Relapsed or Relapsed/Refractory Multiple Myeloma

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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Abstract

Multiple myeloma (MM) is a malignant plasma cell disorder with potential secondary organ effects including renal, bone, and bone marrow effects as well as neurologic and immune dysfunction. Diagnostic evaluation of MM includes laboratory and radiologic studies along with bone marrow biopsy to confirm diagnosis. Multiple myeloma is a clonal plasma cell malignancy that results from complex interactions between malignant progenitor cells, bone marrow stromal cells, and the bone marrow microenvironment. Multiple myeloma is clinically and pathologically heterogeneous, which results in variability in treatment response and survival. The disease trajectory varies for each patient, but relapses are inevitable and many patients become refractory to treatments. Management of relapsed and refractory (RR) MM requires careful evaluation of individual patient characteristics and the course of the disease. When determining treatment options for patients with RR MM, comorbidities, the frailty and vulnerability of the patient, and the specific adverse event profile associated with each treatment should be considered, as well as the patient's goals. The goal of therapy for patients with RR MM is to achieve disease control with acceptable toxicity and quality of life, which may be accomplished with novel agents, most likely in combination regimens. The integration of these novel agents into the treatment paradigm has shifted the perception of MM from incurable to a disease that may be considered chronic in the near future with a hope for long-term survival and maintained quality of life.

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Multiple myeloma (MM) encompasses a heterogeneous group of malignant plasma cell disorders characterized by excess paraprotein secretion, secondary organ effects on the kidneys and bone, and neurologic, immune, and bone marrow dysfunction (Pingali, Haddad, & Saad, 2012; Raab, Podar, Breitkreutz, & Richardson, 2009). According to the American Cancer Society

(ACS; 2013), approximately 22,350 new cases of MM are projected to occur in 2013 (12,440 males, 9,910 females) with 10,710 deaths (6,070 males, 4,640 females), with the average age at diagnosis being 69 years (National Cancer Institute, 2013). Risk factors for MM include advanced age, male gender, obesity, and African American descent (ACS, 2013; Perrotta et al., 2013). An increased incidence of myeloma is present in persons who have been exposed to chemicals, including pesticides, arsenic, cadmium, lead, and various cleaning solutions (Perrotta et al., 2013).

The initial diagnostic evaluation of MM includes both laboratory and radiologic studies to confirm the diagnosis, determine the subtype and stage, and identify the need for immediate intervention (Kurtin, 2012; National Comprehensive Cancer Network [NCCN], 2013; Pingali et al., 2012). The diagnosis of MM is based on the level of M protein in the serum or urine, the percentage of plasma cells present in the bone marrow, and the presence or absence of end-organ damage; see Figure 1 (Dimopoulos & Terpos, 2010; Durie et al., 2006; Kuehl & Bergsagel, 2012). Treatment is indicated for patients with MM-related end-organ dysfunction, commonly described by the CRAB criteria (hypercalcemia, renal impairment, anemia, and bone disease).

The primary goal of treatment for MM is to achieve an early, deep, and durable response with an acceptable level of toxicity. Achieving a durable complete response (CR) has been associated with improved survival (Palumbo & Cavallo, 2012). However, MM is clinically and pathologically heterogeneous, resulting in variability in both response to treatment and survival. Survival can range from a few months to more than 10 years (Kumar et al., 2012). The MM disease trajectory will vary for each patient; however, relapses are inevitable, and the depth and duration of response following each relapse are generally diminished (Figure 2).

THE PATHOBIOLOGY OF MM

The Malignant Clone and Bone Marrow Microenvironment

Multiple myeloma is a diverse clonal plasma cell malignancy that results from complex interactions between malignant progenitor cells (mature B lymphocytes), bone marrow stromal cells, and the bone marrow microenvironment.

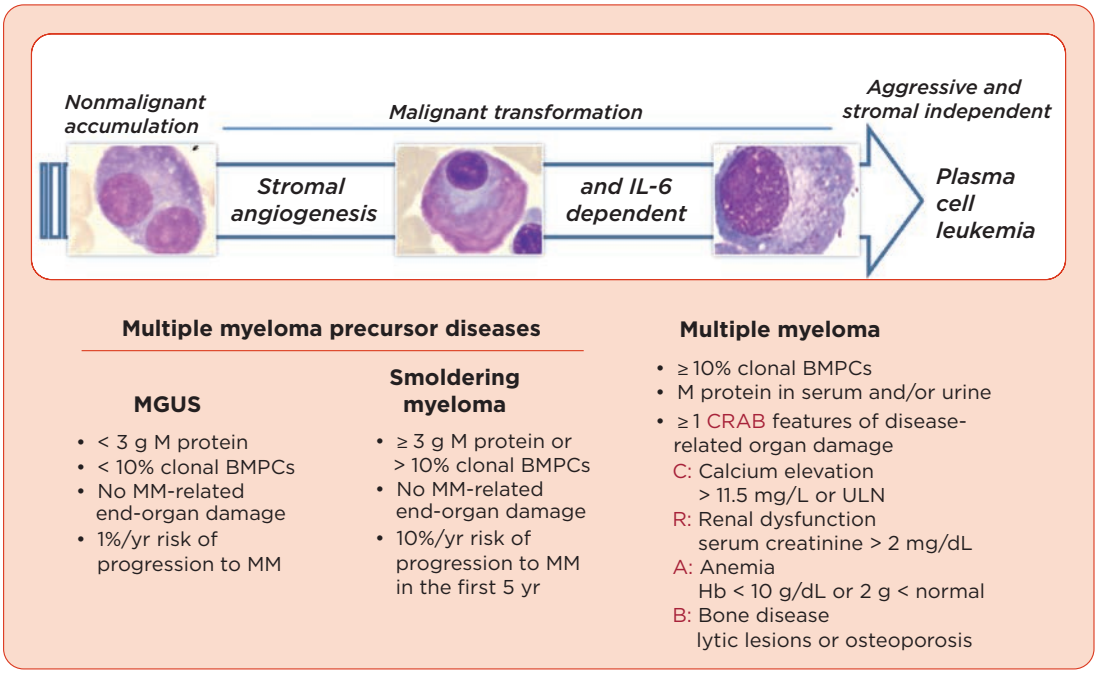

Figure 1. Multiple myeloma disease continuum and disease characteristics. IL-6 = interleukin-6; MGUS = monoclonal gammopathy of unknown significance; M protein = myeloma protein; BMPCs = bone marrow plasma cells; MM = multiple myeloma; ULN = upper limit of normal; Hb = hemoglobin. Information from Agarwal & Ghorbrial (2013); Durie et al. (2003), Kuehl & Bergsagel (2012), Vacca & Ribatti (2006). Adapted with permission from Kurtin (2010).

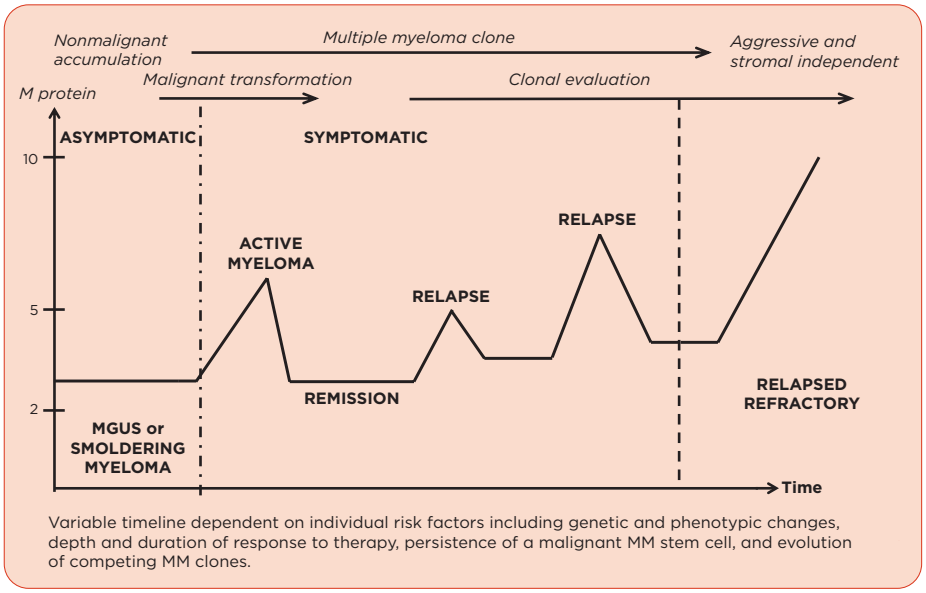

Figure 2. Multiple myeloma disease trajectory characterized by malignant transformation; serial cycles of response, remission, and relapse in the presence of treatment; and clonal evolution with diminished depth and duration of response over time. Information from Agarwal & Ghobrial (2013), Borrello (2012), Durie et al. (2003), Keats et al. (2012).

Several factors are thought to play a role in the malignant transformation of plasma cells: chromosome changes, molecular characteristics, and elements that impact the bone marrow microenvironment. Many of these factors are thought to be associated with high-risk MM, with an increased risk of relapse or progression of disease; see Table 1 (Palumbo & Anderson, 2011).

The initiation of myeloma involves genetic events and environmental factors that, when combined with the normal physiologic processes of generating antibodies and interacting with the bone marrow microenvironment, lead to immortalization of a myeloma-propagating clone (Morgan, Walker, & Davies, 2012). The bone marrow microenvironment is structured in compartments or niches comprising hematopoietic and nonhematopoietic cells. The nonhematopoietic cells include stromal cells, adhesion molecules, fibroblasts, osteoclasts, and osteoblasts. B lymphocytes, including normal plasma cells, interact with the stromal cells and the bone marrow microenvironment via various signaling pathways. Deregulation of one or more pathways as a result of genetic and phenotypic changes in the plasma cell clone leads to changes in the bone marrow microenvironment, is implicated in malignant transformation, and contributes to end organ damage (Agarwal & Ghobrial, 2013; Borrello, 2012; Keats et al., 2012). After accrual of sufficient genetic abnormalities, the deregulated plasma cell acquires a clonal advantage, evolves, and expands, contributing to relapse and progression.

A number of molecular abnormalities have been implicated in development of the propagating clone and are associated with high-risk disease (Agarwal & Ghobrial, 2013; Borrello, 2012; Keats et al., 2012; Siegel, 2012). The most common translocations involve the immunoglobulin heavy gene (IgH) locus on chromosome 14 (present in approximately 75% of patients with MM) and result in oncogene dysregulation (Borrello, 2012). Nonhyperdiploid MM, overexpression of cyclin D, and other phenotypic abnormalities—particularly deletion (17), associated with inactivation of p53; deletion (13); and abnormalities of chromosome 1, including 1p22 and 1p32 deletions—are implicated in the pathogenesis of MM and associated with high-risk disease (Borrello, 2012; Kumar et al., 2012). Fluorescence in situ hybridization (FISH) or cytogenetic analysis of t(4;14)(p16;q32), t(14:16)(q32;q23), 17p13 deletions, t(11;14)(q13;q32), chromosome 13 deletion, ploidy category, and chromosome 1 abnormalities are recommended at the initial diagnosis of MM (Fonseca et al., 2009; Kumar, 2010; Siegel, 2012). More recently, gene expression profiling (GEP) has been incorporated into clinical trials. Cytogenetic or molecular responses

Table 1. Clinical, Molecular, and Genetic Attributes Associated With Progression of Disease and High-Risk Multiple Myeloma

Risk category	Attributes	
Genetic and phenotypic events	Primary genetic events • IgH translocations ➤ t(11;14)(q13;32), t(4;14)(p16;q32), and t(14;16)(q32;q23) • Nonhyperdiploid • Cyclin D dysregulation (associated with early malignant transformation) Secondary genetic events • NRAS, KRAS, and BRAF mutations • NF-κB pathway mutations • p53, PTEN, and RB inactivation Other genetic events • Secondary translocations • Copy number abnormalities • HOXA9 overexpression • mRNA changes • Myc regulation Phenotypic changes • Increased RANKL/OPG ratio: osteoclast activation • Increased DKK1 activity: osteoblast inhibition • Increased homing of MM to BMSC niche • Increased immune invasion • Cytokine and growth factor changes	
Cytogenetic abnormalities, involved oncogene and clinical significance	t(4;14)	RB-1: cell cycle regulator FGFR3: growth factor receptor tyrosine kinase MMSET: transcriptional regulator TACC3: unknown Cyclin D2: cell cycle regulator
	t(14;16)	c-MAF: transcription factor
	17p deletion	p53: cell cycle regulator; DNA repair
	Chromosome 1 abnormalities	KRAS: signal transduction regulator NRAS gene mutations: cell cycle regulator
	t(11;14)	Cyclin D1: cell cycle regulator MYEOV: unknown
Patient-related factors	Complex comorbidities/HCT-CI > 3 Vulnerability Limited caregiver support	
Treatment-related factors	Primary refractory disease Irreversible treatment-related adverse events	

Note. IgH = immunoglobulin heavy gene; NRAS = neuroblastoma RAS viral (v-ras) oncogene homolog; KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; BRAF = v-Rafmurine sarcoma viral oncogene homolog B1; NF-κB = nuclear factor κB; p53 = protein 53; PTEN = phosphatase and tensin homolog; RB-1 = retinoblastoma protein-1; HOXA9 = homeobox protein A9; RANKL = receptor activator of NF-κB ligand; OPG = osteoprotegerin; DKK1 = Dickkopf-related protein 1; MM = multiple myeloma; BMSC = bone marrow stromal cells; FGFR3 = fibroblast growth factor receptor 3; MMSET = multiple myeloma SET domain; TACC3 = transforming, acidic coiled-coil-containing protein 3; c-MAF = v-maf musculoaponeurotic fibrosarcoma oncogene homolog (avian); c-myc = v-myc myelocytomatosis viral oncogene homolog (avian); MYEOV = myeloma overexpressed; HCT-CI = hematopoietic stem cell comorbidity index. Information from Agarwal & Ghobrial (2013), Borrello (2012), Dimopoulos & Terpos (2010), Kurtin (2010), Siegel (2012).

are not currently incorporated into the response criteria for MM, thus repeat cytogenetics, FISH, or GEP profiles are not routinely used to evaluate response outside of the clinical trial or bone marrow transplant settings (Siegel, 2012).

Adhesion molecules promote homing of the MM cells to the bone marrow stroma and subsequent cytokine and growth factor production (Borrello, 2012). The malignant MM clone is also capable of autocrine production of cytokines. These

cytokines promote tumor progression through activation of intracellular pathways, confer a survival advantage to the malignant clone, and contribute to bone involvement and other secondary organ effects common in MM (Siegel, 2012). Interleukin-6 (IL-6) is implicated in the pathogenesis of MM and is thought to confer a proliferative and antiapoptotic advantage that increases treatment resistance and contributes to the pathogenesis of myeloma bone disease and an increased risk of thrombosis (Borrello, 2012; Palumbo & Anderson, 2011).

Tumor necrosis factor–alpha (TNF-α) plays an important role in inflammatory response and bone resorption and is associated with a number of secondary effects that may confer a survival advantage to MM cells, contribute to osteolytic bone disease, and increase the activation of other signaling pathways associated with more aggressive and treatment-resistant disease (Siegel, 2012). Positive cell adhesion-mediated and cytokine-mediated feedback loops support survival of the myeloma clone and can mediate drug resistance. For the patient with RR MM, selection of novel therapies that exploit these highly dysregulated attributes is critical to effective treatment.

Clinical Implications

Inclusion of genetic and phenotypic findings in the original diagnostic evaluation of MM is critical to personalized risk-adapted treatment selection. A number of these attributes are associated with high-risk MM and thought to play a role in decreased survival (Fonseca et al., 2009; Siegel, 2012). Several studies suggest achieving a durable CR is most important in patients with high-risk disease (Durie, 2010; Harousseau, Attal, & Avet-Loiseau, 2009); however, despite achievement of CR, MM remains an incurable disease for the majority of patients. The novel agents bortezomib (Velcade), lenalidomide (Revlimid), carfilzomib (Kyprolis), and pomalidomide (Pomalyst), used in combination with established therapies, including hematopoietic stem cell transplantation (HSCT), are able to neutralize some of these high-risk features and improve outcomes (Richardson et al., 2010). As patients with MM are surviving longer than ever before, patients will be exposed to more MM therapies during the course of their disease.

A percentage of MM patients do not respond to first-line novel agents, and many are not eligible for HSCT, which is the only potentially curative option in MM. Relapse or progression is inevitable for the majority of patients, including those who respond to first-line therapies. Patients who fail first-line proteasome inhibitors or immunomodulatory drugs (IMiDs) have been shown to have poor overall survival, with an average life expectancy of 9 months from the time of becoming refractory to proteasome inhibitors and IMiDs (Kumar et al., 2012).

Responses to RR MM treatment are characteristically short, with a median survival as brief as 6 months (Richardson et al., 2010). Patients with relapsed or relapsed refractory disease represent a heterogeneous population with unique clinical considerations. Effective management of RR MM requires an understanding of the pathobiology of MM, including high-risk features, currently available therapies for all phases of the disease, and the key elements of risk-adapted treatment selection in the RR MM setting, including clinical management of adverse events.

MANAGEMENT OF RELAPSED AND REFRACTORY MULTIPLE MYELOMA TODAY

Relapsed and Refractory Disease

The RR MM population varies based on the type of relapse (early vs. late, or multiple relapses) and the number and types of treatment regimens used. The selection of salvage therapy in this group of patients should be based on careful analysis of individual patient disease characteristics and treatment history (Fonseca et al., 2009). It is essential to understand the definition within the RR MM disease category. The International Myeloma Working Group response criteria and the European Group for Blood and Bone Marrow Transplant include standard definitions for disease progression; see Table 2 (Blade et al., 1998; Durie et al., 2006). Progression of disease is implied in the term "relapsed." The phrase "relapse from complete remission" is used to describe a patient who develops clinically measurable disease or secondary organ effects after achieving a CR, while "progression" is used to describe a patient who has developed clinically measurable signs of increased disease activity after achieving a partial response (PR) or disease plateau (Anderson et al., 2008; Siegel, 2012). Relapsed and refractory disease is defined as either a lack of response or disease progression on or within 60 days of the last

Table 2. International Myeloma Working Group Response Criteria[a]

sCR	CR as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR	Negative immunofixation on the serum and urine plus disappearance of any soft-tissue plasmacytomas and < 5% plasma cells in bone marrow
VGPR	Serum and urine M protein detectable by immunofixation but not by electrophoresis or ≥ 90% reduction in serum M protein plus urine M protein level < 100 mg/24 hr
PR	≥ 50% reduction of serum M protein and reduction in 24-hr urinary M protein by ≥ 90% or to < 200 mg/24 hr. If serum and urine M protein are not measurable: ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required AND if serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of soft-tissue plasmacytomas is also required
MR[b]	All of the following: 25%–49% reduction in serum M protein; 50%–89% reduction in urinary light chain excretion; 25%–49% reduction in the size of soft tissue plasmacytomas; no increase in the size or number of lytic bone lesions; and 25%–49% reduction in plasma cells (for patients with nonsecretory myeloma only)
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD	≥ 25% increase from lowest response value in any 1 or more of M component (serum or urine), difference between involved and uninvolved FLC, bone marrow plasma cell percentage, new bone lesions/plasmacytomas or increase in size of existing lesions/plasmacytomas, hypercalcemia that can be attributed solely to myeloma

Note. sCR = stringent complete response; CR = complete response; FLC = free light chain; VGPR = very good partial response; M protein = myeloma protein; PR = partial response; MR = minimal response; SD = stable disease; PD = progressive disease.
[a]Adapted from Durie et al. (2006). [b]MR from Blade et al. (1998).

therapy (Anderson et al., 2008). Patients with primary refractory disease have failed to achieve any response to initial MM treatments, often a combination regimen of two or three novel agents. These patients should be encouraged to participate in a clinical trial because they have very high-risk disease and poor prognosis.

Characteristics of the Relapsed/Refractory Patient

The traditional measures of eligibility for clinical trials have relied on estimates by clinicians of functional and/or performance status (PS), considering activities of daily living and independent activities of daily living (Oken et al., 1982; Schag, Heinrich, & Ganz, 1984). Similar approaches are used in treatment of patients outside of the clinical trial setting. Performance status information is garnered from both assessment of the patient as well as discussion with the patient and family.

Frailty and vulnerability has been found to correlate with unfavorable outcome. Palumbo and colleagues (Palumbo et al., 2011) introduced the concept of vulnerability, which incorporates evaluation of PS, frailty, and comorbidities. The evaluation of vulnerability is considered critical to the risk-adapted treatment selection for MM patients being considered for HSCT. The hematopoietic stem cell comorbidity index (HCT-CI) attributes numerical scores to 17 different categories of organ dysfunction associated with unfavorable outcomes in the HSCT population; see Table 3 (Sorror, 2013). A HCT-CI score greater than 3 is associated with inferior nonrelapsed mortality in the HSCT population. However, patients may have a better PS because their disease is not as aggressive, which may result in selection bias for HSCT. Multiple myeloma remains the most common diagnosis referred for autologous HSCT (auto-HSCT), and many patients with RR MM have undergone at least one auto-HSCT. Thus, a similar approach to selecting treatment in the RR MM population should incorporate assessment of comorbidities with consideration of the available salvage therapies and their specific adverse event profiles.

Table 3. Hematopoietic Stem Cell Transplant Comorbidity Index

Comorbidity	Definition	Weight
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiovascular comorbidity	Coronary artery disease, congestive heart failure, myocardial infarction, or EF < 50%	1
Inflammatory bowel disease	Chronic disease or ulcerative colitis	1
Diabetes or steroid-induced hyperglycemia	Diabetes or steroid-induced hyperglycemia requiring insulin or an oral hypoglycemic drug	1
Cerebrovascular disease	Transient ischemic attacks or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1
Obesity	Body mass index > 35 kg/m^2	1
Infection	Documented infection or fever of unknown origin or pulmonary nodules of fungal pneumonia or prophylaxis against tuberculosis	1
Rheumatologic	SLE, RA, polymyositis, mixed connective tissue disease, polymyalgia rheumatic	2
Peptic ulcer	Presence of prior endoscopic or radiologic diagnosis	2
Renal, moderate/severe	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Pulmonary, moderate	DLco and/or FEV_1 66%–80% or dyspnea on slight activity	2
Prior malignancies	Treated at any time, excluding nonmelanoma skin cancer	3
Heart valve disease	Moderate to severe degree of valve stenosis, prosthetic mitral or aortic valve, or systematic mitral valve prolapse	3
Pulmonary, severe	DLco and/or FEV_1 < 66% or dyspnea at rest or requiring oxygen	3
Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3

Note. EF = ejection fraction; ULN = upper limit of normal; AST = aspartate transaminase; ALT = alanine transaminase; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; DLco = percentage of measured-to-predicted diffusion capacity of carbon monoxide; FEV_1 = percentage of measured-to-predicted forced expiratory volume in 1 second. Adapted from Sorror (2013).

Treatment Selection for RR MM

Management of RR MM requires careful evaluation of each individual patient to include the characteristics of disease at the time of original diagnosis, changes in disease characteristics over time, treatment history and response, and individual patient characteristics (Table 4). Treatment in the RR MM setting is considered to be salvage therapy; however, patients who have received limited prior therapies may benefit from a number of available novel agents or combinations that are used in the first-line setting (Eshaghian & Berenson, 2012; van de Donk et al., 2011). The goal of salvage therapy in the RR MM population is to achieve disease control with acceptable toxicity and an acceptable or improved quality of life. Treatment should continue until disease progression or unacceptable toxicity and with consideration of the patient's wishes. Care should be used in selecting agents based on transplant eligibility and residual toxicities. The depth and duration of response to prior therapies should be evaluated. Patients who have failed or are intolerant to first-line novel agents—specifically lenalidomide or bortezomib—should be considered for the newly approved novel agents carfilzomib and pomalidomide (see Table 5; NCCN, 2013).

Given the number of emerging treatment options, including combinations using novel agents currently approved as single agents, avoiding irreversible toxicities that may prevent benefit from these treatments is imperative. Supportive care, including bisphosphonate therapy for bone health, infection prophylaxis, nutritional

Table 4. Clinical Considerations in the Selection of Treatment for Relapsed and Relapsed/Refractory Multiple Myeloma

Time from prior therapy to relapse/progression:
- Long-term remission or short front-line treatment duration: May use similar agents
- Relapse < 6 mo or progression while on therapy: Consider alternative agents in combination

Reassess transplant options:
- Prior ASCT: Second ASCT if TTP > 2 yr
- Additional novel therapies as a bridge to HSCT
- Allogeneic stem cell transplant can be considered for high-risk patients only in the setting of a clinical trial

Select agents or regimens based on:
- Prior therapy response, duration of response, tolerance, and current clinical status
- Incorporation of novel agents is recommended for high-risk disease
- Comorbidity profile:
  - Uncontrolled diabetes
  - Dose modify dexamethasone
  - Cardiopulmonary disease, including active or poorly controlled congestive heart failure, pulmonary hypertension, or pulmonary edema
    - Consider lenalidomide, pomalidomide, or thalidomide
  - Neuropathy
    - Consider carfilzomib, lenalidomide, pomalidomide
  - Renal impairment
    - Consider bortezomib, carfilzomib, pomalidomide, thalidomide
  - Current or previous thromboembolic disease
    - Consider bortezomib, carfilzomib
  - Continuing immunomodulatory agents may be considered for patients with non–life-threatening thromboembolic disease with continued therapeutic anticoagulation

Relapsed/refractory disease:
- Disease may be clonally distinct from earlier disease (new mutations)
- Consider clinical trial or newly FDA-approved agents: pomalidomide or carfilzomib

Note. ASCT = autologous stem cell transplant; TTP = time to progression; HSCT = hematopoietic stem cell transplant; FDA = US Food and Drug Administration. Information from Jakubowiak (2012), Moreau (2012), NCCN (2013), Richardson et al. (2010).

support, and maintenance of physical activity, should continue for all patients with MM (Snowden et al., 2011).

CONCLUSIONS AND FUTURE CHALLENGES

The integration of novel agents into the treatment of MM offers the possibility of long-term survival and quality of life (Kumar et al., 2008; Jordan et al., 2013). Patients with RR MM present a unique challenge requiring careful consideration of specific disease, treatment, and individual attributes (Jakubowiak, 2012; Moreau, 2012; Palumbo et al., 2011; Palumbo & Anderson, 2011; Siegel, 2012; van de Donk et al., 2011). Maintaining familiarity with the patient over the course of their disease is optimal but not always possible.

Ongoing evaluation of response requires working knowledge of the pathobiology of MM, clinical findings, current criteria for evaluation of response, and secondary options for treatment. Proteasome inhibitors and IMiDs are the backbone of current standard therapies for the treatment of MM. Recent trials and next-generation agents, including carfilzomib and pomalidomide, are particularly important for patients with relapsed and refractory disease. The advanced practice provider (APP) in oncology plays an integral role in managing patients with MM over the course of their disease, monitoring response to treatment, and identifying progression or relapse. Familiarity with emerging therapies will assist the APP in the early identification and treatment of common adverse events and improve patient care.

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Table 5. FDA-Approved Options for Salvage Treatment in Patients With Relapsed or Refractory Multiple Myeloma Based on Selected Clinical Trials

Preferred regimens[a]

Proteasome inhibitor–containing regimens

Bortezomib
- Bortezomib
- Bortezomib/liposomal doxorubicin
- Lenalidomide/bortezomib/dexamethasone (RVD)
- Bortezomib/dexamethasone
- Bortezomib/thalidomide/dexamethasone
- Cyclophosphamide/bortezomib/dexamethasone (CyBorD)
- Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide, and bortezomib (VTD-PACE)

Carfilzomib
- Indicated as a single agent for patients with MM who have received 2 prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy

Immunomodulatory agent–containing regimens

Lenalidomide
- Lenalidomide/bortezomib/dexamethasone (RVD)
- Lenalidomide/low-dose dexamethasone (Rd) (category 1)
- Cyclophosphamide, lenalidomide, dexamethasone (CRD)

Pomalidomide
- Indicated for patients with MM who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy

Thalidomide
- Thalidomide/dexamethasone

Other regimens

- Dexamethasone/cyclophosphamide/etoposide and cisplatin (DCEP)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide and etoposide (DT-PACE)
- High-dose cyclophosphamide

Note. Information from NCCN (2013), Onyx Pharmaceuticals (2012, 2013).
[a]Regimens to consider after preferred regimens: bendamustine; bortezomib/vorinostat; and lenalidomide/bendamustine/dexamethasone

DISCLOSURE

Ms. Kurtin has acted as a consultant for Onyx, Celgene, and Millennium.

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