Chapter 159: Multiple Myeloma

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UPDATE SUMMARY

Update Summary

November 15, 2023

The following updates were made to this chapter:

- Key Concepts: added two concepts related to the four-drug regimen incorporating daratumumab and bispecific T-cell engager therapies
- Epidemiology and Etiology: updated statistics on diagnosis and mortality
- Treatment: Ixazomib: removed NCCN category 2B recommendation for upfront treatment and added potential use in maintenance setting to align with current guidelines
- Treatment: Daratumumab: updated information regarding upfront use in combination with standard induction therapy with response rates from two trials
- Treatment: Belantamab mafodotin: agent removed from US market after failing to demonstrate survival advantage
- Treatment: Panobinostat: agent removed from US market after inability to complete confirmatory study required for continued FDA approval
- Treatment: Melphalan flufenamide: agent removed from US market
- Treatment: Chimeric Antigen Receptor T-Cell Therapy: added information about ciltacabtagene autoleucel following its FDA approval
- Treatment: Bispecific T-Cell Engager Therapy: added information about teclistamab, elranatamab, and talquetamab as new therapeutic class/agents following their FDA approval
- Treatment: Maintenance: updated guideline recommendations for using two-drug maintenance regimens for high-risk disease

KEY CONCEPTS

KEY CONCEPTS

1. Multiple myeloma (MM) is a cancer that develops in plasma cells, leading to excessive production of a monoclonal immunoglobulin.

2. Most patients have skeletal involvement at the time of diagnosis, including bone pain and fractures. The acronym CRAB summarizes common clinical manifestations of MM and stands for hyper**c**alcemia, **r**enal failure, **a**nemia, and **b**one disease.

3. Primary therapy is initiated in patients with symptomatic MM, while patients with asymptomatic disease, such as smoldering myeloma or monoclonal gammopathy of undetermined significance, may be routinely observed.

4. Patients should be assessed for autologous hematopoietic stem cell transplantation (HSCT) eligibility before the initiation of treatment and, if eligible, hematopoietic stem cells should be harvested for transplantation following primary induction therapy. Autologous HSCT maximizes complete remissions and prolongs survival.

5. Initial therapy for patients with newly diagnosed MM should be personalized and based on their disease presentation, cytogenetic risk stratification, and functional status.

6. Initial therapy often consists of drug regimens incorporating a proteasome inhibitor, immunomodulatory drug, and dexamethasone. The regimen VRd (bortezomib, lenalidomide, and dexamethasone) is recommended for transplant eligible and ineligible patients with MM. A four-drug regimen regimen incorporating daratumumab has shown enhanced efficacy for all risk groups and is recommended by the Mayo mSMART guidelines in patients with high-risk cytogenetics.

7. Novel anti-myeloma drugs continue to be approved with encouraging results. Newer therapies include monoclonal antibodies, which are added to combination therapy, and cellular based therapy including chimeric antigen receptor T-cell and bispecific T-cell engager therapies.

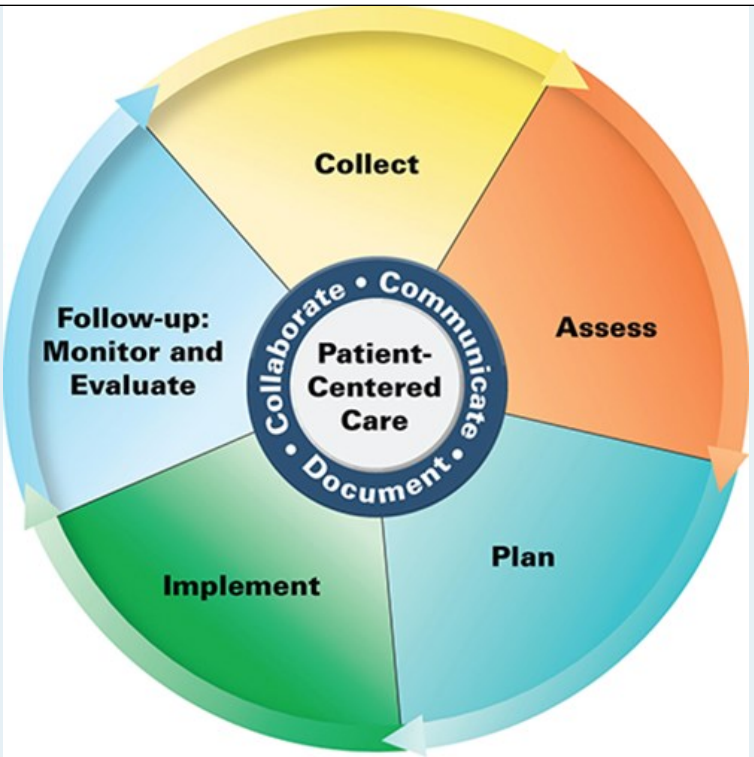
8. Maintenance therapies with lenalidomide or bortezomib may be used in both transplant-eligible and ineligible patients, with the goal of increasing progression-free survival.

9. There are numerous treatment options for patients with relapsed or refractory MM. Treatment selection depends on the patient's performance status, drug toxicity profile, and prior drugs used for treatment.

10. The bisphosphonates, zoledronic acid and pamidronate, and denosumab are used to manage myeloma bone disease, resulting in decreased pain and skeletal-related events and improved quality of life.

PATIENT CARE PROCESS

Patient Care Process for Multiple Myeloma



Collect

- Patient characteristics (eg, age at diagnosis)
- Patient medical history (personal and family)
- Patient comorbidities
- Patient organ function
- Current medications including over-the-counter (OTC) agents
- Prior treatment history for myeloma, if any
- Objective data
  - Labs including CBC, comprehensive metabolic panel, β_2-microglobulin
  - Results of bone scan

Assess

- Indication for therapy
- Candidate for autologous HSCT
- Impact of comorbidities on tolerance of therapy (eg, diabetes)
- Health literacy and adherence
- Emotional status (eg, presence of anxiety, depression)

- Ability/willingness to pay for antimyeloma treatment options (PO vs IV therapy)

Plan

- Drug therapy regimen (primary therapy vs relapsed therapy)
- Supportive care regimen (treatment of anemia, renal dysfunction, use of bone modifying agents)
- Monitoring parameters including efficacy and safety; frequency and timing of follow-up
- Patient education (eg, goal of therapy, schedule of treatments, adherence, self-monitoring)

Implement*

- Provide patient education
- Assess steps needed for insurance approval for oral/at home agents
- Ensure follow-up appointments are scheduled for active and supportive therapy

Follow-up: Monitor and Evaluate

- Response (minimum residual disease [MRD], M-protein)
- Safety (skeletal-related events, adverse drug reactions of antimyeloma therapy)
- Address supportive care concerns
- Adherence

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Watch the online YouTube video (https://www.youtube.com/watch?v=jdytgW5wKa4), "What is multiple myeloma" by Khan Academy Medicine. This 10-minute video provides an overview of multiple myeloma, highlighting classic myeloma disease presentation in the patient "Babs the CRAB," and the pathogenesis and diagnosis of myeloma. This video increases the students' understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

1 Multiple myeloma (MM) is a malignancy of plasma cells (ie, immunoglobulin-producing B lymphocytes).[1] The cancer is characterized by clonal proliferation and accumulation of a monoclonal immunoglobulin secreted from the plasma cell that can be measured in the plasma or urine. Patients with MM often have osteolytic bone lesions at the time of diagnosis, which is probably related to various bone-mobilizing cytokines secreted from the MM clone and bone marrow stromal cells. Other clinical manifestations include end-organ damage such as renal insufficiency, hypercalcemia, and anemia. The treatment of MM often consists of a three-drug combination incorporating a proteasome inhibitor (PI), immunomodulatory drug (IMiD), and dexamethasone. These regimens have improved response rates and outcomes compared to conventional chemotherapeutic agents. Although therapy is not curative, MM continues to be a remarkable example of bench-to-bedside translation in new drug development.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of MM has increased globally, with a 126% increase in cases reported from 1990 to 2016.[2] In the United States, about 35,730 cases of MM were diagnosed in 2023, accounting for 12,590 deaths[3]. MM is a disease that affects older adults, with a median age at diagnosis of 69 years.[1,4] MM occurs more frequently in men than in women. The incidence of MM in Black individuals is twice that of White individuals, with Black patients having poorer survival rates.[5] Socioeconomic factors such as lack of access to care, medications, and clinical trials have been associated with poor outcomes.[5–7]

Risk factors for the development of MM are multifactorial. Inherited, societal, and environmental factors contribute to the incidence and outcomes of MM. Familial clusters of MM and multiple genetic mutations, including immunoglobin gene rearrangements, have been identified in the development and proliferation of MM.[8] Certain environmental influences have also been implicated with MM. Radiation exposure has been historically linked to the development of MM with atomic bomb survivors having a five times higher risk of MM. Even low levels of radiation may be a risk factor.[9] MM has been associated with exposure to various chemicals including pesticides, aromatic hydrocarbons, and petroleum products used in farming, cleaning works, mining, and other occupational groups working with these chemicals.[2]

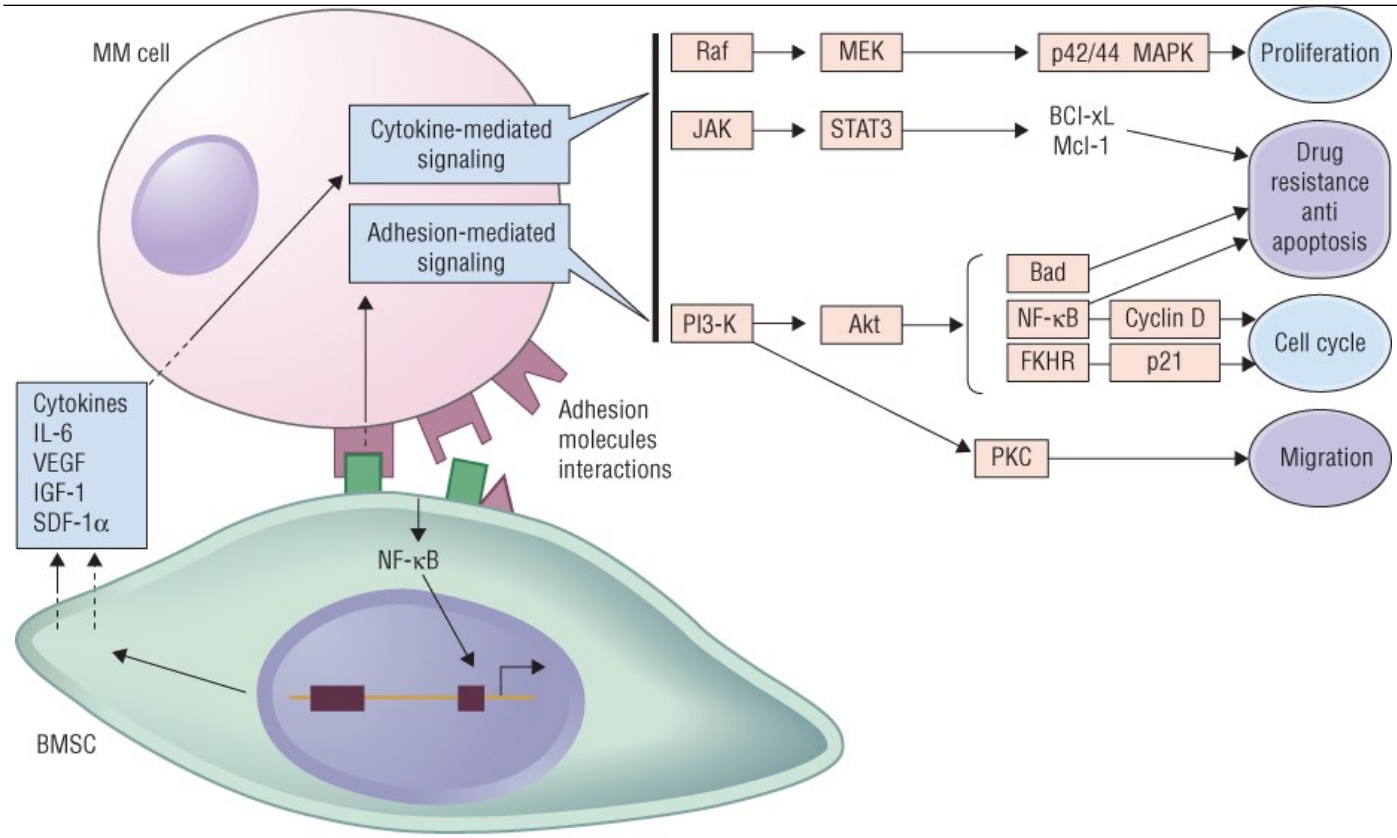
PATHOPHYSIOLOGY

MM is a genetically heterogeneous disease characterized by abnormal clonal plasma cell infiltration in the bone marrow. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (ie, asymptomatic) MM may precede active MM. These conditions do not require treatment but do require active monitoring. MGUS is associated with the presence of monoclonal immunoglobulin in the blood (≤3 g/dL [30 g/L]), less than 10% clonal plasma cells in the bone marrow, and the absence of clinical manifestations of MM (eg, end-organ damage).[10,11] The conversion rate of MGUS to MM is about 1% per year. The molecular changes associated with the conversion of MGUS to MM are not clear, but genome-wide studies have identified several candidate genes associated with disease progression.[10,12] Smoldering MM is an advanced premalignant stage that is clinically distinct from MGUS with criteria including high monoclonal immunoglobulin in the blood (≥3 g/dL [30 g/L]) and 10% to 60% plasma cells in bone marrow with no clinical manifestations of MM. Although patients with smoldering MM have asymptomatic disease, the risk of progression to MM is about 10% per year for the first 5 years after diagnosis, about 3% per year for the next 5 years, and about 1% per year for the next 10 years.[13] Certain cytogenetic characteristics are associated with a higher risk of transformation to active MM including translocation of 4 and 14 (t(4;14)) and deletion of 17p (del (17p)).[10,14] Multiple genetic changes may occur over time leading to more symptomatic disease. Understanding the clinical features of the disease may help clinicians identify which patients are at high-risk for progression from MGUS or smoldering MM to active MM.

MM is characterized by the accumulation of malignant plasma cells in the bone marrow. Both MM and normal plasma cells are produced from differentiated B cells after antigen stimulation. Normal plasma cells will die within days to weeks after differentiation, whereas MM plasma cells are long-lived, with low proliferative activity.[1] MM was thought to originate from a single tumor cell, but it is now believed that MM is composed of genetically diverse clones and subclones that originate from one or more stem cells. The malignant plasma cell is involved in the unregulated production of a monoclonal antibody referred to as *M-protein*. MM cells are seldom seen in large quantities in the peripheral blood because of their close interaction with bone marrow stromal cells. MM cells are supported by a supportive bone marrow microenvironment that promotes the further expansion of MM clones. Molecules such as interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and the transcriptional regulator nuclear factor kappa B (NF-κB) are part of the microenvironment and stimulate clonal growth, disease progression, and promote resistance to therapy (see Fig. 159-1).[15] Disruption of the microenvironment is an important strategy for therapy.

FIGURE 159-1

Pathogenesis of multiple myeloma. Multiple myeloma (MM) cells interact with bone marrow stromal cells (BMSCs) and extracellular matrix proteins via adhesion molecules, triggering adhesion-mediated signaling as well as cytokine production. This triggers cytokine-mediated signaling that provides growth, survival, and antiapoptotic effects as well as development of drug resistance. *(Reproduced, with permission, from Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw Hill; 2019.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Figure 159-1 shows the molecules released during cytokine-mediated signaling and adhesion-mediated signaling. In a BMSC cell, NF-kappa B is added to the nucleus. The cell releases cytokines, IL-6, VEGF, IGF-1, and SDF-1 alpha, which result in cytokine-mediated signaling and adhesion-mediated signaling in the MM cells. During cytokine-mediated signaling, Raf forms MEK, which in turn forms p42/44 MAPK and promotes proliferation. JAK forms STAT3, which produces BCL-xL and Mcl-1 and promotes drug resistance and anti-apoptosis. During adhesion-mediated signaling, P13-K releases Akt and PKC. Akt releases Bad, NF-kappa B, and FKHR. Bad promotes drug resistance and anti-apoptosis. NF-kappa B promotes drug resistance and anti-apoptosis and produces cyclin D which results in cell cycle dysregulation. FKHR produces p21, which results in cell cycle dysregulation. PKC is involved in migration.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Multiple Myeloma

General Criteria

- Most patients present with symptomatic disease

Signs and Symptoms

- Bone pain (fractures, lytic lesions)
- Fatigue (anemia)
- Infection (reduced polyclonal response)
- Neurologic symptoms (nerve compression)

- Polyuria (hypercalcemia)
- Nausea and vomiting (hypercalcemia)

Laboratory Parameters

- Elevated M-protein
  - Plasma electrophoresis
  - Urine electrophoresis
  - Immunofixation
- Elevated serum creatinine
- Hypercalcemia
- Low hemoglobin
- Low albumin
- Elevated β_2-microglobulin
- Elevated C-reactive protein

Bone Marrow

- More than or equal to 10% plasma cells

Imaging

- Skeletal survey with MRI or low-dose CT scan, as indicated

Cytogenetics

- Chromosome 13 deletion
- Translocations of t(4;14), t(11;14), t(14;16), and t(14;20)
- Del (17p)
- Chromosome 1 amplification

2 The clinical manifestations are related to the effects of MM cells on the bone microenvironment and the unregulated production of the M protein. Most patients with MM present with complaints of bone pain and fatigue at diagnosis. Initial laboratory evaluation often reveals hypercalcemia, renal insufficiency, anemia, and other abnormalities. Serum β_2-microglobulin is a useful measure of tumor burden. Skeletal evaluation shows gross abnormalities in most patients. Bone scans show abnormalities that often include lytic lesions, osteoporosis, and fractures. This group of findings—hyper**c**alcemia, **r**enal insufficiency, **a**nemia, and **b**one lesions—is often referred to by the acronym ***CRAB*** and is considered myeloma-defining events and suggests end-organ damage.[1,11] A confirmed diagnosis is defined by a bone marrow biopsy with 10% or more plasma cells, one or more myeloma-defining events, or biomarkers of malignancy.[11] The National Comprehensive Cancer Network (NCCN), International Myeloma Working Group (IMWG), and European Society of Medical Oncology (ESCO) have described criteria to diagnose MM.[11,16,17]

Following the diagnosis of MM, further workup analyzes and measures the quantity of the isotype of M-protein present. M-protein is a surrogate

marker used to assess treatment response and disease progression. Serum protein and urine electrophoresis and serum and urine immunofixation identify the M-protein isotype secreted.[1] About 60% of patients have intact monoclonal immunoglobulin G (IgG), 20% have monoclonal IgA, and the remaining 20% secrete only monoclonal light chains. Antibodies are composed of two light chains, where antigen binds, and two heavy chains. Light-chain immunoglobulins, called Bence Jones proteins, can be secreted by the MM clone and excreted in the urine due to their low molecular weight, resulting in MM-associated renal failure. Serum-free light chains (SFCs) may also be measured, and these results may provide valuable information on the likelihood of disease progression.

Most patients have bone involvement at the time of diagnosis.[11] The effects of MM on the bone result from the abnormal production of cytokines, including IL-1, IL-6, tumor necrosis factor-α (TNF-α), and the receptor for activation of NF-κB ligand (RANK-L).[2] Bone involvement results from the activation of osteoclasts and inhibition of osteoblastogenesis and leads to bone destruction and resorption predisposing the patient to pathologic fractures and lytic lesions. Patients with MM are frequently anemic due to infiltration of the bone marrow with the MM clone and poor erythropoietin response. Patients can have clinically important hypercalcemia, which results from calcium mobilization due to bone resorption. Renal failure can occur as a result of high protein load from the monoclonal protein secretion and dehydration.

STAGING AND PROGNOSTIC FACTORS

Tumor cell features, tumor burden, and patient characteristics influence MM clinical outcomes. The revised International Staging System (R-ISS) is the primary staging system used to predict clinical outcomes for patients with MM. The R-ISS incorporates serum β_2-microglobulin, albumin, and lactate dehydrogenase levels, and high-risk chromosomal abnormalities to stage patients.[2,18] The R-ISS has largely replaced the older staging system, Durie-Salmon. Table 159-1 shows the R-ISS and median survival times for each stage.

TABLE 159-1

Revised-International Staging System (R-ISS) for Multiple Myeloma

Stage	Characteristics	Frequency (% of pts)	5-Year Survival (months)
I	Serum β_2-microglobulin <3.5 μg/mL (mg/L) and Serum albumin ≥3.5 g/dL (35 g/L)	28	82
	No high-risk cytogenetics		
	Normal LDH		
II	Not stage I or stage III	62	62
III	Serum β_2-microglobulin ≥5.5 μg/mL (mg/L) and	10	40
	High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated LDH		

Reprinted, with permission, from Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma, American Society of Clinical Oncology Educational Book 36 (October 29, 2018) e418-e423.

Certain cytogenetic abnormalities are important prognostic factors. High-risk features associated with shortened overall survival include the presence of chromosomal 13 deletion (del 13), translocation of 4 and 14 (t(4;14)), and deletion of 17p (del (17p)).[11] The translocation of 11 and 14 (t(11;14) is the most common translocation, found in 20% of newly diagnosed patients. t(11;14) may be associated with intermediate outcomes and poor response to the novel agents used to treat MM.[19] The Mayo Clinic developed a risk-adapted approach, known as the mSMART (Mayo Stratification for Myeloma and Risk-Adapted Therapy), that categorizes patients into risk groups based on cytogenetics and gene expression profiling: high or standard risk.[20,21] Therapeutic options and treatment length are then recommended for each risk group. Additional prognostic factors generally represent the underlying pathologic changes associated with MM, including proinflammatory biomarkers (elevated C-reactive protein), tumor load (increased β_2-

microglobulin), and dysregulated cellular growth (labeling index and marrow microvessel density).

TREATMENT

Desired Outcomes

The primary goal in the treatment of MM is to prolong the patient's survival and improve quality of life. This can be achieved by inducing a deep response (ie, MRD). Newly diagnosed MM patients who can tolerate chemotherapy will receive primary therapy where the goal is to achieve at least a major response. In transplant-eligible patients, primary therapy may be followed by transplant and maintenance therapy. The goals of these subsequent phases are to further improve response rates. With the integration of novel agents into therapy, progression-free survival and overall survival have steadily improved, and responses have increased in frequency, depth, and duration. Unfortunately, there is no convincing evidence that patients are cured of their disease.

General Approach

3 The decision to initiate treatment depends on whether the patient has symptoms of the disease. Early conventional treatment is not beneficial in patients with MGUS or smoldering MM.[10] Therefore, watchful waiting is the most common practice for patients with asymptomatic disease and is recommended by the NCCN guidelines.[11] However, this treatment paradigm is evolving with the availability of novel agents. Several small published studies, including a phase III randomized trial of 119 patients with high-risk smoldering MM, suggest that early treatment with novel agents may improve overall survival and delay time-to-progression.[10] Clinical trials are highly encouraged and close monitoring every 3 to 6 months should be considered in patients with high-risk smoldering MM.[11]

Pharmacotherapy plays a major role in the management of MM. In the last two decades, the availability of novel drugs such as IMiDs, PIs, and monoclonal antibodies has improved survival in patients with MM. Patients with MM are usually treated initially with combination drug therapy, and most patients will respond to that therapy (see "Initial Therapy" section). Eligible patients will also undergo autologous HSCT. Unfortunately, most patients will eventually relapse and require additional therapies.

The IMWG has developed uniform response criteria to assess response to drug therapy in patients with MM.[22] Clinical response to therapy is generally defined by a reduced serum and urine M-protein by immunofixation and electrophoresis and plasma cells in bone marrow. Numerous response types have been defined, including a stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), and stable disease (SD). The depth-of-response correlates with improved outcomes and a complete response correlates with prolonged overall survival.[17,23] Since the depth of response is important, measurements of MRD with more sensitive assays such as quantitative polymerase chain reaction (Q-PCR) and next generation sequencing are included in the IMWG Response Criteria. Table 159-2 describes the most common types of clinical responses.[17]

TABLE 159-2

IMWG Response Criteria in Multiple Myeloma

Standard IMWG Response Criteria	
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 hr
Partial response	≥50% reduction of serum M-protein plus reduction in 24 hours urinary M-protein by ≥90% or to <20 mg/24 hr If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein is unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL [5 g/L]); Serum M-protein increase ≥1 g/dL (10 g/L), if the lowest M component was ≥5 g/dL (50 g/L); Urine M-protein (absolute increase must be ≥200 mg/24 hr); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be ≥10 mg/dL [100 mg/L]); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in the size of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells/μL [0.2×10^9/L]) if this is the only measure of disease

Data from Reference 17.

Pharmacotherapy

Treatment of MM is based on the combination of dexamethasone with novel agents from two classes of drugs, the IMiDs and PIs. A three-drug regimen is preferred for primary treatment based on increased response rates and improved survival in clinical trials when compared to two-drug

regimens. Although there is a lack of head-to-head comparative trials, several highly active combination regimens are available. VRd (bortezomib, lenalidomide, and dexamethasone) is a frequently used regimen based on improved outcomes and is considered standard of care.[14] Tables 159-3 and 159-4 show dosing and monitoring parameters for the commonly used agents in the treatment of MM. Dose reductions in elderly patients and patients experiencing adverse drug reactions are often required.

TABLE 159-3

Dosing of Drugs Used in the Treatment of Multiple Myeloma

Drug (Brand Name)	Dosing	Comments/Special Population
Lenalidomide (Revlimid®)	Induction therapy 25 mg/day PO on days 1-21 (28-day cycle) Maintenance therapy 10 mg/day, may be increased to 15 mg/day as tolerated	Adjust dose in renal impairment 30-60 mL/min (0.5-1.0 mL/s): 10 mg every 24 hours <30 mL/min (0.5 mL/s): 15 mg every 48 hours <30 mL/min (0.5 mL/s) (dialysis): 5 mg every 24 hours *Note:* Doses noted above are when used in combination therapy
Pomalidomide (Pomalyst®)	4 mg/day PO for 21 days (28-day cycle)	Mild-to-moderate hepatic impairment (Child-Pugh class A or B): 3 mg/day Severe hepatic impairment (Child-Pugh class C): 2 mg/day
Thalidomide (Thalidomide®)	200 mg/day	Start low in elderly adults; increase dose every 1-3 weeks
Bortezomib (Velcade®)	1.3 mg/m^2 SQ Days 1, 4, 8, and 11 Every 21 days	Reduce initial dose in hepatic impairment (serum bilirubin >1.5 × ULN) to 0.7 mg/m^2
Carfilzomib (Kyprolis®)	20 mg/m^2 on day 1 of cycle 1 and then 70 mg/m^2 on day 8; continue with 70 mg/m^2 for subsequent doses	Dosing for relapsed/refractory disease Alternate dosing schedules are available
Ixazomib (Ninlaro®)	4 mg/day PO Days 1, 8, and 15 Every 28 days	Renal impairment <30 mL/min (0.5 mL/s): 3 mg Hepatic impairment serum bilirubin >3 × ULN: 3 mg
Daratumumab (Darzalex®)	16 mg/kg (actual body weight) IV weekly × 8 weeks then 16 mg/kg IV every other week × 8 weeks, then 16 mg/kg every 4 weeks until disease progression	
Elotuzumab (Empliciti®)	10 mg/kg IV weekly on days 1, 8, 15, 22 for cycles 1 and 2; dosing changes with subsequent cycles	
Isatuximab-irfc (Sarclisa®)	10 mg/kg IV on days 1, 8, 15, 22 of a 28-day cycle for cycle 1; 10 mg/kg IV on days 1 and 15 of a 28-day cycle for subsequent cycles	

Panobinostat (Farydak®)	20 mg PO every other day for 3 doses/week (days 1, 3, 5, 8, 10, 12) of a 21-day cycle	Hepatic impairment serum bilirubin >1-1.5 × ULN: 15 mg serum bilirubin >1.5-3 × ULN: 10 mg serum bilirubin >3 × ULN: Not recommended
Selinexor	60-80 mg PO twice weekly (days 1 and 3) 100 mg PO once weekly	Dosing depends on regimen selected
Belantamab mafodotin	2.5 mg/kg IV every 3 weeks	
Melphalan flufenamide	40 mg IV once every 28 days	

TABLE 159-4

Adverse Reactions and Monitoring Parameters for Drugs Used in the Treatment of Multiple Myeloma

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Lenalidomide	Myelosuppression, rash, constipation, VTE, teratogenicity	CBC, LFTs, renal function, REMS Program (pregnancy testing), serum electrolytes and uric acid, thyroid function tests	Adjust dose in renal impairment VTE prophylaxis Secondary malignancies
Pomalidomide	Myelosuppression, rash, VTE, teratogenicity, infection	CBC, LFTs, renal function, REMS Program (pregnancy testing), serum electrolytes and uric acid	Adjust dose in hepatic impairment VTE prophylaxis
Thalidomide	Neuropathy, sedation, constipation, VTE, rash, neutropenia, teratogenicity	CBC, REMS Program (pregnancy testing), serum electrolytes and uric acid	Evening dose to decrease sedation Laxatives VTE prophylaxis
Bortezomib	Myelosuppression, neuropathy, infection including herpes zoster, gastrointestinal	CBC, LFTs, serum electrolytes and uric acid, neurologic examination	Antiviral prophylaxis
Carfilzomib	Myelosuppression, infection including herpes zoster, cardiac toxicity, infusion reactions, renal failure, neuropathy	CBC, LFTs, serum electrolytes and uric acid, renal function	Hydration to reduce risk of renal toxicity and TLS Dexamethasone premedication for infusion reactions Antiviral prophylaxis
Ixazomib	Myelosuppression, rash, neuropathy, infection including herpes zoster, gastrointestinal	CBC, LFTs, serum electrolytes and uric acid, renal function	Antiviral prophylaxis
Daratumumab	Severe infusion reactions, myelosuppression, infections, gastrointestinal	CBC	Premedicate with acetaminophen, diphenhydramine, methylprednisolone for infusion reactions Oral corticosteroid for 2 days following

			infusion Inhaled corticosteroids and bronchodilators may be needed for patients with COPD Antiviral prophylaxis is continued for 3 months after therapy
Elotuzumab	Severe infusion reactions, infections, hepatotoxicity, fatigue	LFTs	Premedicate with acetaminophen, H_1-receptor antagonist (ie, diphenhydramine), H_2-receptor antagonist (ie, ranitidine), dexamethasone for infusion reactions
Isatuximab	Severe infusion reactions, myelosuppression, infections, gastrointestinal, hypertension	CBC	Premedicate with acetaminophen, H_1-receptor antagonist (ie, diphenhydramine), H_2 receptor antagonist (ie, famotidine), dexamethasone for infusion reactions Consider antiviral and antibiotic prophylaxis
Panobinostat	Severe gastrointestinal toxicity (vomiting/diarrhea) resulting in dehydration, cardiac toxicity including QTc prolongation, myelosuppression, infection, hepatotoxicity	CBC, LFTs, serum electrolytes and uric acid, ECG	Anti-diarrheals Anti-emetics
Selinexor	Myelosuppression, infection, gastrointestinal, infection, neurotoxicity, ocular, electrolytes, hepatotoxicity, fatigue	CBC, serum electrolytes, LFTs, serum creatinine, neurologic, vision	Moderate-high emetic risk-administer with 5-HT_3 antagonist Specific dose adjustments for toxicity
Belantamab mafodotin	Infusion reactions, myelosuppression, electrolytes, hepatotoxicity, ocular, including vision loss	CBC, REMS-ophthalmic exam (baseline, before each dose), serum electrolytes	No premedications unless the patient experiences infusion reaction Lubricating eye drops QID while on therapy Avoid contact lenses
Melphalan flufenamide	Myelosuppression, infection, gastrointestinal, secondary malignancies	CBC	Moderate emetic risk-administer with 5-HT_3 antagonist Specific dose interruptions/reductions for toxicity

CBC, complete blood count; REMS, Risk Evaluation and Mitigation Strategy; VTE, venous thromboembolism.

Conventional Chemotherapy

Novel regimens have replaced conventional chemotherapy in the treatment of MM. Conventional drugs such as melphalan and cyclophosphamide may be combined with novel agents to improve overall survival, but their use is limited.[7] High-dose melphalan is commonly used in the conditioning regimen for patients with MM before autologous HSCT.

Corticosteroids

Corticosteroids are the cornerstone of MM therapy. Dexamethasone is incorporated into most treatment regimens, given in higher doses than those used in the treatment of other diseases. High-dose dexamethasone is associated with a higher risk of infection and central nervous system toxicity so it

should be used with caution, particularly in older patients.[24] In current regimens, PIs and IMiDs are combined with dexamethasone to maximize initial response rates.

Immunomodulatory Drugs

IMiDs are incorporated into most treatment regimens for MM. Three IMiDs, thalidomide, lenalidomide, and pomalidomide, are approved for the treatment of MM, with lenalidomide most frequently utilized. Although thalidomide was the initial IMiD studied in MM, it has been largely replaced by lenalidomide due to increased potency and fewer adverse drug reactions. Thus, the discussion below on IMiDs will primarily focus on lenalidomide. IMiDs are often used in combination with a PI and dexamethasone to treat newly diagnosed and previously treated MM.

IMiDs have complex immune effects and block several pathways that are involved in disease progression in MM.[25] While not fully understood, IMiDs have anti-angiogenic and anti-inflammatory properties that directly or indirectly affect MM cells. IMiDs decrease the production of cytokines and growth factors that are believed to have a role in the pathogenesis of the disease, such as IL-6, TNF-α, and VEGF. IMiDs may also inhibit NF-κB activation, either directly or indirectly via TNF, which results in increased apoptosis of the MM clone. Further discussion of NF-κB can be found in the PIs treatment section. IMiDs also induce IL-2 mediated T-cell proliferation including natural killer cell activity. Figure 159-1 shows the proposed involvement of cytokines on MM cells.

A major concern with IMiDs is the rates of VTE. Patients with MM have up to a ninefold increased risk of VTE for the first 6 to 12 months of therapy compared to patients without MM.[26] The risk of VTE is also increased when IMiDs are combined with dexamethasone- or anthracycline-based chemotherapy. The underlying mechanism for thrombosis in these patients is unknown but is likely multifactorial. The IMPEDE VTE score is a VTE risk stratification tool that has been developed and validated to assist clinicians with the identification of high-risk VTE patients and with the appropriate selection of VTE prophylaxis.[27] That tool incorporates IMiD use in addition to other factors. NCCN guidelines have adopted the IMPEDE VTE score in their VTE prevention guidelines because the tool better predicts VTE in MM as compared to previously published guidelines.[27] Prophylactic aspirin may be an option for patients at low risk of VTE. High-risk patients should receive LMWH, warfarin (target INR 2-3) or a direct oral anticoagulant indefinitely while on MM therapy.[11] The use of direct oral anticoagulants is a recent addition to the NCCN guidelines and is based on emerging literature showing them to be safe and effective.[11] Apixaban has the most evidence to support its use in patients with MM.[28,29]

IMiDs are considered teratogenic based on the known teratogenicity of thalidomide. All of the IMiDs have black box warnings for the potential for severe birth defects and embryo-fetal death. The drugs are commercially available through restricted distribution programs and require enrollment into their respective Risk Evaluation and Mitigation Strategy (REMS) programs. The intent is to encourage safe use of the medication and minimize the risk of fetal exposure.

Table 159-4 shows additional adverse drug reactions for IMiDs.

Lenalidomide

Lenalidomide is a potent thalidomide analog and shares a similar mechanism of action to other IMiDs by targeting the microenvironment. Lenalidomide can be used as primary therapy in transplant-eligible or -ineligible patients, in relapsed/refractory MM and as maintenance therapy following transplant. Lenalidomide is preferred over thalidomide because of its improved toxicity profile.

Lenalidomide is Food and Drug Administration (FDA)-approved for the treatment of newly diagnosed patients with MM. In this setting, the doublet of lenalidomide and dexamethasone was compared with dexamethasone alone. The trial was halted when a planned interim analysis showed the combination to be more active than dexamethasone alone, with increased progression-free survival and overall response rate in the combination arm.[30] Subsequent trials examined the addition of a third agent, bortezomib, to the lenalidomide-dexamethasone regimen. A phase III study reported longer median progression-free and overall survival with the triplet regimen compared to the doublet lenalidomide and dexamethasone.[31] The regimen of bortezomib, lenalidomide, and dexamethasone is a category 1 NCCN recommendation for the primary treatment of MM patients regardless of transplant eligibility.[11] Other PIs and monoclonal antibodies may also be combined with lenalidomide and dexamethasone for primary therapy.

Lenalidomide is also used in the treatment of relapsed or refractory MM. Initial trials randomized patients to receive either lenalidomide (25 mg/day on days 1-21 of a 28-day cycle) and high-dose dexamethasone or high-dose dexamethasone alone. In one trial, patients receiving lenalidomide and

dexamethasone had overall response and CR rates of 61% and 14%, respectively, compared with 20% and 0.6% in the dexamethasone alone group.[32] The improved response rates translated into a longer median overall survival in the lenalidomide and dexamethasone groups. Similar results were reported in the second trial.[33] Other trials have evaluated the combination of lenalidomide and dexamethasone with a third agent for relapsed/refractory MM. The triplet regimens of lenalidomide, dexamethasone, and carfilzomib, ixazomib, elotuzumab, or daratumumab show longer progression-free survival, resulting in the approval of these regimens for the treatment of relapsed/refractory disease.[30]

The most appropriate dosing of dexamethasone with lenalidomide has also been evaluated. An open-label noninferiority phase III trial addressed this question in untreated patients with MM.[34] Patients were randomized to lenalidomide and high-dose dexamethasone (40 mg on days 1-4, 9-12, and 17-20 of each 28-day cycle) compared with lenalidomide and low-dose dexamethasone (40 mg/week). Patients who received lenalidomide with low-dose dexamethasone had longer 2-year overall survival and less toxicity than those who received lenalidomide with high-dose dexamethasone. The trial was halted after a second interim analysis and patients were allowed to cross-over to the low-dose arm. Patients in the lenalidomide plus high-dose dexamethasone arm had a 26% incidence of VTE compared to a 12% rate in those randomized to the lenalidomide plus low-dose dexamethasone arm.[34] The improved survival in the low-dose dexamethasone arm is likely related to lower mortality from adverse drug reactions, particularly VTE. Deaths in the high-dose dexamethasone group usually occurred during the first 4 months in older patients.

Lenalidomide is better tolerated than thalidomide. Lenalidomide causes less neurotoxicity, somnolence, and constipation but more myelosuppression than thalidomide. Patients receiving lenalidomide have an increased risk of secondary malignancies, particularly patients >74 years old receiving maintenance lenalidomide.[35] Multiple cycles of lenalidomide can impair stem cell mobilization. The IMWG recommends that transplant-eligible patients receiving lenalidomide have stem cells collected within the first four cycles of therapy.[11,36] Mobilization with chemotherapy or plerixafor may be utilized if stem cell collection is decreased.

Pomalidomide

Pomalidomide is a third-generation IMiD used in the treatment of MM. It is FDA-approved in relapsed MM in patients who have received at least two prior therapies, including lenalidomide and a PI. Pomalidomide is not approved for first-line therapy. Its initial approval was in combination with low-dose dexamethasone, where the pomalidomide combination demonstrated a progression-free and overall survival benefit versus high-dose dexamethasone.[37] Following that approval, pomalidomide was evaluated as part of various three-drug combinations. Pomalidomide shows good efficacy in patients who are refractory to lenalidomide and/or PI therapy. In refractory patients or those experiencing early relapse (<60 days after last therapy), the NCCN recommends pomalidomide, dexamethasone, and any of the available PIs as a preferred regimen after at least two lines of prior therapy. Similarly, regimens including pomalidomide and dexamethasone in combination with an anti-CD38 monoclonal antibody or elotuzumab are recommended for patients previously treated with lenalidomide and a PI.[11] Overall, pomalidomide is well tolerated with a toxicity profile similar to that observed with lenalidomide, except for a slightly higher incidence of peripheral neuropathy.

Proteasome Inhibitors

PIs are incorporated into most treatment regimens for MM. Three PIs, bortezomib, carfilzomib, and ixazomib, are approved for the treatment of MM. Bortezomib is the backbone of many regimens while the newer generation drugs seek to improve the toxicity profile, specifically lessening the degree of neuropathy. PIs are often used in combination with an IMiD and dexamethasone for the treatment of primary and relapsed/refractory MM.

PIs inhibit the proteasome and NF-κB activation. The proteasome is a protease complex responsible for degrading cytosolic proteins that are conjugated to ubiquitin. Ubiquitin is a 76-amino acid protein that tags various proteins for destruction.[38] By reversibly binding to the chymotrypsin site in the catalytic core of the 26S proteasome, bortezomib inhibits the degradation of these targeted proteins. Ixazomib is a reversible inhibitor while carfilzomib irreversibly binds to the chymotrypsin site, which explains the differences in pharmacokinetics among the drugs in this class.[38]

As discussed earlier, NF-κB activity is increased in MM. In the cytosol, NF-κB is bound to and is inhibited by IκB. The proteasome degrades IκB. When the proteasome is inhibited, cytosolic concentrations of IκB remain high, and NF-κB is retained in the cytosol as an inactive complex. The resulting inhibition of the NF-κB signal leads to a reduction in cytokine production and growth inhibition of the MM clone. Other proteins involved in cell-cycle regulation and apoptotic signaling that may be affected by PIs include p53 and map kinase.[38]

Bortezomib

Bortezomib was the first drug in the class of PIs and continues to be the backbone of many regimens used in the treatment of MM. A 2016 Cochrane review concluded that bortezomib treatment improves response rates, progression-free survival, and overall survival and should be considered standard of care for the treatment of MM.[39] Bortezomib has been extensively studied and is approved as primary therapy for newly diagnosed and relapsed/refractory MM. Bortezomib was initially approved in 2003 under the FDA's accelerated approval process for relapsed or refractory MM in patients who had failed at least two prior therapies. The approval was based on a phase II trial in which refractory MM received 1.3 mg/m^2 of bortezomib twice weekly for 2 weeks followed by 1 week of rest. Patients received up to eight cycles. The overall response rate was 35% (includes minor responses) with seven (3.6%) patients achieving a CR.[40] Subsequently, a large phase III study (Assessment of Proteasome Inhibition for Extending Remissions [APEX] trial) demonstrated that bortezomib had superior activity compared with high-dose dexamethasone in relapsed MM. Bortezomib-treated patients had higher CR and PR rates, longer median time-to-progression, and improved 1-year overall survival compared with patients receiving dexamethasone.[41] The differences in each of these end points were statistically significant. The results from this study led to expanded FDA approval in 2005 to include patients who had relapsed after one therapy. Numerous trials have examined bortezomib in combination with monoclonal antibodies, IMiDs, and/or traditional chemotherapy for relapsed and refractory MM. Various triplet combinations include bortezomib and dexamethasone with lenalidomide or daratumumab.[11]

Bortezomib is extensively used in the primary treatment of MM. As discussed earlier, the triple drug regimen of lenalidomide, bortezomib, and dexamethasone is the preferred treatment regimen for primary therapy in patients regardless of transplant eligibility. The inclusion of bortezomib in three- or four-drug combinations improves response rates and increases progression-free and overall survival. Bortezomib-based therapies may also be preferred in patients with high-risk disease, based on data that shows bortezomib may be able to overcome certain cytogenetic abnormalities, including the t(4;14) translocation.[42]

Bortezomib can cause serious adverse drug reactions. The most common adverse drug reactions are mild-to-moderate fatigue and gastrointestinal toxicities. Neuropathy occurs frequently and is the most common cause of discontinuation of therapy. Other important toxicities are listed in Table 159-4. An increased risk of shingles has been reported in bortezomib-treated patients, and the NCCN guidelines recommend herpes zoster prophylaxis.[11] Bortezomib-based therapy is an attractive option for those patients with renal dysfunction since renal dose modifications are not required. In patients with renal dysfunction, the NCCN recommends the combination of bortezomib-cyclophosphamide-dexamethasone, as lenalidomide requires renal dose adjustments. If the patient's renal function improves after initial treatment with bortezomib-cyclophosphamide-dexamethasone, it is reasonable to switch to bortezomib-lenalidomide-dexamethasone.[11] Unlike lenalidomide, bortezomib does not affect stem cell mobilization.

Since neurotoxicity is a concern with bortezomib, investigators have explored modifying the route of administration and dosing schedule of bortezomib. In a phase III trial in relapsed MM, therapeutic equivalence was found between intravenous and subcutaneous routes of administration.[11] In addition, subcutaneous administration offers the potential advantage of administration in patients without IV access, is more convenient, and has a lower risk of peripheral neuropathy. Subcutaneous bortezomib administration is now the preferred route of administration.[11] Dose schedules have also been modified to decrease toxicity-related treatment delays. Once-weekly bortezomib has been compared with twice-weekly dosing with similar overall response rates.[11] The once-weekly schedule was associated with fewer dose reductions, and the risk of neuropathy was similar.

Carfilzomib

Carfilzomib is a second-generation, irreversible PI approved for patients with relapsed and refractory disease. Its mechanism, higher selectivity for the chymotryptic site of the 20S proteasome, and toxicity profile are distinct compared to bortezomib.[38] The dosing schedule is also different than bortezomib. Carfilzomib is more potent, yet tolerable with two consecutive daily doses or once weekly dosing. Collectively, clinical trials start with carfilzomib 20 mg/m^2 IV over 10 to 30 minutes on the first cycle/week and increase to 27 to 70 mg/m^2 depending on tolerability and dosing frequency.[43,44]

Numerous trials have examined carfilzomib in the treatment of progressive or relapsed MM. The ASPIRE trial showed the addition of carfilzomib to a lenalidomide-dexamethasone backbone improved progression-free survival, overall survival, and health-related quality of life without any change in adverse drug reactions.[44] The incidence of neuropathy was similar in both arms. Carfilzomib-dexamethasone was compared to bortezomib-

dexamethasone in relapsed or refractory MM in the head-to-head Phase III trial (ENDEAVOR). Median progression-free survival was longer with carfilzomib as compared to the bortezomib group.[45] A second interim analysis showed that carfilzomib also improved median overall survival as compared to bortezomib.[46] Based on these data, carfilzomib in combination with lenalidomide-dexamethasone or dexamethasone is an NCCN category 1 recommendation for previously treated MM.[11] Additional studies are evaluating carfilzomib with traditional chemotherapy and other novel drugs.

The activity of carfilzomib in combination regimens as first-line treatment is also impressive. The phase III, open-label, ENDURANCE trial compared bortezomib, lenalidomide and dexamethasone and carfilzomib, lenalidomide and dexamethasone in the first-line setting for standard and intermediate-risk patients with MM.[47] The trial showed similar progression-free survival between the two arms. Carfilzomib was associated with less neuropathy but increased pulmonary and cardiac adverse events.[47] According to the NCCN guidelines, certain carfilzomib-containing regimens may be used for primary therapy, especially in patients with peripheral neuropathy.[11]

The toxicity profile of carfilzomib differs from that of bortezomib. The incidence of peripheral neuropathy is less with the second-generation PIs which should be considered when treatment is selected. The ENDEAVOR trial reported a lower risk of grade 2 or higher peripheral neuropathy in patients who received carfilzomib as compared with bortezomib.[45,46] Carfilzomib is associated with serious cardiac and pulmonary toxicities. The cardiovascular adverse events include congestive heart failure, hypertension, arrhythmias, and ischemia. A meta-analysis of 24 studies reported the rate of cardiovascular events as 18.1%, with higher doses of carfilzomib (≥45 mg/m^2) associated with higher rates of cardiovascular events.[47] The pulmonary adverse events of dyspnea, cough, respiratory tract infections, and pneumonia are also of concern.[48] Clinicians should monitor patients for carfilzomib-related cardiac and pulmonary symptoms and initiate symptom management when necessary.

Ixazomib

Ixazomib is the first oral PI approved for the treatment of MM. It is given once-weekly as second-line therapy in combination with lenalidomide and dexamethasone. The approval is based on the TOURMALINE-MM1 phase III trial, which showed the addition of ixazomib to lenalidomide and dexamethasone prolonged progression-free survival in patients with relapsed or refractory MM as compared with lenalidomide and dexamethasone alone.[49] The TOURMALINE-MM2 phase III trial evaluated ixazomib, lenalidomide, and dexamethasone in newly diagnosed patients with MM. The trial showed improved response rates with the addition of ixazomib to lenalidomide and dexamethasone but failed to reach statistical significance in progression-free survival.[50] The results of this study led to an NCCN category 2B recommendation for ixazomib, lenalidomide, dexamethasone in the first-line setting for transplant-eligible patients.[11] This regimen is an attractive option for some patients because it allows for a completely oral triple-drug combination. Similarly, ixazomib can be administered in combination with oral cyclophosphamide and dexamethasone. This may be beneficial in patients with renal dysfunction but lacks the supporting evidence associated with bortezomib-containing regimens. As discussed in a previous section, ixazomib combined with pomalidomide and dexamethasone is highly effective in patients experiencing early progression following two lines of IMiD and PI therapy therapy and can be considered as maintenance therapy in certain situations. Table 159-4 lists the adverse drug reactions of ixazomib. Unlike carfilzomib, cardiac toxicity with ixazomib is minimal.[51]

Monoclonal Antibodies

Three monoclonal antibodies and one antibody-drug conjugate are FDA-approved for the treatment of MM. These monoclonal antibodies are often added to a combination drug regimen, with daratumumab incorporated into regimens for high-risk patients with MM.

Daratumumab

Daratumumab is an IgG1-κ fully human monoclonal antibody that targets CD38, a glycoprotein highly expressed on MM cells. Accelerated FDA approval for daratumumab in relapsed/refractory MM was granted after two open-label phase II trials of daratumumab showed single-agent activity (overall response rates of 29% and 36%).[52] Subsequent studies confirmed the role of daratumumab in combination therapy. A phase III trial of daratumumab, bortezomib, and dexamethasone reported a higher 12-month progression-free survival as compared to bortezomib and dexamethasone.[52] Similar findings were reported with daratumumab, lenalidomide, and dexamethasone, with a higher 12-month progression-free survival as compared with lenalidomide and dexamethasone.[52] Daratumumab, in combination with bortezomib, carfilzomib, lenalidomide, or pomalidomide and

dexamethasone are NCCN category 1 recommendations for patients with relapsed and refractory MM.

Daratumumab combinations are also used in front-line therapy for newly diagnosed MM patients. The combination of daratumumab with bortezomib, melphalan, and prednisone was the first regimen approved for newly diagnosed, transplant-ineligible patients with MM. FDA approval was based on the phase III trial that showed that the addition of daratumumab to the regimen resulted in a higher overall response rate and a lower risk of disease progression and death as compared to bortezomib, melphalan, and prednisone.[53] Additional studies have reported the benefits of daratumumab combination therapy. The three-drug regimen of daratumumab, lenalidomide, and dexamethasone is considered a NCCN category 1 preferred recommendation as primary therapy for transplant-ineligible patients, and a four-drug regimen of daratumumab, bortezomib, thalidomide/lenalidomide, and dexamethasone may be used as primary therapy for transplant eligible candidates.[11] Four-drug or "quadruplet" therapy is a treatment option in both standard and high-risk patients. Mayo Clinic mSMART guidelines recommend the four-drug regimen—daratumumab, lenalidomide, bortezomib, and dexamethasone—as initial treatment for patients with high-risk cytogenetics.[21]

Daratumumab is well-tolerated (Table 159-4). Infusion-reactions are common, occurring in 48% of patients.[53] Patients should be pre-medicated with a corticosteroid, acetaminophen, and an antihistamine to reduce the risk of a severe infusion reaction. Since daratumumab can interfere with cross-matching and red blood cell antibody screening, blood typing should occur before starting therapy.

Isatuximab-irfc

Isatuximab-irfc is a chimeric IgG-derived monoclonal antibody that also targets CD38 but at a different epitope than daratumumab. This leads to enhanced direct apoptosis without the need for effector cells or the complement system.[54] Isatuximab also inhibits the enzymatic activity of CD38 more effectively than daratumumab. This suggests more potent MM activity in vitro, although it is unknown if this will translate into increased clinical efficacy. Isatuximab may be active in patients who were refractory to daratumumab.[54] Isatuximab was initially approved in the third-line setting, following progression after lenalidomide and a PI, in combination with pomalidomide and dexamethasone. The combination with isatuximab showed improved response rates and progression-free survival over pomalidomide and dexamethasone alone.[55] Isatuximab is approved for patients who have received at least one prior line of therapy in combination with carfilzomib and dexamethasone. The adverse drug reaction profile of isatuximab is similar to that of daratumumab.

Elotuzumab

Elotuzumab is a monoclonal antibody directed against signaling lymphocyte activation molecule family 7 (SLAMF7), which is expressed on MM cells.[56] The binding of elotuzumab to SLAMF7 results in cytotoxicity through various mechanisms including antibody-dependent cellular cytotoxicity. Elotuzumab was evaluated in a phase III trial in combination with lenalidomide and dexamethasone in patients with relapsed and refractory MM. The elotuzumab combination improved progression-free survival and overall response rate as compared to lenalidomide and dexamethasone. Elotuzumab also improves progression-free survival when combined with either bortezomib or pomalidomide and dexamethasone. The elotuzumab, lenalidomide, and dexamethasone regimen is considered an NCCN category 1 recommendation for previously treated patients with MM.[11] Common adverse effects are listed in Table 159-4. Patients should be pre-medicated with dexamethasone, diphenhydramine, ranitidine, and acetaminophen to reduce the risk of an infusion reaction. Infusion reactions occurred in 10% of patients despite premedication, and most of the infusion reactions occurred with the first dose.[56] Patients receiving an elotuzumab-containing combination should also be monitored for infections because infections are the most common cause of non-myeloma-related death.

Belantamab mafodotin

Belantamab mafod is an antibody-drug conjugate targeting B cell maturation antigen (BCMA). Upon binding to BCMA, belantamab mafodotin is internalized and releases its monomethyl auristatin F (MMAF) payload, which inhibits microtubule formation.[57] Belantamab mafodotin was approved for patients who have received at least four prior lines of therapy, including a CD38 antibody, a PI, and an IMiD. The approval was based on the results of a phase II, DREAMM-2 study, in which belantamab mafodotin had an overall response rate of 31%.[57] Of those responders, nearly 75% of patients had a duration of response of 6 months or greater. However, belantamab mafodotin failed to demonstrate a survival advantage over pomalidomide/dexamethasone in its confirmatory phase III, DREAMM-3 study[58], which led to the withdrawal of belantamab mafodotin for the US market in November 2022. This agent remains available for compassionate use and is still being investigated in other combination therapies. The most

common adverse drug reactions observed during the study were cytopenias, liver function test abnormalities, infusion reactions, and ocular toxicity, including vision loss. Due to the risk of ocular toxicity, belantamab mafodotin is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). The REMS program requires the patient to undergo a thorough ophthalmic exam prior to each dose. Patients should use lubricating eye drops while on therapy and avoid the use of contact lenses.

Panobinostat

Panobinostat is an oral inhibitor of histone deacetylase enzymes and has shown activity in MM. Panobinostat was evaluated in a phase III trial in patients with refractory or relapsed MM who had received prior therapy with an IMiD and bortezomib.[59] Patients were randomized to receive bortezomib, dexamethasone, and panobinostat or bortezomib, dexamethasone, and placebo. The addition of panobinostat significantly improved progression-free survival.[59] In November 2021, the manufacturer of panobinostat withdrew the agent from the market due to the inability to complete a confirmatory study of efficacy which was required for continued FDA approval.Adverse drug reactions for this agent are listed in Table 159-4.

Selinexor

Selinexor is the first in a new class of drugs that inhibits the nuclear export of tumor suppressor proteins (TSPs) and exportin 1 (XPO1).[60] The inhibition of XPO1 allows the cell to restore endogenous tumor suppressing proteins resulting in cancer cell apoptosis. Selinexor received accelerated FDA approval in 2019 for use with dexamethasone in patients with relapsed or refractory MM who have received at least four prior therapies, including an anti-CD38 monoclonal antibody (eg, daratumumab).[11] Serious adverse drug reactions are listed in Table 159-4. Following its initial approval, selinexor was combined with bortezomib and dexamethasone in patients progressing after at least one therapy, where the regimen showed an increase in progression-free survival compared to bortezomib and dexamethasone alone.[60] Weekly dosing of selinexor improves the tolerability of the drug, with less grade >3 hematologic toxicity when compared to twice weekly dosing.[60]

Melphalan Flufenamide

Melphalan flufenamide is a first-in-class peptide-drug conjugate, combining melphalan with a modified phenylalanine amino acid. The drug requires cleavage by an aminopeptidase for activation. Aminopeptidases are often overexpressed in malignant cells which allows for more targeted activity in MM cells. The FDA granted melphalan flufenamide, in combination with low-dose dexamethasone, accelerated approval for patients who have received at least four lines of therapy. The approval was based on a single-arm phase II trial that showed an overall response rate of 24%, with a median duration of response of 4.2 months.[61] Adverse drug reactions are listed in Table 159-4. While the phase III confirmatory study comparing melphalan flufenamide to pomalidomide and dexamethasone was being conducted, a significant increase in mortality was observed in patients receiving melphalan flufenamide. This caused the FDA to issue a safety warning in July 2021 and required the manufacturer to suspend all studies involving melphalan flufenamide pending further evaluation.[62] The drug was withdrawn from the market later that year at the request of the FDA.

Chimeric Antigen Receptor T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is a novel form of immunotherapy in which a patient's T-cells are collected and genetically modified to target malignant cells. Multiple CAR T-cell products, directed at CD19, are FDA-approved for the treatment of B-cell malignancies. In 2021, the FDA-approved idecabtagene vicleucel for the treatment of relapsed or refractory MM after four or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody. The CAR T-cell product targets BCMA found on the surface of mature B lymphocytes and plasma cells. In the phase II trial that led to its approval, idecabtagene vicleucel showed an overall response rate of 73%, with 33% of patients achieving a complete response or better. MRD negative status was reached in 79% of those with a complete response.[63] In many cases, the responses are durable with a median progression-free survival of 19 months in patients achieving a complete response. Patients achieving a VGPR had a lower median progression-free survival of 10.4 months. These results are impressive considering the heavily pretreated patient population (median six lines of prior therapy, 95% prior autologous transplant). The most common adverse events observed were cytopenias, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS).[63] Neutropenia was the most common cytopenia, occurring in 90% of patients but is often attributed to the lymphodepleting chemotherapy given prior to CAR T-cell infusion. CRS was observed in 84% of patients, with the most patients experiencing low grade CRS. ICANS occurred in 18% of patients.

In February 2022, the FDA approved a second BCMA-targeted CAR T-cell product, ciltacabtagene autoleucel. In the phase Ib/II CARTITUDE-1 trial, ciltacabtagene autoleucel demonstrated impressive activity with an overall response rate of 97%, with 67% of patients achieving a stringent CR. Median PFS and OS were not reached, but the 12-month PFS and OS were 77% and 89% respectively.[64] Adverse effects were similar to those observed with idecabtagene vicleucel, with cytopenias (neutropenia, 95%), CRS (95%) and ICANS (21%). Both CAR T-cell products have REMS programs that require specific training and supportive care availability to ensure appropriate treatment of CRS and ICANS is available prior to infusion.

CRS is characterized by immune activation and release of inflammatory cytokines secondary to CAR T-cells interacting with target cells. CRS presentation can range from mild, flu-like symptoms to severe life-threatening organ dysfunction. CRS is treated with supportive care, tocilizumab (an interleukin-6 receptor antagonist), and steroids. The pathophysiology of ICANS is less completely understood but may be related to immune activation and vascular dysfunction. Similar to CRS, ICANS can present with a wide variety of symptoms, ranging from mild somnolence to cerebral edema and seizures. ICANS and CRS often present together but can occur independently. ICANS is treated with steroid therapy, antiepileptics, and other supportive care.[65] The NCCN has added idecabtagene vicleucel and ciltacabtagene autoleucel to its guidelines, but further studies are needed to determine its optimal place in therapy.

Bispecific T-cell Engager Therapy

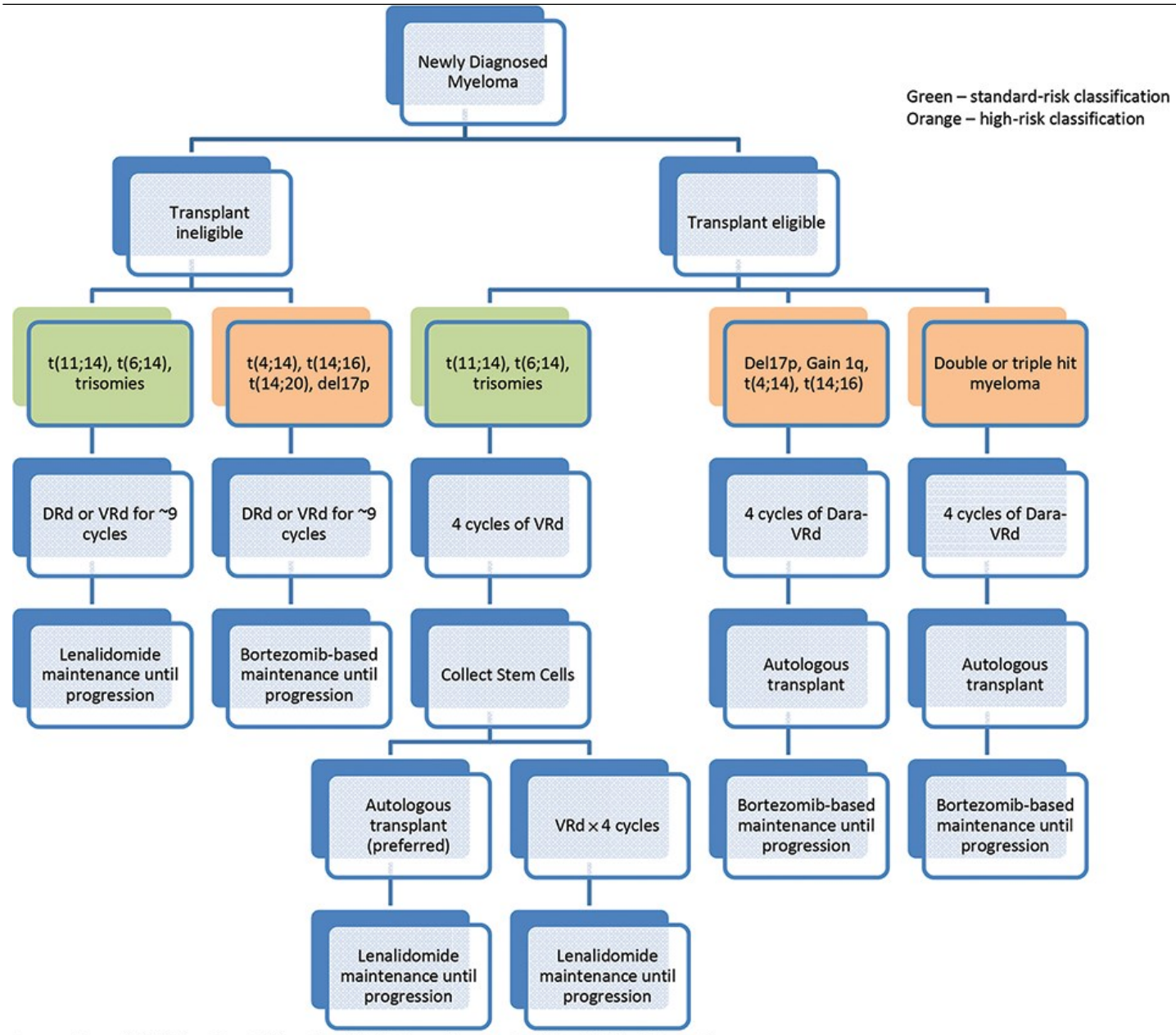
Bispecific T-cell engager (BTCE) therapy is another way that clinicians are able to utilize a patient's immune system to destroy malignant cells. BTCEs are fusion proteins consisting of two antibody fragments. One fragment binds to the CD3 protein complex found on T-cells, and the other to a tumor specific marker. Currently there are three BTCEs that are approved by FDA. Two BCTEs are teclistamab and elranatamab, which are CD3-B cell maturation antigen (BCMA) also known as CD269 and TNFRS17, these antigens are known to mediate the survival and growth of B cells and plays a critical role in the maturation and differentiation of B cells to plasma cells. Another BTCE, talequetamab, is a G protein-coupled receptor, family C, group 5, member D (GPRC5D)-CD3 BTCE. The adverse effect profile of BTCEs are similar tothose observd with CAR T therapy. Patients are at risk for cytopenias, CRS and ICANS, but these adverse effects tend to occur less frequently and/or be less severe when compared to CAR T-cell therapy. CRS occurred in 60-80% of patients receiving teclistamab, elranatamab, or talquetamab, but less than 2% of these events were grade 3 or higher. In comparison, about 5% of trial patients receiving CAR T-cell therapy experience high grade CRS. ICANS is rare for patients receiving BTCE therapy, with a reported incidence of less than 3%. CRS and ICANS are most common during the dose ramp up phase. Many patients receiving talquetamab experience skin and nail toxicities because GPRC5D is expressed in these tissues. About 70% of patients experienced a skin-related adverse effect, with rash, pruitis, and dry skin being the most common. These side effects were generally low grade and responded to steroids if necessary.

Initial Therapy

Initial therapy is guided by the NCCN, IMWG, ESMO, and mSMART recommendations and depends on whether the patient is symptomatic and a candidate for autologous HSCT (see Fig. 159-2). Eligibility factors for HSCT include patient age, renal function, performance status, and comorbidities. All patients with symptomatic MM are treated with primary therapy, with the selected regimen depending on transplant eligibility. Patients who are candidates for autologous HSCT will often receive 4 to 6 months of therapy before proceeding to hematopoietic stem cell collection, harvesting enough stem cells for two transplants.[11] Most patients will undergo autologous HSCT immediately following collection, but some patients may decide to delay the transplant until first relapse. Therapies that may compromise stem cell reserve are avoided in transplant-eligible patients. The selected regimen will often be composed of agents from multiple, distinct classes. Triplet combination regimens are commonly used and often include dexamethasone, a PI, and an IMiD. Patients who are not candidates for autologous HSCT usually continue their MM therapy or receive maintenance therapy, although the optimal duration of therapy after the desired response is achieved is unknown. Single-agent maintenance therapy, consisting of lenalidomide or bortezomib, may be given in both transplant-eligible and ineligible patients.

FIGURE 159-2

Risk-adapted treatment of multiple myeloma based on eligibility for hematopoietic stem cell transplantation. (Dara-VRd, daratumumab, bortezomib, lenalidomide, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.) *(Adapted from mSMART.org. http://www.msmart.org/mm-treatment-guidelines. Accessed October 1, 2021.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

VRd is frequently used for primary therapy in both transplant-eligible and ineligible patients. Daratumumab, carfilzomib, or ixazomib-based therapy are additional treatment options for select patients. Treatment decisions are made based on physician preference, patient characteristics, and transplant eligibility. Some experts recommend a risk-adapted approach that personalizes treatment based on cytogenetics and gene expression profiling. The high cost of medications can pose a financial challenge for patients and clinicians who must consider the financial implications when selecting a regimen.

Some clinicians use a risk-adapted approach to select therapies (eg, mSMART). Bortezomib-containing induction regimens are recommended in patients with high-risk cytogenetics (see Fig. 159-2).[21] In this approach, high-risk patients receive a combination of daratumumab, bortezomib, lenalidomide, and dexamethasone as primary therapy. The combination of VRd is recommended in standard-risk patients. These regimens are continued in transplant-eligible patients for four cycles before transplant, but transplant can be delayed depending on patient preference. Transplant-ineligible patients will receive therapy for about 1 year and then possibly maintenance therapy. Lenalidomide- and bortezomib-based therapies may be used for maintenance therapy depending on risk.

5 A flow diagram shows the management of newly diagnosed myeloma. If the patient is transplant ineligible, there are two pathways. The first pathway is for patients with t(11;14), t(6;14), or trisomies, and is classified as standard risk. These patients should be treated with DVd or VRd for nine cycles, followed by lenalidomide maintenance until disease progression. The second pathway is for patients with t(4;14), t(14;16), t(14;20), or del17p and is classified as high risk. These patients should be treated with DVd or VRd for nine cycles, followed by bortezomib-based maintenance until progression. If the patient is transplant eligible, there are three pathways. The first pathway is for patients with t(11;14), t(6;14), or trisomies, and is classified as standard risk. These patients should be treated with four cycles of VRd, followed by stem cell collection. The patient then either proceeds with autologous transplant (preferred), followed by lenalidomide maintenance for a minimum of 2 years, or proceeds with four cycles of VRd, followed by lenalidomide until disease progression. The second pathway is for patients with Del17p, Gain 1q, t(4;14), or t(14;16) and is classified as high risk. These patients should be treated with four cycles of Dara-VRd followed by autologous transplant, and then bortezomib-based maintenance until progression. The third pathway is for patients with double or triple hit myeloma and is classified as high risk. These patients should be treated with four cycles of Dara-VRd followed by autologous transplant, and then bortezomib-based maintenance until progression.

Autologous Hematopoietic Stem Cell Transplantation

4 Although MM is a chemosensitive tumor with significant response rates after treatment with conventional chemotherapy, the duration of response is usually short. To improve outcomes with chemotherapy, high-dose chemotherapy regimens with autologous stem cell support is used after initial induction therapy. The intent of the induction therapy before transplant is to reduce tumor burden. With newer treatment regimens being used for induction, higher rates of quality responses (CR, VGPR, nCR) can be obtained which may improve the outcomes associated with autologous HSCT.

Randomized, controlled trials have evaluated the role of high-dose chemotherapy followed by autologous HSCT in patients with MM. Studies have confirmed that primary therapy followed by high-dose chemotherapy and autologous HSCT improves overall survival and increases complete response rates.[11,66] The timing of autologous HSCT has also been explored. An induction regimen of lenalidomide and dexamethasone followed by either chemotherapy (melphalan/prednisone/lenalidomide) or tandem melphalan-based autologous transplants was evaluated.[66] Results of this trial showed a progression-free survival and overall survival benefit for the autologous transplant arm. In a separate trial, patients received induction therapy with VRd, with either upfront or delayed consolidation with autologous HSCT, followed by lenalidomide maintenance therapy. Results of this trial showed that upfront transplant followed by maintenance resulted in significant improvements in progression-free survival but no difference in overall survival.[67] Based on available data, autologous HSCT improves response rates, symptom-free and progression-free survival but may not prolong overall survival. The lack of an overall survival advantage is likely due to improved salvage therapy. Despite this, current recommendations support high-dose chemotherapy and autologous HSCT in eligible patients with a first remission after primary therapy.[11,16,21]

The optimal timing of autologous HSCT (early vs late) in MM has also been investigated. In a landmark trial, patients were randomized to early (within 12 months of diagnosis) or late transplantation (>12 months after diagnosis), and no significant difference in 5-year overall survival was observed between the groups.[68] Event-free survival, however, was significantly longer in the early transplantation group (39 vs 13 months). In an analysis that factors in the time without symptoms, treatment, or treatment toxicity (TWiSTT), patients receiving early transplantation had a longer time in a state associated with a good quality of life (27.8 vs 22.3 months). The results of this study supported early autologous HSCT because of its effects on event-free survival and quality of life. Since then, two retrospective studies comparing early versus delayed autologous HSCT have been published.[69,70] These studies included MM patients who received an induction regimen that included either lenalidomide, thalidomide or another novel therapy. Both trials demonstrated similar time-to-progression and overall survival in the early (within 12 months) and delayed transplant groups. While most of the phase III trials have shown improvements in progression-free survival with transplantation, not all trials have shown an improvement in overall survival with transplantation.[71] This has been attributed to variations in primary treatment and study design. The collective results of these trials may support the idea that, in the setting of novel therapies, delaying transplant may be feasible for certain standard-risk patients, but the lack of rigorous, prospective, randomized data prevents the uniform recommendation to delay transplant. For patients with high-risk disease, current data do not support delaying transplant. Enrollment in clinical trials is highly recommended for most patients when evaluating the appropriate timing of HSCT in MM.[11]

A specialized form of autologous HSCT, tandem transplantation, involves the use of two separate autologous HSCT procedures separated by a rest period of several months. It was hypothesized that this more intensive approach would lead to improvements in therapeutic outcomes. Since the initial report of a benefit to the tandem transplant approach, several trials investigated this approach to therapy. Many of these trials were conducted before the availability of novel drugs and were shown to have conflicting results regarding overall survival.[71] Thus, the current data do not support the routine

use of tandem transplants. Tandem autologous HSCT may be considered in selected patients with high-risk disease or those failing to achieve a VGPR after the first transplant, but any such decision would be best evaluated in the context of a clinical trial.[11,16,71]

The primary conclusion from the current data on autologous HSCT as consolidation therapy in MM is that it should be used in patients with good performance status. Advanced age and/or renal dysfunction should not be considered contraindications to transplant.[11] Before transplant, all patients should receive primary therapy to reduce tumor burden. Prolonged exposure to drugs such as lenalidomide and daratumumab can decrease the yield of stem cell harvest, so cells should be collected early on in therapy. Similarly, alkylating agents and nitrosoureas should be avoided before stem cell collection. NCCN recommends collecting sufficient hematopoietic stem cells for a second, salvage transplant in younger patients. The Mayo Clinic mSMART guidelines recommend autologous HSCT in transplant-eligible high-risk patients after the bortezomib-based induction therapy.[21] Standard-risk patients are given the option of autologous HSCT followed by maintenance therapy or continued induction followed by maintenance therapy (see Fig. 159-2).

Maintenance Therapy

Even with the advances in induction therapy and autologous HSCT, most patients will eventually progress within 3 to 5 years, suggesting that effective maintenance therapy could control or delay disease progression. Lenalidomide is frequently used as maintenance therapy in both transplant-ineligible and post-autologous HSCT patients with MM. Numerous trials have investigated the use of lenalidomide maintenance after autologous HSCT, showing improvements in progression-free and, possibly, overall survival compared to no maintenance therapy.[72] A 2017 meta-analysis examined the use of lenalidomide maintenance in newly diagnosed post-autologous HSCT patients with MM.[72] The analysis found significant benefits with lenalidomide maintenance compared to placebo or observation, extending median progression-free and overall survival.[72] While there are no direct head-to-head comparisons, a 2018 meta-analysis examined all regimens used for maintenance therapy and concluded that lenalidomide was the only maintenance therapy to improve progression-free and overall survival.[73] One unique adverse effect noted in these trials was second primary malignancy, including solid tumors, hematologic malignancies, and nonmelanoma skin cancers. These second malignancies occurred at a significantly higher rate as compared to placebo or control arms. Based on these data, the FDA issued a safety announcement to be added to the warning section of the lenalidomide drug labeling. Some practitioners advocate limiting the duration of maintenance lenalidomide to 2 years after transplant to minimize risk.[11]

Bortezomib may also be used for maintenance therapy in transplant-ineligible and post-autologous HSCT high-risk patients with MM. The 2018 meta-analysis of maintenance therapy showed that bortezomib-based therapies prolonged progression-free survival but did not improve overall survival.[73] Additionally, patients who do not achieve at least a VGPR after autologous transplant may benefit from bortezomib maintenance.[11]

Ixazomib has also been studied as maintenance therapy following autologous HSCT. The phase III TOURMALINE-MM3 trial randomized patients to oral ixazomib dosed on days 1, 8, and 15 in 28-day cycles or placebo as maintenance therapy for 2 years.[74] The trial showed that ixazomib maintenance therapy prolonged progression-free survival in newly diagnosed patients who received a single autologous HSCT within 12 months of diagnosis. While lenalidomide is the preferred maintenance medication by the NCCN guidelines, the guidelines added ixazomib as an option.[11] Ixazomib's convenient weekly dosing schedule, lack of secondary malignancies and low risk of peripheral neuropathy may make ixazomib a reasonable desirable alternative to lenalidomide.

The NCCN and mSMART guidelines recommend a two-drug maintenance regimen for patients with high risk cytogenic features. mSMART suggests bortezomib/lenalidomide as maintenance following autologous stem cell transplant or VRd induction in transplant ineligible patients. The NCCN recommends a two-drug regimen and lists bortezomib/lenalidomide, carfilzomib/lenalidomide, and daratumumab/lenalidomide as options. Future comparative trials are needed to determine the preferred maintenance therapy, particularly in patients with high-risk MM. The decision to use any of these agents in the maintenance setting must include careful consideration of the benefits and risks.

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT uses a stem cell source other than the patient and is therefore a transplant across immunologic barriers. Unlike autologous HSCT, which is simply a method of increasing the dose intensity of chemotherapy, allogeneic HSCT is a form of immunotherapy. The interest in allogeneic transplantation for MM is based on the use of a stem cell source free of tumor, which may potentially offer longer disease control and possible cure.

The major posttransplant complications associated with allogeneic transplants are acute and chronic graft-versus-host disease (GVHD). GVHD may be accompanied by a graft-versus-myeloma effect. The graft-versus-myeloma effect, which is mediated by antitumor effector cells from the GVHD reaction, reduces relapse risk and may offer the patient the best chance for long-term disease-free survival.

Myeloablative allogeneic HSCT has traditionally been associated with high treatment-related mortality, between 20% and 60%.[75] Historically, allogeneic transplant has been used after patients have received and progressed after an autologous HSCT. Several trials have compared tandem autologous transplants to autologous followed by allogeneic stem cell transplant, although there is wide variability in trial design patient selection and protocols for the prevention and treatment of GVHD.[76] In all trials to date, no consistent improvement in overall survival or progression-free survival has been reported. Meta-analyses show that allogeneic HSCT may result in a higher CR rate, including long term remissions, but this comes at the cost of a higher rate of transplant-related mortality.[11]

Allogeneic HSCT may have a role in the management of patients with high-risk disease. Ongoing clinical trials are evaluating the role of allogeneic HSCT in patients with MM who have high-risk cytogenetic characteristics, who are not likely to respond to upfront therapy or who relapse quickly after upfront therapy or autologous HSCT. There is increasing interest in the use of reduced-intensity conditioning regimens. Based on the available data, upfront myeloablative allogeneic HSCT is not routinely recommended.

Relapsed or Refractory Disease

9 The most appropriate therapy for an individual who relapses depends on the type and duration of previous therapies, whether the patient received a transplant, presence or absence of adverse prognostic factors, toxicity of prior therapies (eg, peripheral neuropathy), organ dysfunction (eg, renal impairment), and how much time has elapsed from initial response to relapse.[11] The same drugs used to treat MM initially can also be used as salvage therapy in patients who have relapsed more than 6 months after primary induction therapy.[11] Patients with relapsed or refractory MM can be treated with active agents in combination or single agents used sequentially. With the growing number of highly active agents, combination therapy is more commonly given. There are no direct comparisons of the frequently utilized regimens for relapsed and refractory disease making it difficult to determine the best treatment option. The NCCN has seventeen category 1 recommendations (13 triplet and 4 doublet regimens) and lists many other additional regimens.[11] Combination therapy continues to incorporate a PI, IMiD, and dexamethasone. Daratumumab, elotuzumab, and isatximab-irfc may also be used in various regimens. A systematic review suggests the combination of daratumumab, lenalidomide, and dexamethasone may be superior in patients with progressive disease.[77] Other meta-analyses have reported triplet-based combinations with monoclonal antibodies are superior (extending progression-free survival) compared to other regimens in patients with relapsed and refractory disease.[78] CAR T-cell therapy with idecabtagene vicleucel or ciltacabtagene autoleucel haves reported encouraging results and may be considered in patients who have progressed after multiple lines of therapy. Bispecific T-cell engager therapy has also shown promise in heavily pretreated patient populations. The optimal sequencing of CAR T-cell, BiTE, and other salvage therapies remains to be determined. Despite clear progress, most salvage therapies produce less than a 50% response rate, and new drugs and drug combinations are needed.

Questions remain on the optimal timing for autologous HSCT. For patients who are eligible for autologous HSCT and did not receive a transplant as part of initial therapy, autologous HSCT should be considered at first relapse. Autologous HSCT in first remission trends toward longer progression-free survival compared to those transplanted beyond first remission.[79] Salvage autologous HSCT may be beneficial in patients who were heavily pretreated and refractory to daratumumab.[80] The role of salvage autologous transplant may continue to be minimized with the approval of additional drugs and the use of maintenance therapy.

Supportive Care

Bone-Modifying Agents

10 Along with anti-MM therapy, supportive care measures are aggressively used to stabilize skeletal abnormalities. Patients with MM have a high rate of bone involvement. The mechanism of MM-associated bone disease is thought to be mediated through several pathways, including IL-6, IL-1, and TNF-α, but the most targeted pathway is that involving receptor activator factor kappa B ligand (RANK-L) and osteoprotegerin (OPG).[23] Skeletal homeostasis is complex. In normal bone, RANK-L and OPG are both produced by osteoblasts. RANK-L binds to RANK receptors on osteoclasts, to stimulate bone resorption, and to OPG, a “decoy receptor,” to inhibit bone resorption and stimulate bone formation. A balance between RANK-L and

OPG is the basis for normal bone remodeling. In MM, an imbalance in normal bone homeostasis leads to increased osteoclast activity and the formation of osteolytic bone lesions which can lead to clinically significant skeletal-related events, including fracture, hypercalcemia, and bone pain. Based on the 2019 ASCO guidelines, clinical indications for bone modifying therapies include hypercalcemia, renal dysfunction, anemia, and bone disease. In the absence of these features, patients with >60% plasma cells in the bone marrow or more than one site of bone disease are now recommended for treatment.[81] The NCCN guidelines recommend bone modifying therapies for all patients regardless of documented bone disease. Preventative therapies are initiated early to delay myeloma bone disease. Myeloma bone modifying therapies should be continued for at least 2 years with discontinuation based on clinical judgment.[11]

The primary therapies for the prevention of myeloma bone disease include antiresorptive bisphosphonates (ie, zoledronic acid and pamidronate) and denosumab. Bisphosphonates bind to hydroxyapatite and are incorporated into the bone matrix, suppressing osteoclast activity.[82] There are two classes of bisphosphonates (ie, nitrogen and non-nitrogen containing) based on their binding affinity with hydroxyapatite. The nitrogen-containing bisphosphonates of zoledronic acid and pamidronate are 100 to 10,000 fold more potent than the non-nitrogen containing bisphosphonates (ie, etidronate).[82] For this reason, zoledronic acid and pamidronate are used in the management of myeloma bone disease. Bisphosphonates may also promote apoptosis in MM cells, modify the cytokine microenvironment, inhibit the adhesion of MM cells to bone marrow matrix cells, and inhibit angiogenesis.[83] A meta-analysis in patients with MM shows bisphosphonates reduce pain, overall fractures, and fractures of the vertebrae.[82]

Pamidronate and zoledronic acid are usually well tolerated. Acute-phase reactions consisting of flu-like symptoms can occur after the administration of bisphosphonates. Acute renal impairment can occur with both agents and is related to both infusion time and dose. Patients with moderate renal impairment (creatinine clearance: 30-60 mL/min [0.5-1.0 mL/s]) require renal dose adjustments of zoledronic acid, and the use of zoledronic acid is not recommended in patients with severe renal impairment.[84] This is important as patients with MM often have renal dysfunction. Osteonecrosis of the jaw (ONJ) is a serious adverse effect of bisphosphonates. ONJ is characterized by an area of exposed necrotic bone and often affects the mandible and the maxilla, but it can also affect the soft palate. The development of ONJ may be related to dental disease and tooth extraction, dependent on the dose and duration, and is more common with IV bisphosphonates (vs oral) and zoledronic acid (vs pamidronate).[81] The incidence of ONJ is unknown but may be as high as 10% in MM patients receiving zoledronic acid for extended periods. A meta-analysis found no difference between the bisphosphonate used and the incidence of ONJ.[85] Patients should be advised to have dental work completed before the initiation of bisphosphonates, if possible.

Denosumab has also been shown to reduce the incidence of myeloma skeletal-related events and is used in the prevention of myeloma bone disease. Denosumab is a monoclonal antibody directed toward RANK-L. By binding to RANK-L, denosumab prevents binding of RANK-L to RANK, reducing osteoclast activity and allowing bone formation and osteoblast function to predominate. A phase III trial evaluated the efficacy and safety of denosumab compared to zoledronic acid in patients with newly diagnosed MM.[86] Results from this study found denosumab to be noninferior to zoledronic acid in delaying time to first skeletal-related event. Rates of overall survival and ONJ were similar between groups. In an exploratory analysis of an international phase III study, denosumab showed an increase in median progression-free survival compared to zoledronic acid, which suggests that denosumab may have antimyeloma activity.[87] The results were most favorable in the subset of patients who had received PI-based triple therapy and were transplant eligible. While the risk of ONJ with denosumab and zoledronic acid is similar, the risk of renal adverse effects is higher with zoledronic acid.[86] The NCCN guidelines recommend denosumab for patients with renal disease because denosumab does not worsen renal function or require dose adjustments with renal impairment.[11]

EVALUATION OF THERAPEUTIC OUTCOMES

The goals of therapy are to prolong survival and improve quality of life. Patients with asymptomatic MM are usually observed and not treated. Asymptomatic patients are assessed every 3 to 6 months for disease progression, which would then warrant therapy. Assessment involves measurement of M protein in blood and urine and laboratory tests that include complete blood count, serum creatinine, and calcium. Patients are treated as the disease produces symptoms. Disease response is defined by a decline in M protein. After completion of the initial course of therapy and once a response is obtained, patients should be monitored every 3 months. NCCN guidelines have been updated to include assessment of MRD status after treatment. Bone surveys are performed yearly or as required because of changes in symptoms. Various other tests, including bone marrow biopsy, magnetic resonance imaging, and positron emission tomography, or computed tomography scan, are performed as needed to evaluate disease status.

CONCLUSION

MM is a cancer that occurs due to the abnormal proliferation of plasma cells. Hallmark symptoms are associated with the acronyms CRAB. While MM is an incurable disease, novel drug classes have improved response rates and overall survival compared to conventional chemotherapeutic agents. Triple regimens are often used and include dexamethasone, a PI, and an IMiD. Autologous HSCT plays a role in patients who are transplant eligible. Unfortunately, most patients will eventually experience refractory/relapsed disease where multiple agents and classes of drugs may be utilized to manage disease progression. To improve quality of life, clinicians should address and manage disease symptoms and adverse effects. Future advances in the treatment of MM depend on a better understanding of the pathophysiology of MM, identification of new drug targets, and development of new drugs.

ABBREVIATIONS

ASCO	American Society of Clinical Oncology
CAR	chimeric antigen receptor
CI	confidence interval
CR	complete remission
CRS	cytokine release syndrome
HSCT	hematopoietic stem cell transplantation
ICANS	immune effector cell-associated neurotoxicity syndrome
IκB	inhibitory factor kappa B
IFN	interferon
IGF-1	insulin-like growth factor
IgG	immunoglobulin G
IL	interleukin
IL-6	interleukin-6
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
ISS	International Staging System
LMWH	low-molecular-weight heparin
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma

MRD	minimal residual disease
mSMART	Mayo Stratification for Myeloma and Risk-Adapted Therapy
NCCN	National Comprehensive Cancer Network
NF-κB	nuclear factor kappa B
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin
PI	proteasome inhibitor
PR	partial response
RANK	receptor activator of nuclear factor-κB
RANK-L	receptor for activation of NF-κB ligand
SFC	serum-free light chains
TNF-α	tumor necrosis factor-α
VEGF	vascular endothelial growth factor
VGPR	very good partial response
VRd	bortezomib, lenalidomide, dexamethasone
VTE	venous thromboembolism

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SELF-ASSESSMENT QUESTIONS

1. Multiple myeloma is a malignancy involving which cell type?

   A. Platelets

   B. Lymphoid

   C. Plasma

   D. Myeloid

2. Which features are characteristics of myeloid-related events and suggest end-organ damage?

   A. Bone involvement, anemia, and renal insufficiency

   B. Hyperbilirubinemia, increased serum creatinine, and anemia

   C. Thrombocytopenia, hypoalbuminemia, and bone involvement

   D. Lymphocytosis, hypogammaglobulinemia, renal insufficiency

3. DM is a 57-year-old male who presents to his primary care provider for his annual well-check. He reports feeling great and he does not have any concerns. His physical assessment is unremarkable. Routine labs are drawn, and the result of his serum protein electrophoresis profile reveals 3.8 g/dL (38 g/L) monoclonal immunoglobulin in the blood. Further work-up from a bone marrow biopsy shows 30% clonal plasma cells, suggestive of smoldering myeloma. What is the recommended approach?

   A. Autologous HSCT

   B. Primary therapy with bortezomib, lenalidomide, and dexamethasone

   C. Maintenance therapy with lenalidomide

   D. Observation

4. SB is a 78-year-old female with newly diagnosed multiple myeloma. She is meeting today with her oncologist to discuss possible treatment options. SB is unable to drive and has concerns about finding rides for her appointments this winter. Which regimen consists of all oral agents, alleviating the need to travel to the infusion center?

   A. Bortezomib, lenalidomide, dexamethasone

   B. Carfilzomib, lenalidomide, dexamethasone

   C. Daratumumab, bortezomib, melphalan, prednisone

   D. Ixazomib, lenalidomide, dexamethasone

5. WR is a 52-year-old male who was recently diagnosed with high-risk multiple myeloma. Based on the risk-adapted mSMART approach, what induction regimen is preferred for WR?

   A. Cyclophosphamide, bortezomib, melphalan, dexamethasone

   B. Daratumumab, bortezomib, lenalidomide, dexamethasone

   C. Elotuzumab, lenalidomide, dexamethasone

   D. Panobinostat, carfilzomib, melphalan, prednisone

6. The preferred method of bortezomib administration is:

   A. Continuous infusion

   B. Intramuscular

   C. Oral

   D. Subcutaneous

7. A 66-year-old man is receiving ixazomib as part of his treatment regimen for multiple myeloma. Which of the following supportive medications is recommended?

   A. Antibacterial prophylaxis with levofloxacin

   B. Antifungal prophylaxis with fluconazole

   C. Antiviral prophylaxis with valacyclovir

   D. Antibacterial prophylaxis with Bactrim DS

8. Which drug is associated with cardiac and pulmonary toxicities warranting close monitoring and assessment?

   A. Lenalidomide

   B. Elotuzumab

   C. Carfilzomib

   D. Daratumumab

9. What is the optimal timing for autologous HSCT in patients with multiple myeloma?

   A. No role for autologous HSCT

   B. At the point of disease relapse following first-line therapy

   C. Following induction therapy, within 12 months of diagnosis

   D. At the point of disease relapse after failing first- and second-line therapy

10. Which of the following patients is the BEST candidate for autologous stem cell transplantation for multiple myeloma?

    A. An 82-year-old man who has received six cycles of induction therapy, complicated by sepsis and renal failure, is now in a complete response. He has ongoing significant renal insufficiency, mild dementia, and uncontrolled hypertension.

    B. A 54-year-old man who has received six cycles of induction therapy with refractory disease. No other significant comorbidities.

    C. A 73-year-old woman who completed six cycles of induction therapy, achieved a complete response, underwent an autologous stem cell transplant 4 months ago and has relapsed. She is receiving reinduction therapy cycle 2, with a partial response.

    D. A 62-year-old woman who has completed 6 months of induction therapy and is in a very good partial response. She has a past medical history of Type II diabetes, controlled with oral medications, and obesity.

11. Which agent would be most appropriate in the maintenance setting for a patient experiencing significant peripheral neuropathy following induction therapy and autologous stem cell transplant?

A. Thalidomide

B. Carfilzomib

C. Ixazomib

D. Bortezomib

12. When should allogeneic stem cell transplantation be used in patients with myeloma?

A. Upon failure of at least two prior autologous transplants

B. For patients under the age of 50 years with aggressive disease

C. For all patients under 60 years, due to the benefits of graft versus myeloma

D. Only in the context of a clinical trial

13. Which of the following adverse effects are associated with idecabtagene vicleucel treatment?

A. Cardiotoxicity

B. Cytokine release syndrome

C. Ocular toxicity

D. Peripheral neuropathy

14. LL is a 58-year-old receiving VRd for multiple myeloma. He has a past medical history of a pulmonary embolism and is considered high risk for thrombosis. What is the most appropriate venous thromboembolic agent?

A. Aspirin

B. Apixaban

C. Clopidogrel

D. Heparin

15. CS is a 57-year old with newly diagnosed MM. Her renal function is 45 mL/min (0.75 mL/s). Which is the best bone modifying agent for the prevention of skeletal-related events?

A. Pamidronate

B. Zoledronic acid

C. Denosumab

D. Calcium carbonate

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** MM is characterized by the accumulation of malignant plasma cells in the bone marrow.

2. **A.** Hypercalcemia, renal insufficiency, anemia, and bone lesions (acronym *CRAB*) are considered myeloma-defining events, and suggest end-organ damage.

3. **D.** Patients with smoldering myeloma are asymptomatic and do not warrant immediate pharmacotherapeutic treatment. Instead, the disease should be observed (watchful waiting) unless the patient is considered high-risk.

4. **D.** Ixazomib is an oral proteasome inhibitor. Thus, ixazomib, lenalidomide, dexamethasone is a completely oral triple-drug oral regimen.

5. **D.** The four-drug regimen of daratumumab, bortezomib, lenalidomide, and dexamethasone is preferred for high risk, transplant-eligible patients per mSMART guidelines. Bortezomib-based therapy is preferred for patients with high-risk characteristics determined by the mSMART criteria.

6. **D.** Subcutaneous bortezomib is more convenient and has a reduced incidence of peripheral neuropathy over intravenous bortezomib.

7. **C.** Antiviral prophylaxis against the herpes virus is recommended for patients receiving proteasome inhibitors.

8. **C.** Carfilzomib is associated with cardiac and pulmonary toxicities, including hypertension and dyspnea.

9. **C.** Available literature supports the use of autologous stem cell transplantation in patients with myeloma in their first remission, within 12 months of the completion of induction therapy. Remission does not need to be a complete remission but should represent a significant response to therapy (PR, VGPR, or CR). Patients with disease refractory to induction therapy are unlikely to benefit from transplant. Waiting to transplant until after relapse is associated with poorer outcomes when compared to transplant in first response.

10. **D.** Autologous stem cell transplant is a rigorous treatment modality that provides the best result in patients with myeloma who are in their first remission, and who have either no or few uncontrolled comorbidities. Patients who are older or have uncontrolled comorbidities, poor performance status, or fail to respond to induction therapy are unlikely to derive clinical benefit from the autologous transplant, and may experience more severe toxicities from therapy.

11. **C.** Lenalidomide, bortezomib, and ixazomib are all approved in the maintenance setting. Thalidomide and carfilzomib are not indicated for maintenance. Bortezomib and ixazomib can be used for maintenance; however, bortezomib could potentially worsen the patient's neuropathy.

12. **D.** Allogeneic stem cell transplant has limited utility in myeloma, except in cases of relapsed disease in young patients with good performance status. The risks of allogeneic transplant usually outweigh the benefits. To better understand the potential utility of this modality of therapy, it is recommended that patients considered for allogeneic transplant be referred to centers conducting clinical trials to determine the optimal use in myeloma.

13. **B.** Cytokine release syndrome is a common complication of CAR T-cell therapy. Cardiotoxicity is most associated with carfilzomib. Belantamab mafodotin has been shown to cause reversible ocular damage. Neuropathy is associated with PI therapy.

14. **B.** Therapeutic anticoagulation is warranted for patients who have a high risk of thrombosis and are receiving immunomodulatory therapy. The combination of dexamethasone with lenalidomide further increases the risk of a venous thromboembolic event. Anticoagulation with a direct oral anticoagulant is a reasonable choice for this patient. Other options would include warfarin or LMWH.

15. **C.** Both zoledronic acid and denosumab reduce the risk of skeletal complications of myeloma. Zoledronic acid, however, requires dose adjustments for mild-to-moderate renal dysfunction and is not recommended in patients with severe dysfunction. In these settings, denosumab is the preferred agent because it does not require dose adjustment for renal dysfunction and has comparable efficacy to bisphosphonates.