kg every 6 hours, with an onset of action usually within 4–6 hours of first administration. However, tachyphylaxis can occur within 72 hours as cells down-regulate calcitonin receptors.

Bisphosphonates are another backbone of therapy for hypercalcemia management. Bisphosphonates induce osteoclast apoptosis and neutralize RANKL stimulation, resulting in the blockage of bone resorption. The preferred intravenous bisphosphonates in MM treatment include zoledronic acid (4 mg) and pamidronate (90 mg). Bisphosphonates can take up to 2–4 days for the initiation of their therapeutic effect, so they should be administered soon after the diagnosis of hypercalcemia.

For hypercalcemia that is refractory to initial bisphosphonate therapy, denosumab can be used. Denosumab is a RANKL inhibitor that inhibits osteoclast activity and bone resorption. In a study of patients with hypercalcemia of malignancy refractory to bisphosphonates, defined as a serum calcium concentration greater than 12.5 mg/dL, who had received a bisphosphonate within the previous 7–30 days, denosumab was given at a dose of 120 mg subcutaneously weekly for the first month. Serum calcium concentrations were lowered to less than 11.5 mg/dL in 64% of patients within 10 days, with a median duration of action of 104 days (Hu 2014).

Hypercalcemia seen at a time other than at diagnosis usually indicates that a patient's disease has relapsed or is not responding to current therapy. It is therefore important to provide systemic MM therapy as soon as possible to prevent recurrence of symptoms as the result of hypercalcemia (Table 9). In practice, for patients who present with symptomatic hypercalcemia, several agents are typically initiated in combination. Bolus and maintenance fluids should be administered together with calcitonin. In addition, a bisphosphonate should be added up front so that, as calcitonin begins to lose effectiveness, the bisphosphonate will begin to take clinical effect.

Renal Impairment

Renal insufficiency can occur in up to one-half of patients with a diagnosis of MM. The pathophysiology of renal damage can be the result of a variety of mechanisms such as deposition of monoclonal light chains in the renal tubules, dehydration, and hypercalcemia. The IMWG defines renal insufficiency as an elevated SCr (greater than 2.0 mg/dL) or a reduced CrCl (less than 40 mL/minute) (Dimopoulos 2016). At diagnosis, all patients and providers should take adequate measures to minimize the potential for permanent renal damage. Nephrotoxins such as aminoglycosides, NSAIDs, furosemide, and contrast media should be avoided, when possible. Patients should maintain adequate hydration (greater than 3 L/day) with a goal urine output of 100–150 mL/hour, and underlying hypercalcemia should be managed as discussed earlier, if necessary. In addition, medications commonly used to treat MM or complications from MM, such as lenalidomide and zoledronic acid, should be renally dose adjusted as indicated so that they do not further contribute to renal toxicity. Treatment of renal failure in MM initially includes treating the disease itself and using hemodialysis in the setting of actual acute kidney injury.

Table 10. Lenalidomide Dosing in Renal Impairment

Creatinine Clearance (mL/min)	Lenalidomide Dosing
≥ 60	25 mg once daily
30–59	10 mg once daily; may increase to 15 mg once daily in the absence of toxicity
15–29	15 mg once every other day; may adjust to 10 mg once daily
< 15	5 mg once daily
End-stage renal disease on dialysis	5 mg once daily

Information from: Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol 2016;34:1544-57.

For patients presenting in acute renal failure, initial bortezomib-based treatment regimens such as a combination of cyclophosphamide, bortezomib, and dexamethasone (CyBORd) or bortezomib, melphalan, and prednisone (VMP) are preferred (Dimopoulos 2016). Bortezomib is safe and effective in patients with renal impairment and improves renal function. The IMWG recommends that bortezomib be initiated at the standard dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 3-week cycle in combination with high-dose dexamethasone for at least the first month of therapy (Dimopoulos 2016). Typically, renal failure improves upon initiation of therapy, and treatment regimens or drug combinations can be adjusted at that time if the clinician prefers. Immunomodulatory drugs may be administered to patients with mild to moderate renal dysfunction; however, lenalidomide dose adjustments should be based on the degree of renal impairment, and patients should be monitored closely for myelosuppression and thrombocytopenia (Table 10).

Anemia

Anemia, defined as an Hgb less than 10 g/dL or as 2 g/dL less than the lower limit of normal, is present in around 73% of patients at the time of MM diagnosis and often leads to weakness, shortness of breath, and fatigue (Chanan-Khan 2008). Initial evaluation and workup of anemia in patients with myeloma should include other non–disease-related causes of anemia such as iron or vitamin deficiencies, and any deficiencies should be corrected accordingly. Timing and treatment of anemia depend on the severity of patient symptoms. For patients with significant anemia-related symptoms, blood transfusions should be given. For patients with moderate symptoms on active MM therapy, an erythropoiesis-stimulating agent (ESA) can be used. However, before treating anemia with an ESA in patients with newly diagnosed disease, clinicians should initiate MM-directed therapy and observe the hematologic response because MM treatment often resolves the underlying anemia. Clinicians should be especially cautious about using ESAs in patients with MM who are currently being treated with other high venous thromboembolism (VTE) risk agents, such as IMiDs and high-dose corticosteroids (Bohlius 2019). The FDA label for ESAs limits their use to patients receiving chemotherapy for noncurative intent, and ESAs should only be considered if anemia for myeloma does not improve with treatment of the underlying malignancy and cannot be supported with blood transfusions. The standard dose of subcutaneous epoetin alfa is 40,000 units once weekly, and the standard dose of subcutaneous darbepoetin alfa is 2.25 mcg/kg once weekly or 500 mcg every 3 weeks. Choice of agent is often institution- and formulary-dependent. If there is no improvement in the anemia or transfusion requirements within 6–8 weeks of treatment initiation, ESA use should be discontinued.

Bone Complications

At diagnosis, almost 70% of patients with MM present with lytic bone disease, and 20% of patients have osteoporosis, pathologic fractures, or compression fractures of the spine (Kyle 2003). In the past, skeletal surveys were commonly used to diagnose these bone complications, but more recently, MRI, CT, and positron emission tomography/CT are preferred because they have significantly higher sensitivity rates (NCCN 2021). Complications from bone involvement can include severe pain as well as skeletal-related events (SREs) such as pathologic fracture, cord compression, and hypercalcemia.

Two classes of medications, bisphosphonates and RANKL inhibitors, are used to manage pain and prevent MM-induced SREs. In May 2013, the IMWG published practice guidelines for the treatment of MM-related bone disease (Terpos 2013). The IMWG guidelines recommended consideration of bisphosphonates administered every 3–4 weeks for all patients receiving antimyeloma therapy, even without the presence of osteolytic bone lesions, with zoledronic acid being the preferred bisphosphonate. In a clinical trial of zoledronic acid compared with pamidronate in both breast cancer and MM, the proportion of patients with an SRE was similar between agents. However, compared with pamidronate, zoledronic acid reduced the overall risk of developing skeletal complications, including hypercalcemia, by an additional 16% and had a shorter infusion time (15 minutes vs. 2 hours) (Rosen 2003). In addition, for patients receiving either a bisphosphonate or a RANKL inhibitor, calcium (600 mg/day) and vitamin D_3 (400 international units/day) supplementation should be advised to prevent potential episodes of hypocalcemia (Terpos 2013).

The NCCN guidelines recommend either bisphosphates or denosumab for all patients receiving MM therapy (NCCN

2021). Patients should be monitored closely for the emergence of either renal toxicity or osteonecrosis of the jaw (ONJ). Denosumab is preferred for patients with renal disease (NCCN 2021). A large randomized, placebo-controlled noninferiority trial of 1718 patients compared the efficacy of denosumab with that of zoledronic acid in patients with newly diagnosed MM with at least one bone lesion (Raje 2018). Denosumab was noninferior to zoledronic acid in time to first SRE (HR 0.98; $p_{non\text{-}inferiority}$ = 0.010) and overall survival (HR 0.9; p=0.41). Denosumab had lower rates of renal toxicity (10% vs. 17%) but higher rates of hypocalcemia (17% vs. 12%) and similar rates of ONJ (4% vs. 3%). Bone-modifying therapy should be continued for up to 2 years and potentially beyond 2 years, depending on clinical judgment (NCCN 2021). Frequency of dosing, every 3 months compared with monthly, depends on the individual patient and the patient's response to treatment. In a multicenter noninferiority trial, 1822 patients received zoledronic acid either monthly or on an-every-3-month dosing interval for 2 years (Himelstein 2017). Rates of SREs were similar in both arms (29.5% vs. 28.6%), as were rates of ONJ and kidney dysfunction.

The IMWG recommends consideration of kyphoplasty for vertebral compression fractures and low-dose radiation for palliation of pain, impending fracture, or spinal cord compression (Terpos 2013).

Osteonecrosis of the Jaw

Osteonecrosis of the jaw is one of the most serious and painful complications that can arise from the use of bisphosphonates and RANKL inhibitors such as denosumab (Raje 2014). Osteonecrosis of the jaw is exposed, necrotic bone in the jaw that does not heal. Zoledronic acid has been associated with the highest-reported rates of any bisphosphonate (Terpos 2013). Both cumulative dose and therapy duration contribute to the risk of developing ONJ. Dental extractions are another major risk factor for developing ONJ. Before initiation of a bone-modifying agent, patients should have any existing dental conditions treated and a comprehensive dental examination and be educated regarding optimal dental hygiene. After bisphosphonate initiation, invasive dental procedures should be avoided, and dental health should be monitored at least annually by a physician and dentist to reduce the risk of ONJ (Terpos 2013). Patients should maintain good oral hygiene during therapy. The IMWG guidelines recommend suspending bisphosphonate therapy 90 days before and after dental procedures (i.e., tooth extraction, dental implants, and surgery to the jaw). Bisphosphonates do not need to be discontinued for routine dental cleanings or root canals. Treatment of ONJ includes discontinuing the offending agent until healing occurs and supportive care. The IMWG recommends resuming bisphosphonate therapy once the wound is healed on an individual basis and in consultation with a dental professional (Terpos 2013). A long-term follow-up study of 97 patients with MM and ONJ showed that patients who developed ONJ after dental procedures were less likely to have recurrence of ONJ after restarting a bisphosphonate than were patients who developed spontaneous ONJ (Badros 2008).

Peripheral Neuropathy

Peripheral neuropathy is a common complication in MM because it can be caused by the medications used to treat the disease as well as the disease itself. Up to 20% of patients with a diagnosis of MM have some degree of peripheral neuropathy at diagnosis, and up to 75% have peripheral neuropathy as a direct result of treatment (Richardson 2012). Similar to the neuropathy in diabetes, MM treatment–related neuropathy usually involves the longest axons in the extremities, following a distal-to-proximal, stocking and glove distribution. Symptoms typically include numbness, tingling, and pinprick sensations, beginning with the toes and fingers. This neuropathy is often painful, with sharp and burning sensations. Effective management and prevention of neuropathy are essential to improve patient quality of life and maintain patients on active therapy.

In initial clinical trials using intravenous bortezomib administered on a twice-weekly dosing schedule as part of a treatment regimen, peripheral neuropathy rates commonly reached 35%, with grade 3 and higher neuropathy in 13% of patients (Raje 2014). To improve neuropathy rates, researchers compared the possibility of once-weekly instead of twice-weekly bortezomib infusions (Bringhen 2010). Long-term outcomes were similar between groups, given that 3-year overall survival rates were 88% and 89% (p=0.54), with a significant decrease in the incidence of grade 3 or 4 peripheral neuropathy (8% in those receiving once-weekly infusions and 28% in those receiving twice-weekly infusions, p<0.001). Only 5% of patients in the once-weekly arm discontinued treatment because of neuropathy compared with 15% of patients in the twice-weekly group. Because the incidence of neuropathy was decreased using weekly intravenous bortezomib, this practice is also often used for the subcutaneous formulation of bortezomib.

Investigators then looked at the route of administration of bortezomib to potentially reduce neuropathy rates even further. An open-label, randomized, noninferiority phase III clinical trial (MMY-3021) randomized 222 patients to receive up to eight 21-day cycles of subcutaneous or intravenous bortezomib on a twice-weekly schedule (Arnulf 2012). Times to progression (9.7 vs. 9.6 months), progression-free survival (9.3 vs. 8.4 months), and overall survival at 1 year (76.4% vs. 78.0%, p=0.788) were similar between the subcutaneous and intravenous bortezomib arms. Peripheral neuropathy rates were significantly lower in the subcutaneous arm (all-grade neuropathy, 38% vs. 53%, p=0.044; grade 3 or higher neuropathy, 6% vs. 16%, p=0.026) (Arnulf 2012). Because of the equivalent efficacy of the subcutaneous and intravenous routes and improved adverse effect profile, many providers

have changed to using the subcutaneous route of administration in both the relapsed and newly diagnosed settings.

In addition, carfilzomib, a newer-generation irreversible proteasome inhibitor, is associated with much lower rates of peripheral neuropathy than bortezomib. In a clinical trial of patients with newly diagnosed disease receiving a combination of carfilzomib, lenalidomide, and dexamethasone, peripheral neuropathy rates were 17% for grade 1, 6% for grade 2, and 0% for grade 3 or higher (Jakubowiak 2012).

Incidence of peripheral neuropathy can also reach up to 75% in patients treated with thalidomide (Richardson 2012). In contrast, neuropathy rates are much lower with the newer IMiDs lenalidomide and pomalidomide. The incidence and severity of neuropathy associated with thalidomide are both dose- and duration-dependent, with incidence increasing during therapy.

Treatment of either myeloma- or drug-induced neuropathy in MM is typically supportive. Early recognition and patient education about the signs and symptoms of neuropathy are imperative because discovering neuropathy early on allows for early treatments, dosage adjustments, or discontinuation of the offending agent. Treatment is often extrapolated from other disease states, such as diabetes, and includes the use of opioids, gabapentin or pregabalin, tricyclic antidepressants, and topical agents (Raje 2014). After discontinuation, drug-induced peripheral neuropathy is typically at least partly reversible in most patients (Richardson 2012).

Thrombosis Risk and VTE Prophylaxis

Patients with MM have a 9-fold increased risk of VTE compared with the general population, in which the incidence is 3%–10% (Carrier 2011). This risk can further be increased with the use of concomitant IMiDs, high-dose dexamethasone, ESAs, and certain chemotherapies. The IMiDs thalidomide, lenalidomide, and pomalidomide have antiangiogenic properties and increase the risk of VTE in patients with MM, though rates have varied widely across clinical trials (NCCN 2020). Rates of VTE with IMiDs are especially high when used together with high-dose dexamethasone, doxorubicin, or multiagent chemotherapy regimens. Venous thromboembolism risk is increased when glucocorticoids are added to lenalidomide and increased even further with high-dose corticosteroids compared with lower dose (Carrier 2011). In a phase III clinical trial of 445 previously untreated patients with MM receiving lenalidomide plus dexamethasone, VTE rates were higher in those assigned to the high-dose dexamethasone arm dosed at 40 mg on days 1–4, 9–12, and 17–20 of a 28-day cycle than in those in the lower-dose dexamethasone arm dosed at 40 mg on days 1, 8, 15, and 22 of a 28-day cycle (26% vs. 12%, p=0.0003) (Rajkumar 2010). Package inserts for the IMiDs include a black box warning regarding these VTE risks.

For patients with MM, the NCCN guidelines recommend prophylaxis on the basis of a risk-assessment model published by IMWG (Palumbo 2008). Risk of VTE is greatest in the first 6–12 months of treatment, and prophylaxis should be continued as long as treatment is ongoing. Choice of prophylaxis should be modified according to the baseline risk of VTE, and the safest and least cumbersome form of treatment should be used to reduce the risk of VTE to below 10% (Palumbo 2008). Patients treated with an anthracycline-containing chemotherapy regimen or those receiving high-dose dexamethasone (480 mg/month or greater) are considered at high risk of VTE. In addition, patients with two or more of the risk factors listed in Table 11 are considered at high risk. Patients with no or one VTE risk factor are considered at standard risk of VTE.

Patients are recommended to receive prophylaxis with low-molecular-weight heparin (enoxaparin 40 mg once daily or equivalent) or dose-adjusted warfarin (target INR 2–3) if receiving IMiD-based combination regimens associated with high thrombotic risk, as are patients who have two or more individual or disease-related factors. Aspirin prophylaxis (81–325 mg daily) is recommended for patients receiving IMiD therapy with one or fewer individual- or MM-specific risk factors (Palumbo 2008). If two or more risk factors are present, the choice between warfarin and LMWH depends on the clinical situation. For example, in patients with a GFR less than 30 mL/minute, warfarin might be preferred.

Clinical data are currently limited regarding the prophylactic use of direct oral anticoagulants (DOACs) in patients receiving IMiD therapy. In a phase IV, single-arm pilot study, 50 patients receiving IMiD therapies, lenalidomide (58%) and pomalidomide (42%), were prospectively given VTE prophylaxis with apixaban 2.5 mg orally twice daily (Cornell 2020). During the 6-month observation, no patients had a VTE or major hemorrhagic episode, the main efficacy and safety outcomes. In addition, no patients experienced stroke, myocardial infarction, or death. Three patients had clinically relevant, nonmajor hemorrhage, but all were able to subsequently resume apixaban after medical management (Cornell 2020). In a nonrandomized phase II study, prophylactic use of apixaban, 2.5 mg orally twice daily, was evaluated in 104 patients receiving melphalan/prednisone/thalidomide as initial therapy, or lenalidomide/dexamethasone for relapsed disease over 6 months (Pegourie 2019). Two of the patients receiving lenalidomide/dexamethasone had a deep venous thrombosis while apixaban was on hold for lenalidomide-induced thrombocytopenia. During this period, one nonfatal major hemorrhage and 11 clinically relevant bleeding events were reported. As more data are published in this area, use of DOACs in patients receiving IMiD therapy will further be defined.

Infection Prophylaxis

Infectious complications are a major cause of both morbidity and mortality in patients with MM because of reduced humoral and cellular immunity as well as the myelosuppressive effects of chemotherapy treatments. The risk of infection

Table 11. Individual or Disease-Related Risk Factors for VTE

Risk Factors	Action Taken
1. Associated diseases (cardiac disease, chronic renal disease with GFR < 30 mL/min, diabetes, acute infection, immobilization) 2. Blood clotting disorders 3. Central venous catheter or pacemaker 4. General surgery, anesthesia, or trauma 5. Myeloma-related risk factors (diagnosis of multiple myeloma, hyperviscosity) 6. Obesity (BMI ≥ 30 kg/m^2) 7. Previous VTE 8. Use of erythropoietin	• If no risk factor or any one risk factor is present: Aspirin 81–325 mg orally once daily • If ≥ 2 risk factors present: Low-molecular-weight heparin (LMWH) or equivalent of enoxaparin 40 mg once daily or full-dose warfarin (target INR 2–3)
Myeloma Therapy Risk Factors 1. High-dose dexamethasone (≥ 480 mg/mo) 2. Doxorubicin 3. Multiagent chemotherapy	• LMWH or equivalent of enoxaparin 40 mg once daily or full-dose warfarin (target INR 2–3)

GFR = glomerular filtration rate; VTE = venous thromboembolism.

Information from: Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-23.

is increased with active disease but decreases as patients respond to treatment. Early in the disease course, infections from encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are more common, whereas *Staphylococcus aureus* and gram-negative pathogens typically occur in later months (Raje 2014).

During the first 3 months of chemotherapy, after stem cell transplantation, or for patients receiving regimens that include high-dose dexamethasone, *Pneumocystis jiroveci* pneumonia prophylaxis with sulfamethoxazole and trimethoprim (1 double-strength tablet daily or three times a week) is recommended. For patients with a sulfa allergy, an alternative agent such as dapsone or inhaled pentamidine can be used (Bohlius 2019; Raje 2014). In addition, in patients treated with high-dose dexamethasone, antifungal and herpes simplex virus prophylaxis should be considered (NCCN 2021).

Although the total amount of immunoglobulin production is increased in patients with MM, the functionality of these antibodies is restricted. Because of this functional hypogammaglobulinemia, immunoglobulin replacement (intravenous immunoglobulin) can be considered, though this is not routine practice. Infusions of intravenous immunoglobulin may be considered in selected patients with severe, life-threatening or recurrent infections and low IgG concentrations (less than 400 mg/dL) (Raje 2014). In addition, the NCCN guidelines currently recommend vaccination with PCV13 (pneumococcal conjugate vaccine), followed by PPSV23 (pneumococcal polysaccharide vaccine) 1 year later (NCCN 2021); however, with the approval of new vaccines such as PCV20 (pneumococcal conjugate vaccine), these recommendations are subject to change. Patients with MM should also receive an annual influenza vaccine.

Treatment for MM with the proteasome inhibitors bortezomib, ixazomib, and carfilzomib is associated with a risk of herpes zoster infection. In the phase III APEX trial, the incidence of herpes zoster was 13% among patients treated with bortezomib compared with 5% in the control arm among those treated with dexamethasone (p=0.0002) (Chanan-Khan 2008). In addition, the risk of herpes zoster reactivation is increased in patients with MM receiving antibody therapies (daratumumab, isatuximab, and elotuzumab). Prophylaxis with antiviral agents such as acyclovir (400 mg orally twice daily) is recommended while on these treatments and for 6 weeks after discontinuation of proteasome inhibitors.

ROLE OF THE PHARMACIST

Pharmacists play a critical role in treating patients with MM, starting with diagnosis and continuing throughout treatment. Pharmacists are essential in providing medication and disease state education, identifying adherence issues, and ensuring that supportive care measures are in place. As the complexity of drug regimens increases, it is essential that pharmacists ensure patients understand how and when to take their medications by providing comprehensive education as well as adherence tools, such as monthly calendars. Drug interaction screens, renal dose adjustments, and compliance with anticoagulation with each new regimen also help optimize outcomes and prevent hospital admissions.

Similar to other targeted orally available therapies for cancer, many of the newer agents introduced for the treatment

Patient Care Scenario

J.T. is a 63-year-old man with newly diagnosed high-risk (del(17p), t(4;14)) MM. Baseline renal dysfunction is present with a CrCl of 45 mL/minute. J.T. is eligible for an autologous hematopoietic stem cell transplant, and his oncologist decides to initiate an induction regimen with lenalidomide, bortezomib, and dexamethasone. The prescriber writes a prescription for lenalidomide 10 mg daily on days 1–21 of a 28-day cycle in combination with subcutaneous bortezomib and dexamethasone. The patient plans to spend the winter in Florida and asks the physician to write a 90-day supply of his oral medications to cover while he is away. Which one of the following is the most appropriate pharmacist intervention for lenalidomide for J.T.?

A. Dose adjust lenalidomide to 5 mg daily on the basis of the patient's baseline renal function.

B. Initiate VTE prophylaxis with aspirin 81 mg orally once daily on the days that lenalidomide is administered.

C. Convert lenalidomide to thalidomide to minimize the incidence of peripheral neuropathy.

D. Discuss with the patient that the Risk Evaluation and Mitigation Strategies (REMS) requirements for lenalidomide only allow for a 1-month supply and that a new prescription will be needed each month.

ANSWER

Answer D is correct; according to the REMS guidelines, a new prescription is required for each cycle (maximum of 28-day supply) of IMiDs, and refills are not allowed. Answer A is incorrect because the dose should not be adjusted to 5 mg daily until the CrCl is less than 15 mL/minute. Answer B is incorrect because aspirin should be given continuously, not just on days of lenalidomide administration. Answer C is incorrect because thalidomide has a higher incidence of neuropathy than lenalidomide.

1. Shane R. Risk Evaluation and Mitigation Strategies: impact on patients, healthcare providers, and health systems. Am J Health Syst Pharm 2009;66(24 suppl 7):S6-S12.
2. Loeser KK, McKoy JM, Schumock GT. Anatomy of Risk Evaluation and Mitigation Strategies (REMS). Cancer Treat Res 2019;171:93-105.

of MM are metabolized by the CYP isoenzyme system and have many drug-drug interactions as a result. Given the many drugs routinely used in patients with cancer undergoing MM treatment, including antibacterial drugs, antifungal agents, and antihypertensives, the risk of drug-drug interactions looms large. Pharmacists providing care to patients with MM maintain a primary role in mitigating the potential toxicity risk of these agents used concurrently. Agents such as bortezomib, ixazomib, and panobinostat have documented drug-drug interactions mediated by CYP isoenzymes 3A4/5, and pomalidomide has interactions documented with isoenzymes 1A2. Concomitant drug therapy with these agents must be assessed carefully to minimize the risk of potential adverse interactions. Furthermore, minimizing the impact of potentially hepato- and nephrotoxic drugs is crucial in treating this group of patients, who often have advanced disease and may have end-organ compromise from anticancer drugs in prior lines of treatment.

Pharmacists' knowledge base allows them to be the perfectly situated health care professional to help patients understand their disease, treatment regimens, and supportive care, which will in turn help optimize outcomes and quality of life.

Procurement of IMiDs

Because of the significant risk of embryo-fetal toxicity if handled incorrectly, IMiDs are only available through a REMS program. This REMS program requires registration for providers and pharmacists as well as for individual patients. Surveys of both the provider and the patient are required to ensure compliance with these regulations. In addition, a new prescription is required for each cycle because refills are not allowed. Prescribers are required to do a monthly survey, which provides an authorization number that must be included on each prescription sent to the dispensing pharmacy. The dispensing pharmacy also does a monthly survey to obtain a confirmation number to allow the prescription to be filled. For female patients of reproductive potential, monthly pregnancy tests are needed as well as two negative pregnancy tests before initiation of an IMiD. For females not of reproductive potential, surveys are only needed every 6 months, and male patients are required to complete monthly surveys.

CONCLUSION

Multiple myeloma has been transformed from a disease with largely ineffective treatment that yielded a poor quality of life to a disease that, for most patients, can be treated effectively for up to 10 years or longer. The improvement in overall survival and disease response for patients with MM is directly attributable to the approval of seven new classes of targeted agents since 2000 and the research platform that has been executed to study these agents either alone or in combination with each other, corticosteroids, and/or classic cytotoxic agents. Appropriate implementation of these agents requires a high degree of knowledge and skill to optimize the antimyeloma impact of the sequencing of several lines of therapy while keeping in mind strategies to maintain quality of life and minimize the cumulative toxicities of the individual drugs. Pharmacists are uniquely qualified to collaborate with

Practice Points

MM has evolved over the past 2 decades with a doubling of median overall survival as a direct result of the development of novel therapeutics and improved supportive care.

- **Initial treatment selection is risk stratified by the patient's ability to tolerate stem cell transplantation as well as the patient's cytogenetic abnormalities.**
- **IMiDs were the first class of therapeutic medications introduced for the treatment of MM and continue to remain a backbone of therapy.**
- **Immunomodulatory agents have significant toxicity with both short- and long-term use and must be managed through continued supportive care. This requires extensive patient education to improve patient morbidity and quality of life.**
- **First- and second-generation proteasome inhibitors are integral components in induction, salvage, and maintenance regimens. Pharmacists must be vigilant for surveillance of cardiac toxicity, myelosuppression, and neuropathy with these agents.**
- **The role of autologous stem cell transplantation is in consolidation after induction therapy to optimize the depth of clinical response and maintain remission duration. Stem cell transplantation is not a means of cure for patients with MM.**
- **Salvage therapy is composed of several agents with different mechanisms of action. Salvage therapy is considered effective in inducing disease response; however, it is not curative.**
- **Monoclonal antibody therapy and monoclonal antibody drug conjugate therapy directed at myeloma-specific antigens, such as CD-38 and SLAMF-7, and antibody drug conjugate therapy directed at B-cell maturation antigen are safe and effective and have shown their role in both initial combination regimens and the relapsed setting. However, these agents require strict toxicity monitoring.**
- **Patients with MM often present with disease-induced renal dysfunction. Pharmacists play a crucial role on the health care team in ensuring that all medications (both for treatment and for home) are appropriately dose adjusted to prevent toxicity.**
- **Pharmacists are essential in ensuring that appropriate prophylaxis for both infection and VTE is initiated in tandem with treatment regimens.**

physicians, nurses, and patients and their families to educate and counsel on how best to use MM regimens safely and use appropriate supportive care measures, when needed.

REFERENCES

Alexander DD, Mink PJ, Adami HO, et al. Multiple myeloma: a review of the epidemiologic literature. Int J Cancer 2007;120(suppl 12):40-61.

Arnulf B, Pylypenko H, Grosicki S, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. Haematologica 2012;97:1925-8.

Asonitis N, Angelousi A, Zafeiris C, et al. Diagnosis, pathophysiology and management of hypercalcemia in malignancy: a review of the literature. Horm Metab Res 2019;51:770-8.

Badros A, Terpos E, Katodritou E, et al. Natural history of osteonecrosis of the jaw in patients with multiple myeloma. J Clin Oncol 2008;26:5904-9.

Bird JM, Owen RG, D'Sa S, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. Br J Haematol 2011;154:32-75.

Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol 2019;37:1336-51.

Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood 2010;116:4745-53.

Carrier M, Le Gal G, Tay J, et al. Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: a systematic review and meta-analysis. J Thromb Haemost 2011;9:653-63.

Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 2008;26:4784-90.

Cornell RF, Goldhaber SZ, Engelhardt BG, et al. Primary prevention of venous thromboembolism with apixaban for multiple myeloma patients receiving immunomodulatory agents. Br J Haematol 2020;190:555-61.

Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol 2016;34:1544-57.

Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. J Clin Oncol 2020;38:2782-97.

Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: a randomized clinical trial. JAMA 2017;317:48-58.

Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcemia of malignancy. J Clin Endocrinol Metab 2014;99:3144-52.

Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 2012;120:1801-9.

Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc 2009;84:1095-110.

Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33.

National Cancer Institute (NCI). Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Myeloma. 2021.

National Comprehensive Cancer Network (NCCN). Cancer-Associated Venous Thromboembolic Disease. Version 1.2020 [registration required].

National Comprehensive Cancer Network (NCCN). Multiple Myeloma. Version 4.2021 [registration required].

Oyajobi BO. Multiple myeloma/hypercalcemia. Arthritis Res Ther 2007;9(suppl 1):S4. associated thrombosis in myeloma. Leukemia 2008;22:414-23.

Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 2015;33:2863-9.

Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide- associated thrombosis in myeloma. Leukemia 2008;22:414-23.

Pegourie B, Karlin L, Benboubker L, et al. Apixaban for the prevention of thromboembolism in immunomodulatory-treated myeloma patients: Myelaxat, a phase 2 pilot study. Am J Hematol 2019;94:635-40.

Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol 2018;19:370-81.

Raje NS, Yee AJ, Roodman GD. Advances in supportive care for multiple myeloma. J Natl Compr Canc Netw 2014;12:502-11.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538-48.

Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomized controlled trial. Lancet Oncol 2010;11:29-37.

Richardson PG, Delforge M, Beksac M, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. Leukemia 2012;26:595-608.

Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003;98:1735-44.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.

Sirohi B, Powles R. Multiple myeloma. Lancet 2004; 363:875-87.

Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. J Clin Oncol 2013;31:2347-57.

Warrington R, Watson W, Kim HL, et al. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol 2011;7(suppl 1):S1.

Self-Assessment Questions

1. A woman presents with new-onset anemia. After ruling out nonmalignant causes of anemia, a bone marrow biopsy is performed that is remarkable for 30% plasma cells. Which one of the following best evaluates this patient's presentation?

   A. T-cell acute lymphoblastic leukemia
   B. Diffuse large B-cell lymphoma
   C. Myelodysplastic syndrome
   D. Multiple myeloma (MM)

2. A 64-year-old African American man presents to the clinic with newly diagnosed monoclonal gammopathy of undetermined significance (MGUS). He asks for information regarding the potential for future disease progression. Which one of the following disease progression scenarios is this patient most likely to experience?

   A. Onset of Richter transformation resulting in transformation to diffuse large B-cell lymphoma
   B. Rate of progression to MM at about 1% per life-year
   C. Presence of high-risk cytogenetics resulting in a risk of transformation to acute myeloid leukemia in less than 6 months
   D. Clinical course marked by exacerbations of clinical manifestations of MM and then reverting to clinical MGUS in a repeating pattern

3. A 72-year-old white man presents to his primary care provider with concerns of fatigue. After starting a workup, the primary care provider refers him to a hematologist/oncologist for suspected MM. Which one of the following was most likely found on this patient's workup?

   A. Anemia, bone disease, hypercalcemia, renal insufficiency
   B. Anemia, granulocytopenia, neutropenia, thrombocytopenia
   C. Fever, night sweats, weight loss, lymphadenopathy
   D. Anemia, lymphocytosis, lymphadenopathy, thrombocytopenia

Questions 4 and 5 pertain to the following case.

K.K. is a 54-year-old man who presents with newly diagnosed MM. His presentation is notable for Hgb 11.2 g/dL, SCr 1.8 mg/dL calcium 8.2 mg/dL, albumin 3.4 g/dL, normal LDH, β_2-microglobulin 6.1 mg/L, two lytic lesions on bone scan, and the presence of t(4;14) on bone marrow cytogenetic analysis.

4. K.K. asks whether information is available that can tell how likely he is to respond to treatment. Which one of the following would provide the most prognostic information for K.K.?

   A. Patient's relatively young age
   B. Anemia
   C. t(4;14) cytogenetics
   D. Presence of lytic lesions on bone scan

5. On the basis of the Revised International Staging System, which one of the following best assesses K.K.'s stage of MM?

   A. I
   B. II
   C. III
   D. IV

6. A 68-year-old man with newly diagnosed MM comes to the clinic. Applying a risk-adapted strategy for selecting a treatment regimen for newly diagnosed MM, which one of the following factors is most likely to guide this patient's prescriber toward a specific initial treatment regimen?

   A. Presence of lytic bone disease
   B. Patient performance status for eligibility for autologous hematopoietic stem cell transplantation
   C. Estimation of the need for hemodialysis for patients with documented renal disease
   D. Assessment for the need for an adjuvant erythropoiesis-stimulating agent (ESA)

Questions 7 and 8 pertain to the following case.

W.Y. is a 71-year-old man who presents with newly diagnosed MM. His presentation is notable for Hgb 12.3 g/dL, SCr 1.1 mg/dL, calcium 8.7 mg/dL, albumin 3.8 g/dL, β_2-microglobulin 4.4 mg/L, 40% plasma cells on bone marrow biopsy, and the presence of t(6;14) on bone marrow cytogenetic analysis. W.Y. has an excellent performance status and is otherwise healthy.

7. Which one of the following is best to recommend as W.Y.'s induction regimen?

   A. Bortezomib/lenalidomide/dexamethasone
   B. Melphalan/thalidomide/prednisone
   C. Daratumumab/lenalidomide/dexamethasone
   D. Ixazomib/cyclophosphamide/dexamethasone

8. After induction therapy, W.Y. undergoes an autologous hematopoietic stem cell transplant. Which one of the following is best to monitor for after W.Y.'s transplant?

   A. Aplasia after conditioning chemotherapy and stem cell reinfusion lasting months
   B. Acute graft-vs.-host disease up to day +100 after transplantation
   C. Chronic graft-vs.-host disease following day +100 after transplantation
   D. Reactivation with herpes simplex virus for up to 1 year after transplantation

Questions 9 and 10 pertain to the following case.

J.Z., a 76-year-old man with MM, has been deemed ineligible for an autologous hematopoietic stem cell transplant with standard-risk cytogenetics. He receives induction therapy with daratumumab 16 mg/kg once weekly for the first eight doses, followed by once every 2 weeks for eight doses; lenalidomide 25 mg orally daily on days 1–21; and dexamethasone 20 mg orally weekly. J.Z.'s laboratory test results are unremarkable except for Hgb 9.2 g/dL, calcium 9.4 mg/dL, and SCr 0.8 mg/dL.

9. Which one of the following supportive care measures is best to recommend for J.Z.?

   A. Administer antiemetic prophylaxis for highly emetogenic regimens, including a serotonin antagonist and neurokinin-1 receptor antagonist.
   B. Administer low-dose aspirin for prophylaxis against thromboembolism.
   C. Administer 1000 mL of normal saline before and after each infusion clinic visit to prevent nephrotoxicity.
   D. Avoid concomitant drugs with potential nephrotoxicity such as zoledronic acid.

10. J.Z. presents to the clinic for cycle 3 of treatment with daratumumab/lenalidomide/dexamethasone. He is responding well to therapy; however, his SCr is 2.6 mg/dL and CrCl is 24 mL/minute. All other laboratory values are within normal limits. Given this change in clinical status, which one of the following is best to recommend for J.Z.?

    A. Discontinue the regimen and consider an alternative regimen.
    B. Continue the regimen; however, modify the lenalidomide dose to 15 mg orally every other day.
    C. Discontinue daratumumab; continue lenalidomide and dexamethasone as prescribed.
    D. Maintain the standard regimen with the same dose and schedule.

11. A patient with MM and high-risk cytogenetics has completed induction therapy followed by consolidation with an autologous hematopoietic stem cell transplant. Which one of the following is best to recommend as this patient's maintenance therapy?

    A. Interferon alfa
    B. Thalidomide
    C. Bortezomib
    D. Selinexor

Questions 12 and 13 pertain to the following case.

P.L., a 57-year-old otherwise healthy woman, has MM with cytogenetic findings remarkable for t(11;14). She received induction therapy with bortezomib/lenalidomide/dexamethasone (VRd) × 4 cycles followed by autologous hematopoietic stem cell transplant consolidation therapy and then lenalidomide maintenance. P.L.'s disease remained in remission for 20 months; however, evidence of relapse is now confirmed with 60% plasma cells found on bone marrow biopsy and new lytic bone disease in the ribs, scapula, and tibia that is accompanied by an asymptomatic serum calcium of 11.3 mg/dL.

12. Which one of the following is best to recommend as P.L.'s salvage therapy?

    A. Resume lenalidomide maintenance therapy.
    B. Initiate daratumumab/bortezomib/dexamethasone.
    C. Initiate pomalidomide/cyclophosphamide/dexamethasone.
    D. Initiate bortezomib/dexamethasone/thalidomide/cisplatin/doxorubicin/cytarabine/etoposide.

13. Which one of the following is best to recommend to manage P.L.'s hypercalcemia and lytic bone disease?

    A. Initiate calcitonin and administer for 3 months.
    B. Administer a single dose of zoledronic acid.
    C. Initiate zoledronic acid and administer every 4 weeks thereafter.
    D. Administer 2000 mL/day of normal saline × 3 days.

14. A woman is being treated with a twice-weekly bortezomib-based regimen for induction therapy. She has developed grade II peripheral neuropathy after cycle 2 of a planned four cycles before transplantation. Which one of the following is best to recommend for this patient?

    A. Modify the bortezomib dosing interval from twice weekly to once weekly.
    B. Discontinue bortezomib and initiate carfilzomib.
    C. Continue bortezomib at the same dose and schedule.
    D. Ensure the patient receives bortezomib intravenously.

15. A woman is receiving carfilzomib/lenalidomide/dexamethasone as a salvage regimen for a first-relapse post-autologous hematopoietic stem cell transplant. Which one of the following supportive care measures is best to recommend for this patient?

    A. Acyclovir prophylaxis for herpes simplex reactivation
    B. Antiemetic prophylaxis with ondansetron
    C. Intravenous immune globulin monthly supplementation
    D. ESA (support with darbepoetin is required beginning with cycle 1)