Multiple Myeloma: Diagnosis and Treatment

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) list the criteria for diagnosis of multiple myeloma and related disorders; (2) identify high-risk prognostic markers for multiple myeloma and smoldering multiple myeloma; and (3) summarize the approach to treatment of multiple myeloma.

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Abstract

The diagnosis and treatment of multiple myeloma has changed dramatically in the past decade. The disease definition has been updated to include highly specific biomarkers in addition to established markers of end-organ damage. The staging system has been revised to combine both measures of tumor burden and disease biology. Advances in therapy have resulted in a marked improvement in overall survival. New drugs introduced in the past few years include carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab. In this review, we outline the current approach to the diagnosis, prognosis, and management of multiple myeloma.

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Multiple myeloma (MM) is a clonal plasma cell malignant neoplasm that accounts for approximately 10% of hematologic malignant disorders.[1,2] The annual incidence, age-adjusted to the 2000 US population, is 4.3 per 100,000, resulting in over 20,000 new patients in the United States each year.[3] Multiple myeloma is twice as common in blacks compared with whites, and this racial disparity is related to the higher prevalence of monoclonal gammopathy of undetermined significance (MGUS) in blacks.[4,5] There is a slight male predominance. The median age at onset is 66 years, and only 2% of patients are younger than 40 years of age at diagnosis.[6]

Multiple myeloma evolves from a premalignant condition clinically recognized as MGUS.[7] Monoclonal gammopathy of undetermined significance is present in 3% to 4% of the general population older than 50 years.[8,9] Because MGUS is mostly asymptomatic and detected often as an incidental laboratory finding, only 10% of patients with newly diagnosed MM have a history of preexisting MGUS. However, studies have found that MGUS almost always precedes MM and is associated with a risk of

progression to MM of approximately 1% per year.[7,10] Smoldering MM (SMM) is an intermediate stage between MGUS and MM and is associated with a higher risk of progression of approximately 10% per year.[11]

Until 2000, the mainstay of therapy for MM was use of alkylators and corticosteroids[12] and in selected patients, high-dose chemotherapy with autologous stem cell transplant (ASCT).[13,14] Subsequently, thalidomide,[15] bortezomib,[16] and lenalidomide[17] emerged as effective agents and greatly improved clinical outcome.[18,19] More recently, carfilzomib, pomalidomide, panobinostat, daratumumab, ixazomib, and elotuzumab have been approved in the United States for the treatment of MM, substantially expanding the number of treatment regimens available for patients in all stages of the disease.

DIAGNOSIS

The most common presenting symptoms of MM are fatigue and bone pain.[6] Anemia occurs in approximately 75% of patients and contributes to fatigue. Osteolytic skeletal lesions can be detected in approximately 80% of patients. Other common findings at presentation include hypercalcemia (15%) and elevated serum creatinine level (≥2 mg/dL) (20%).[6] Approximately 1% to 2% of patients with MM have extramedullary disease (EMD) at the time of initial diagnosis, and 8% have development of EMD later in the disease course.[20]

A monoclonal (M) protein in the serum or urine is a cardinal feature of MM but is seen in only 82% of patients on serum protein electrophoresis.[6] The sensitivity increases to 93% when serum immunofixation is added and to 97% with the addition of either the serum free light chain (FLC) assay or 24-hour urine studies.[21] Thus, if MM is suspected, the recommended screening strategy is serum protein electrophoresis, serum immunofixation, and either a serum FLC assay or 24-hour urinary protein electrophoresis with immunofixation. The M protein type is IgG in approximately 50%, IgA in 20%, immunoglobulin light chain only in 20%, IgD in 2%, and IgM in 0.5%.[6] About 2% to 3% of MM has no detectable M protein and is referred to as nonsecretory MM.[22]

The baseline diagnostic work-up required for the diagnosis of MM includes a complete blood cell count, measurement of serum calcium and creatinine levels, serum and urinary protein electrophoresis with immunofixation, serum FLC assay, and bone marrow examination. In addition, low-dose whole-body computed tomography or [18F]-fluorodeoxyglucose–positron emission tomography/computed tomography or, at minimum, plain radiography of the entire skeleton are required to detect osteolytic bone lesions.[23] The osteolytic bone lesions in MM exhibit no new bone formation, and nuclear medicine bone scans are therefore not helpful.[24] Magnetic resonance imaging of the whole body or spine/pelvis is needed in patients with suspected SMM and whenever the diagnosis of MM is in doubt to look for focal bone marrow lesions.[25] Magnetic resonance imaging is also often needed in patients with osteolytic bone disease involving the spine to rule out cord compression and to determine the need for interventional procedures such as vertebroplasty or kyphoplasty.

DISEASE DEFINITION

In 2014, the International Myeloma Working Group updated the diagnostic criteria for MM and related disorders (Table 1).[1] The main revision was to add 3 highly specific biomarkers (clonal bone marrow plasma cells ≥60%, serum FLC ratio ≥100, and >1 focal lesion on magnetic resonance imaging) to existing markers of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) that were used to diagnose the disease. The updated criteria represent a paradigm shift because they allow early diagnosis and initiation of therapy before end-organ damage. As shown on Table 1, the diagnosis of MM requires 10% or more plasma cells on bone marrow examination or a biopsy-proven plasmacytoma plus one or more myeloma-defining events. The major differential diagnosis of MM includes MGUS, SMM, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.

MOLECULAR CLASSIFICATION

Although MM is still considered a single disease, it is in reality a collection of several different cytogenetically distinct plasma cell malignant neoplasms (Table 2).[26,27] On fluorescence in situ hybridization studies of the bone marrow, approximately 40% of MM cases are characterized by the presence of trisomies in the neoplastic plasma cells (trisomic MM), while most of the

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TABLE 1. International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma and Related Plasma Cell Disorders

Disorder	Disease definition
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	All 3 criteria must be met: • Serum monoclonal protein (non-IgM type) <3 g/dL • Clonal bone marrow plasma cells <10%[a] • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Smoldering multiple myeloma	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥3 g/dL, or urinary monoclonal protein ≥500 mg/24 h and/or clonal bone marrow plasma cells 10%-60% • Absence of myeloma defining events or amyloidosis
Multiple myeloma	Both criteria must be met: • Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma • Any one or more of the following myeloma defining events: ○ Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: ▪ Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) ▪ Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >177 μmol/L (>2 mg/dL) ▪ Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL ▪ Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) ○ Clonal bone marrow plasma cell percentage ≥60% ○ Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved FLC level must be ≥100 mg/L) ○ >1 Focal lesion on magnetic resonance imaging (MRI) studies (at least 5 mm in size)
IgM monoclonal gammopathy of undetermined significance (IgM MGUS)	All 3 criteria must be met: • Serum IgM monoclonal protein <3 g/dL • Bone marrow lymphoplasmacytic infiltration <10% • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder
Light chain MGUS	All criteria must be met: • Abnormal FLC ratio (<0.26 or >1.65) • Increased level of the appropriate involved light chain (increased κ FLC in patients with ratio >1.65 and increased λ FLC in patients with ratio <0.26) • No immunoglobulin heavy chain expression on immunofixation • Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder • Clonal bone marrow plasma cells <10% • Urinary monoclonal protein <500 mg/24 h
Solitary plasmacytoma	All 4 criteria must be met: • Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Normal bone marrow with no evidence of clonal plasma cells • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder
Solitary plasmacytoma with minimal marrow involvement[b]	All 4 criteria must be met: • Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Clonal bone marrow plasma cells <10% • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

[a]A bone marrow biopsy can be deferred in patients with low-risk MGUS (IgG type, M protein <15 g/L, normal FLC ratio) in whom there are no clinical features concerning for myeloma.
[b]Solitary plasmacytoma with 10% or more clonal plasma cells is considered as multiple myeloma.
From *Lancet Oncol*.[1]

TABLE 2. Primary Molecular Cytogenetic Classification of Multiple Myeloma

Subtype	Gene(s)/chromosomes affected[a]	Percentage of myeloma patients
Trisomic multiple myeloma	Trisomies of one or more odd-numbered chromosomes	42
IgH translocated multiple myeloma		30
t(11;14) (q13;q32)	*CCND1* (cyclin D1)	15
t(4;14) (p16;q32)	*FGFR3* and *MMSET*	6
t(14;16) (q32;q23)	*C-MAF*	4
t(14;20) (q32;q11)	*MAFB*	<1
Other IgH translocations[a]	*CCND3* (cyclin D3) in t(6;14) multiple myeloma	5
Combined IgH translocated/trisomic multiple myeloma	Trisomies plus any one IgH translocation	15
Isolated monosomy 14		4.5
Other cytogenetic abnormalities in absence of IgH translocations or trisomy or monosomy 14		5.5
Normal		3

[a]Includes the t(6;14)(p21;q32) translocation and, rarely, other IgH translocations involving uncommon partner chromosomes.
Adapted from *Blood*.[26]

rest have a translocation involving the immunoglobulin heavy chain (IgH) locus on chromosome 14q32 (IgH translocated MM).[28-31] A small proportion of patients have both trisomies and IgH translocations. Trisomies and IgH translocations are considered primary cytogenetic abnormalities and occur at the time of establishment of MGUS. In addition, other cytogenetic changes termed *secondary cytogenetic abnormalities* arise along the disease course of MM, including gain(1q), del(1p), del(17p), del(13), *RAS* (for expansion of gene symbols, see www.genenames.org) mutations, and secondary translocations involving *MYC*. Both primary and secondary cytogenetic abnormalities can influence disease course, response to therapy, and prognosis (Table 3).[27]

PROGNOSIS AND RISK STRATIFICATION

Although median survival in patients with MM is approximately 5 to 7 years, there is major variation in survival depending on host factors, tumor burden (stage), biology (cytogenetic abnormalities), and response to therapy.[32] Tumor burden in MM has traditionally been assessed using the Durie-Salmon staging system[33] and the International Staging System (ISS).[34,35] Disease biology is best reflected on the basis of the molecular subtype of MM and the presence or absence of secondary cytogenetic abnormalities (Table 4).[26,36] The revised ISS combines elements of tumor burden (ISS) and disease biology (presence of high-risk cytogenetic abnormalities or elevated lactate dehydrogenase level) to create a unified prognostic index that helps in clinical care as well as in comparison of clinical trial data (Table 5).[37]

Importantly, to ensure uniform availability, only 3 widely available cytogenetic markers are used in the revised ISS; the Mayo Stratification for Myeloma and Risk-Adapted Therapy (Table 4) has additional detail that is valuable in formulating a therapeutic strategy.[38] Ideally, to complete accurate molecular classification and risk stratification, we recommend fluorescence in situ hybridization probes to detect trisomies, IgH translocations, *MYC* translocations, and abnormalities of chromosomes 1, 13, and 17.[27]

TREATMENT

The approach to treatment of newly diagnosed MM is outlined in the Figure. The most important phases of therapy are initial therapy, stem cell transplant (if eligible), consolidation/maintenance therapy, and treatment of relapse. Transplant-eligible patients typically receive approximately 4 cycles of initial therapy followed by stem cell collection and ASCT. Selected patients with standard-risk MM who respond well to induction can opt for delayed ASCT; in this strategy, stem cells are collected after 4 cycles of initial therapy and cryopreserved for future use (Figure). Transplant-ineligible patients are usually treated for 12 to 18 months. Following initial therapy and/or ASCT, consideration should be given to consolidation/maintenance therapy. The choice of maintenance and duration of therapy is often driven by the presence or absence of high-risk cytogenetic features.

Tables 6 and 7 list the major drugs used in the treatment of MM. The most common treatment regimens used in MM are listed in Table 8.[39-59] Results of recent randomized trials using new active agents for MM are provided in Table 9.[60-63]

Initial Therapy

Initial therapy for MM varies across countries depending on drug availability. The most

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TABLE 3. Cytogenetic Abnormalities on Clinical Course and Prognosis in Multiple Myeloma

Cytogenetic abnormality	Clinical setting in which abnormality is detected	
	Smoldering multiple myeloma	Multiple myeloma
Trisomies	Intermediate risk of progression, median TTP of 3 years	Good prognosis, standard-risk MM, median OS 7-10 years Most have myeloma bone disease at diagnosis Excellent response to lenalidomide-based therapy
t(11;14) (q13;q32)	Standard risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7-10 years
t(6;14) (p21;q32)	Standard risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7-10 years
t(4;14) (p16;q32)	High risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years Needs bortezomib-based initial therapy, early ASCT (if eligible), followed by bortezomib-based consolidation/ maintenance
t(14;16) (q32;q23)	Standard risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years Associated with high levels of FLC and 25% present with acute renal failure as initial MDE
t(14;20) (q32;q11)	Standard risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years
gain(1q21)	High risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years
del(17p)	High risk of progression, median TTP of 2 years	High-risk MM, median OS 3 years
Trisomies plus any one of the IgH translocations	Standard risk of progression, median TTP of 5 years	May ameliorate adverse prognosis conferred by high-risk IgH translocations and del(17p)
Isolated monosomy 13, or isolated monosomy 14	Standard risk of progression, median TTP of 5 years	Effect on prognosis is not clear
Normal	Low risk of progression, median TTP of 7-10 years	Good prognosis, probably reflecting low tumor burden, median OS >7-10 years

ASCT = autologous stem cell transplant; FLC = free light chain; MDE = myeloma-defining event; MM = multiple myeloma; OS = overall survival; TTP = time to progression.
From *Blood Cancer J.*[27]

common regimens used in the treatment of newly diagnosed MM are lenalidomide plus dexamethasone (Rd), bortezomib, lenalidomide, and dexamethasone (VRD), bortezomib, thalidomide, and dexamethasone (VTD), and bortezomib, cyclophosphamide, and dexamethasone (VCD). In a recent randomized trial conducted by the Southwest Oncology Group, progression-free survival (PFS) and overall survival (OS) were significantly superior with VRD compared with Rd (Table 9).[61] Other studies have reported superior response rates and PFS with VTD compared with other doublet regimens.[49,64] A recent randomized trial also found that the triplet regimen of VTD, which contains a proteasome inhibitor (bortezomib) and an immunomodulatory agent (thalidomide), is superior to VCD (Table 9).[62] On the basis of these data, VRD or VTD are the preferred regimens for initial therapy in transplant-eligible patients and in fit transplant-ineligible patients (Figure).

The low-dose dexamethasone regimen (40 mg once a week) is preferred in all regimens (Rd, VRD, VTD, VCD, etc) to minimize toxicity. In a randomized trial conducted by the Eastern Cooperative Oncology Group, the low-dose

TABLE 4. Mayo Clinic Risk Stratification for Multiple Myeloma

Risk group	Percentage of newly diagnosed patients with the abnormality
Standard risk	75
Trisomies	
t(11;14)	
t(6;14)	
Intermediate risk	
t(4;14)	10
gain(1q)	
High risk	
t(14;16)	
t(14;20)	15
del(17p)	

Adapted from *Am J Hematol*.[2]

dexamethasone approach was associated with superior OS and significantly lower toxicity.[42] Similarly, the once-weekly subcutaneous schedule of bortezomib is preferred in all regimens. Studies have revealed that the neurotoxicity of bortezomib can be greatly diminished by administering bortezomib once a week instead of twice weekly[47,48] and by administering the drug subcutaneously instead of intravenously.[65] The regimens listed in Table 8 reflect these recommendations to lower the dose of dexamethasone and bortezomib from what was used in many of the initial trials. Higher doses of dexamethasone and twice-weekly bortezomib can be considered if a rapid response is desired, as in the case of patients with acute renal failure due to cast nephropathy, extensive EMD, plasma cell leukemia, or impending cord compression.[2]

TABLE 5. Revised International Staging System for Myeloma

Stage	Frequency (% of patients)	5-Year survival rate (%)
Stage I	28	82
• ISS stage I (serum albumin >3.5 g/dL, serum β_2-microglobulin <3.5 mg/L) and		
• No high-risk cytogenetics		
• Normal lactate dehydrogenase		
Stage II	62	62
• Neither stage I or III		
Stage III	10	40
• ISS stage III (serum β_2-microglobulin >5.5 mg/L) and		
• High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated lactate dehydrogenase		

From *J Clin Oncol*.[37]

Frail, Elderly Patients. Patients who are 75 years of age or older or are frail may not tolerate a triplet regimen.[66] In these patients, Rd is a reasonable choice for initial therapy, especially for standard-risk patients. In a large randomized trial, Rd was found to be superior to melphalan, prednisone, and thalidomide (Table 9).[67] The use of melphalan-containing regimens such as melphalan, prednisone, and thalidomide and bortezomib, melphalan, and prednisone has decreased considerably, and they are recommended only if other regimens are not available. If Rd is chosen, data indicate that it should be administered until progression.[67] This may not be feasible in many countries or in patients with limited insurance or financial means. In these circumstances, a limited duration (12-18 months) of a triplet therapy such as VCD can be a reasonable option; in our opinion, VCD is a better tolerated, more predictable alternative to bortezomib, melphalan, and prednisone.

High-Risk Myeloma. The triplet regimen of carfilzomib, lenalidomide, and dexamethasone (KRD) has had high activity in phase 2 trials, with stringent complete response rates and minimal residual disease (MRD)–negative rates that appear superior to historical results with VRD.[68] However, these are nonrandomized comparisons, and there are concerns about cardiac toxicity in a small proportion of patients with carfilzomib. Further, KRD is more cumbersome and expensive compared with VRD. Thus, we recommend the use of KRD at this point only to patients with high-risk MM in whom it may be reasonable to administer a regimen with the highest possible complete response rates and based on data from a relapsed MM trial that suggest a possible advantage of carfilzomib over bortezomib.[69]

Acute Renal Failure Due to Cast Nephropathy. The diagnosis of light chain cast nephropathy can be made presumptively if the circulating FLC levels are high in the presence of MM and acute renal

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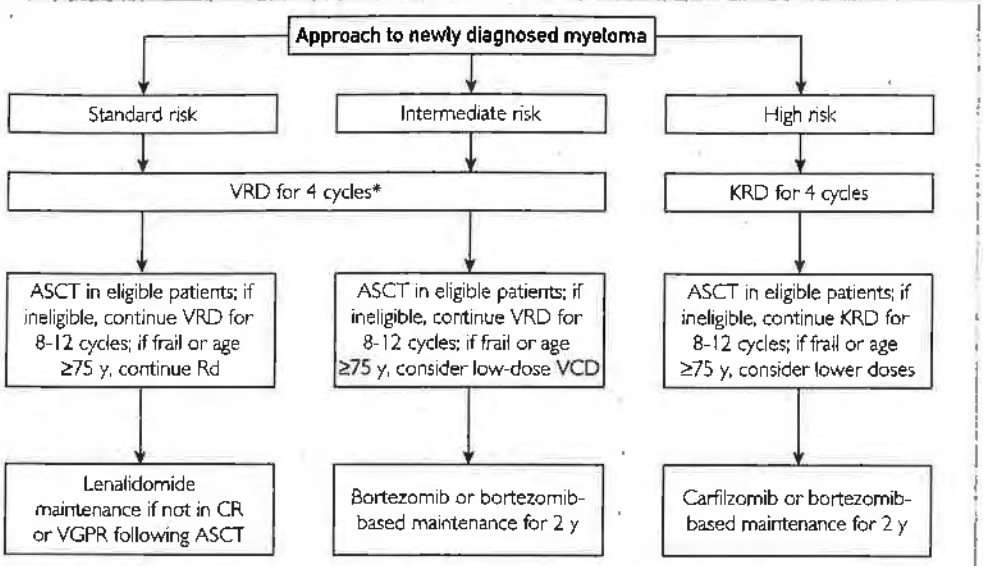

FIGURE. Approach to the treatment of newly diagnosed multiple myeloma. ASCT = autologous stem cell transplant; CR = complete response; KRD = carfilzomib, lenalidomide, and dexamethasone; Rd = lenalidomide plus dexamethasone; VCD = bortezomib, cyclophosphamide, and dexamethasone; VGPR = very good partial response; VRD = bortezomib, lenalidomide, and dexamethasone. * = Rd if frail or age ≥75.

failure.[1] However, a renal biopsy is required if serum FLC levels are below 500 mg/L. Patients presenting with acute renal failure due to light chain cast nephropathy need urgent treatment to lower circulating FLC levels.[70] We recommend a triplet regimen that does not require major dose adjustment such as VCD or VTD.[71] The role of plasmapheresis to remove circulating light chains is controversial, and randomized trials indicate a lack of benefit.[72] However, the trials so far have had some limitations, and the risk of the intervention is minimal compared with the major impact on prognosis that occurs if renal dysfunction is not reversed.[73] Therefore, we recommend plasmapheresis or dialysis using high-cutoff filters to rapidly reduce FLCs. Close monitoring of serum FLC and creatinine levels is needed for the first few weeks.

Autologous Stem Cell Transplant

Autologous stem cell transplant improves complete response rates and prolongs median OS in MM by approximately 12 months.[13,14,74,75] The treatment-related mortality (TRM) rate is 1% to 2%, and the procedure can be performed entirely on an outpatient basis in more than 50% of patients.[76] Eligibility for ASCT is based on age, performance status, and comorbidities. In the United States, the upper age limit is flexible, and patients can undergo transplant up to age 75 years if they are have good functional status and minimal comorbidities. In contrast, in many other countries, the upper limit for ASCT is 65 years. The preferred conditioning regimen is melphalan (200 mg/m^2).[77] Studies are ongoing to determine if the conditioning regimen can be improved with the addition of bortezomib or carfilzomib.

Timing of ASCT. Four randomized trials found that survival is similar whether ASCT is done early (immediately following 4 cycles of induction therapy) or delayed (at the time of relapse as salvage therapy).[63,78-80] A recent trial by the Intergroupe Francophone du Myelome and the Dana-Farber Cancer Institute compared early vs delayed ASCT in patients treated with VRD followed by lenalidomide maintenance.[63] Patients were randomized to receive either VRD (3 cycles) followed by ASCT and then VRD consolidation (2 cycles) vs VRD for 8 cycles with ASCT reserved for relapse. Both arms received lenalidomide maintenance for 1 year. A significant improvement in PFS was seen as expected with early ASCT, but this improvement has so far not translated into a difference in OS

TABLE 6. Selected Drugs With Major Single-Agent Activity in Multiple Myeloma

Agent	Usual starting dose	Postulated mechanism of action	Adverse effects
Thalidomide	50-200 mg orally days 1-28 every 4 wk	Binds to cereblon and activates cereblon E3 ubiquitin ligase activity, resulting in the rapid ubiquitination and degradation of 2 specific B-cell transcription factors, Ikaros family zinc finger proteins Ikaros (IKZF1) and Aiolos (IKZF3); antiangiogenesis, immunomodulation, and inhibition of tumor necrosis factor α. Direct cytotoxicity by inducing free radical–mediated DNA damage	Sedation, fatigue, rash, bradycardia, peripheral neuropathy, and constipation. Deep venous thrombosis is a serious adverse event necessitating routine prophylaxis with aspirin or other anticoagulant in all patients. Teratogen
Bortezomib	1.3 mg/m^2 subcutaneously days 1, 8, 15, 22 every 28 d	Inhibits the ubiquitin-proteasome catalytic pathway in cells by binding directly with the 20S proteasome complex	Gastrointestinal, transient cytopenias, fatigue, and peripheral neuropathy
Lenalidomide	25 mg orally days 1-21 every 28 d	Cereblon-mediated ubiquitination and degradation of Ikaros (IKZF1) and Aiolos (IKZF3); antiangiogenesis, immunomodulation, and inhibition of tumor necrosis factor α. Direct cytotoxicity by inducing free radical –mediated DNA damage	Fatigue, rash, thrombocytopenia, and neutropenia. Deep venous thrombosis is a serious adverse event necessitating routine prophylaxis with aspirin or other anticoagulant in all patients. Diarrhea and leg cramps with long-term use. Teratogen
Pomalidomide	4 mg orally days 1-21 every 28 d	Same as thalidomide and lenalidomide	Fatigue, rash, thrombocytopenia, and neutropenia. Deep venous thrombosis is a serious adverse event necessitating routine prophylaxis with aspirin or other anticoagulant in all patients. Teratogen
Carfilzomib	27 mg/m^2 intravenously days 1, 2, 8, 9, 15, 16 every 28 d	Proteasome inhibitor	Gastrointestinal, hypokalemia, hypertension, dyspnea. Serious cardiac dysfunction in approximately 5%
Daratumumab	16 mg/kg intravenously weekly for 8 wk, then every 2 wk for 16 wk, then once monthly	Monoclonal antibody targeting CD38	Infusion-related reactions, fatigue, anemia, nausea

(Table 9). Importantly the trial found that the 3-year OS in both arms was very high, which reflects the remarkable improvement that has occurred in MM therapy over the past decade. The trial also found that patients achieving an MRD-negative state had superior OS compared with those who remained MRD positive. Care should be taken in interpretation of these data; they confirm the value of MRD-negative state as a prognostic marker, but randomized trials are needed to determine if MRD negativity should be a goal of therapy and if therapy should be altered for patients based on MRD-status.

As discussed previously, there are no data so far that early ASCT prolongs OS compared with delayed ASCT. However, given the inconvenience and the impact on quality of life with prolonged chemotherapy, insurance, and other issues, we favor early ASCT if patients do not have a strong preference regarding the timing. We also prefer early ASCT in patients with intermediate- and high-risk MM on the bassis of studies that found that patients with t(4;14) and del(17p) have achieved outcomes closer to those of standard-risk patients in trials that have incorporated early ASCT.[81] Delayed ASCT is reasonable in patients with standard-risk MM who respond and tolerate initial therapy well and who seek to delay the procedure because of personal preference.

Tandem Transplant. With tandem (double) ASCT, patients receive a second planned ASCT after recovery from the first procedure.[82,83] The Intergroupe Francophone du

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TABLE 7. Selected Drugs With Activity in Combination With Other Active Agents in Multiple Myeloma

Agent	Usual starting dose	Postulated mechanism of action	Adverse effects
Elotuzumab	10 mg/kg intravenously weekly for 8 wk, then every 2 wk	Immunostimulatory monoclonal antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7)	Infusion-related reactions, fatigue, infections
Panobinostat	20 mg orally thrice weekly 2 wk on, 1 wk off	Pan-deacetylase inhibitor; blocks aggresome pathway	Diarrhea, thrombocytopenia, fatigue

Myelome 94 randomized trial found significantly better event-free survival and OS in recipients of double vs single ASCT.[84] A similar benefit was also found in a randomized trial conducted in Italy.[85] These trials were done before the availability of lenalidomide, bortezomib, and other new agents. In both trials, the benefit of a second ASCT was restricted to patients who did not achieve a complete response or very good partial response (VGPR) (>90% reduction in M-protein level) with the first transplant. With modern induction regimens and ASCT, the vast majority of patients have VGPR or better status following the first ASCT, limiting the role of tandem ASCT. Further, 2 other randomized trials have not found a significant improvement in OS with tandem ASCT.[86,87] The Bone Marrow Transplant Clinical Trials Network 0702 trial will clarify the role of tandem ASCT in patients receiving VRD initial therapy and lenalidomide maintenance. Until these results are available, we typically collect enough stem cells for 2 transplants in all eligible patients younger than 65 years. However, rather than performing tandem ASCT, the purpose of collecting additional stem cells is to preserve the possibility of a second ASCT at the time of relapse.

Allogeneic Transplant. The high TRM and morbidity related to graft-vs-host disease has made conventional allogeneic transplants unacceptable for most patients with MM. Data from randomized trials regarding the benefit of allogeneic ASCT are conflicting.[88,89] Even with a tandem approach of ASCT followed by an HLA-identical sibling donor mini-allogeneic transplant, the TRM is high at approximately 10% to 15%. Given excellent outcomes with current therapy, allogeneic transplant has a limited role in MM. We recommend it primarily in young patients with high-risk MM in first or second relapse who are willing to accept a high TRM and graft-vs-host disease–related morbidity in return for a small chance at long-term OS.

Consolidation/Maintenance Therapy

Numerous trials have been conducted over the years testing maintenance therapy in MM, either after ASCT or after 12 to 18 months of standard-dose therapy. However, the agents used were either ineffective, toxic, or both, and none of these approaches gained ground in clinical practice. Thalidomide had modest PFS and OS benefit as maintenance therapy in 2 randomized trials but has drawbacks of significant nonhematologic toxicity.[90,91]

Posttransplant Maintenance Therapy. In the post-ASCT setting, maintenance therapy with lenalidomide, and with bortezomib, has shown promise. Two randomized trials reported better PFS with lenalidomide as post-ASCT maintenance therapy, and in one of these trials, an OS benefit was also observed.[92,93] The OS benefit was primarily in patients who received lenalidomide as part of initial therapy before ASCT. One concern in the interpretation of these data is that patients in the control arm of these trials lacked uniform access to lenalidomide at relapse, and it is not clear whether the PFS improvement will be neutralized because patients in the control arm can always initiate the same therapy at the time of first relapse.[94,95] There was also a clear increased risk of second cancers with lenalidomide maintenance therapy in both trials. The pros and cons of lenalidomide maintenance therapy should be considered carefully. We recommend lenalidomide maintenance therapy in standard-risk patients who do well with lenalidomide-containing initial therapy and do not achieve a VGPR following ASCT.[38]

In patients with intermediate- and high-risk MM, we prefer bortezomib-based maintenance

TABLE 8. Major Treatment Regimens in Multiple Myeloma

Regimen	Usual dosing schedule[a]
Melphalan-prednisone (7-d schedule)[39]	Melphalan: 8-10 mg orally on days 1-7 Prednisone: 60 mg orally on days 1-7 Repeated every 6 wk
Thalidomide-dexamethasone[40,41,b]	Thalidomide: 200 mg orally on days 1-28 Dexamethasone: 40 mg orally on days 1, 8, 15, 22 Repeated every 4 wk
Lenalidomide-dexamethasone[42]	Lenalidomide: 25 mg orally on days 1-21 every 28 d Dexamethasone: 40 mg orally on days 1, 8, 15, 22 every 28 d Repeated every 4 wk
Bortezomib-dexamethasone[43,b]	Bortezomib: 1.3 mg/m^2 intravenously on days 1, 8, 15, 22 Dexamethasone: 20 mg orally on day of and day after bortezomib (or 40 mg on days 1, 8, 15, 22) Repeated every 4 wk
Melphalan-prednisone-thalidomide[44,45]	Melphalan: 0.25 mg/kg orally on days 1-4 (use 0.20 mg/kg/d orally on days 1-4 in patients >75 y) Prednisone: 2 mg/kg orally on days 1-4 Thalidomide: 100-200 mg orally on days 1-28 (use 100-mg dose in patients >75 y) Repeated every 6 wk
Bortezomib-melphalan-prednisone[46-48,b]	Bortezomib: 1.3 mg/m^2 intravenously on days 1, 8, 15, 22 Melphalan: 9 mg/m^2 orally on days 1-4 Prednisone: 60 mg/m^2 orally on days 1-4 Repeated every 35 d
Bortezomib-thalidomide-dexamethasone[49,b]	Bortezomib: 1.3 mg/m^2 intravenously on days 1, 8, 15, 22 Thalidomide: 100-200 mg orally on days 1-21 Dexamethasone: 20 mg orally on day of and day after bortezomib (or 40 mg on days 1, 8, 15, 22) Repeated every 4 wk for 4 cycles as pretransplant induction therapy
Bortezomib-cyclophosphamide-dexamethasone[50,51]	Cyclophosphamide: 300 mg/m^2 orally on days 1, 8, 15, 22 Bortezomib: 1.3 mg/m^2 intravenously on days 1, 8, 15, 22 Dexamethasone: 40 mg orally on days 1, 8, 15, 22 Repeated every 4 wk[c]
Bortezomib-lenalidomide-dexamethasone[51,52,b]	Bortezomib: 1.3 mg/m^2 intravenously on days 1, 8, 15 Lenalidomide: 25 mg orally on days 1-14 Dexamethasone: 20 mg orally on day of and day after bortezomib (or 40 mg on days 1, 8, 15, 22) Repeated every 3 wk[d]
Carfilzomib[55]	Carfilzomib: 20 mg/m^2 (cycle 1) and 27 mg/m^2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Repeated every 4 wk[c]
Carfilzomib-cyclophosphamide-dexamethasone[56,e]	Carfilzomib 20 mg/m^2 (cycle 1) and 36 mg/m^2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Cyclophosphamide: 300 mg/m^2 orally on days 1, 8, 15 Dexamethasone: 40 mg orally on days 1, 8, 15 Repeated every 4 wk[c]
Carfilzomib-lenalidomide-dexamethasone[57]	Carfilzomib: 27 mg/m^2 intravenously on days 1, 2, 8, 9, 15, 16 (Note: cycle 1 day 1 and 2, carfilzomib dose is 20 mg/m^2) Lenalidomide: 25 mg orally on days 1-21 Dexamethasone: 20 mg orally on day of and day after bortezomib (or 40 mg on days 1, 8, 15, 22) Repeated every 4 wk
Pomalidomide-dexamethasone[58]	Pomalidomide: 4 mg orally on days 1-21 Dexamethasone: 40 mg orally on days 1, 8, 15, 22 Repeated every 4 wk

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TABLE 9. Continued

Regimen	Usual dosing schedule[a]
Carfilzomib-pomalidomide-dexamethasone[59]	Carfilzomib: 27 mg/m^2 intravenously on days 1, 2, 8, 9, 15, 16 (Note: cycle 1 day 1 and 2, carfilzomib dose is 20 mg/m^2) Pomalidomide: 4 mg orally on days 1-21 Dexamethasone: 40 mg orally on days 1, 8, 15, 22 Repeated every 4 wk

[a]All doses must be adjusted for performance status, renal function, blood counts, and other toxicities.
[b]Doses of dexamethasone and/or bortezomib reduced based on subsequent data showing lower toxicity and similar efficacy with reduced doses.
[c]The day 22 dose of all 3 drugs is omitted if counts are low, or after initial response to improve tolerability or when the regimen is used as maintenance therapy; when used as maintenance therapy for high-risk patients, further delays can be instituted between cycles.
[d]Omit day 15 dose if counts are low or when the regimen is used as maintenance therapy; when used as maintenance therapy for high-risk patients, lenalidomide dose may be decreased to 10-15 mg/d, and delays can be instituted between cycles as done in total therapy protocols.[53,54]
[e]Dosing based on trial in newly diagnosed patients; in patients with relapse, cycle 2 carfilzomib dose is 27 mg/m^2 intravenously.
Adapted from *Am J Hematol*.[2]

therapy. In a randomized trial, patients receiving bortezomib given every other week as posttransplant maintenance therapy for 2 years had superior outcomes compared with thalidomide maintenance therapy.[81] In high-risk patients, empirical use of a triplet regimen such as VRD as posttransplant therapy may be reasonable.[96] Randomized trials with the new proteasome inhibitor ixazomib are ongoing; ixazomib is administered orally once weekly and is hence ideally suited to the maintenance setting.

Maintenance After Standard-Dose Therapy. The role of maintenance therapy after an initial 12 to 18 months of treatment for newly diagnosed MM in patients not receiving an ASCT is evolving. Some data indicate that continuous therapy with Rd is superior in terms of PFS to Rd given for 18 months,[67] but whether this benefit will be seen after 18 months of a triplet therapy such as VRD is unclear. In one randomized trial, melphalan, prednisone, and lenalidomide (MPR) followed by lenalidomide maintenance therapy had superior PFS compared with MPR alone.[97] However, in this trial, the MPR arm was identical in terms of PFS to the melphalan plus prednisone arm, and no OS differences were seen, limiting more definitive conclusions concerning the value of maintenance therapy. If Rd is used as initial therapy, we recommend continuing it until progression. If a triplet regimen is used, we recommend stopping therapy after 12 to 18 months in patients with standard-risk disease and continuing with bortezomib maintenance therapy in those with intermediate- and high-risk disease. Randomized trials with the new oral proteasome inhibitor ixazomib are ongoing in this setting as well.

Treatment of Relapsed MM

The approach to treatment of relapsed MM is complicated. Numerous effective regimens are available, and the choice of treatment depends on numerous factors such as drug availability, response to previous therapy, aggressiveness of the relapse, eligibility for ASCT, and whether the relapse occurred while the patient was receiving or not receiving therapy. In eligible patients, ASCT should be included in the consideration if the patient has never had an ASCT or if the remission duration with a previous ASCT exceeds 18 months (no maintenance therapy) or 36 months (with maintenance therapy).[98] Recent data support the use of triplet therapy for relapsed MM, but selected patients with indolent relapse can often be treated with a doublet regimen such as Rd or pomalidomide plus low-dose dexamethasone (PD). Multiple myeloma is characterized by relapses and remissions, with each remission typically lasting less than the previous one.[99] In the absence of toxicity, most regimens are continued until progression in the relapsed setting. However, in some regimens such as those employing

TABLE 9. Results of Recent Randomized Studies in Newly Diagnosed Myeloma[a]

Reference, year	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	Progression-free survival (mo), median	*P* value for progression-free survival	Overall survival	*P* value for overall survival
Facon et al,[60] 2013	MPT	547	62	28	21.2	<.001	48 mo (median)	.016[b]
	Rd for 18 mo	541	73	43	20.7		53 mo (median)	
	Rd until progression	535	75	44	25.5		56 mo (median)	
Durie et al,[61] 2015	Rd	232	N/A	N/A	31.0	.007	63	.011
	VRD	242	N/A	N/A	43.0		NR	
Moreau et al,[62] 2015	VTD	170	92	77	N/A	N/A	N/A	N/A
	VCD	170	84	66	N/A		N/A	
Attal et al,[63] 2015	VRD-ASCT	350	N/A	58% CR	NR; 61% at 3 y	<.001	88% at 3 y	.25
	VRD	350	N/A	46% CR	NR; 48% at 3 y		88% at 3 y	

[a]ASCT = autologous stem cell transplant; CR = complete response; MPT = melphalan, prednisone, and thalidomide; N/A = not available; NR = not reached; NS = not significant; Rd = lenalidomide plus dexamethasone; VCD = bortezomib, cyclophosphamide, and dexamethasone; VGPR = very good partial response; VRD = bortezomib, lenalidomide, and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone.

[b]Rd until progression vs MPT.

bortezomib, carfilzomib, or alkylators, it may be reasonable to stop therapy with these drugs once a stable plateau has been reached in order to minimize risks of serious toxicity.

New agents approved for the treatment of relapsed MM include carfilzomib, pomalidomide, and panobinostat. The most common regimens and new drugs used in the treatment of relapsed refractory MM are discussed in the subsequent sections.

Bortezomib- and Lenalidomide-Based Regimens. Lenalidomide plus dexamethasone is an effective regimen in relapsed MM, although the dose of dexamethasone must be reduced from the schedules used in the original pivotal trials.[100,101] Triplet regimens such as VRD, VCD, and VTD can also be used in the relapsed refractory MM setting and are well tolerated when low-dose dexamethasone and weekly subcutaneous bortezomib schedules are used.[102-104]

Carfilzomib- and Pomalidomide-Based Regimens. Carfilzomib is a keto-epoxide tetrapeptide proteasome inhibitor approved for the treatment of relapsed refractory MM in patients who have been treated previously with lenalidomide and bortezomib.[55] In a phase 3 trial of 792 patients, KRD was associated with better response rates, PFS, and OS compared with Rd.[105] Progression-free survival was 26.3 months with KRD vs 17.6 months in the control group (P=.0001). The 2-year survival rates were 73.3% and 65.0%, respectively (P=.04). On the basis of these results, KRD is now an important option for the treatment of relapsed MM. There is debate about whether KRD (or similar carfilzomib-based regimens) should be used before bortezomib-based regimens in relapsed MM. Support for carfilzomib as a more potent proteasome inhibitor than bortezomib comes from a randomized trial in which carfilzomib-dexamethasone doubled PFS compared with bortezomib-dexamethasone in relapsed MM (PFS, 18.7 vs 9.4 months, respectively; P<.001).[69] However, the dose of carfilzomib used in this trial (56 mg/m^2) was twice the approved dose and has a much higher cost compared with bortezomib. Further, the dosing of bortezomib used in this trial was suboptimal (twice-weekly schedule), making it difficult to make definitive conclusions. Carfilzomib does have lower risk of neurotoxicity than bortezomib, but a small proportion of patients (5%) may experience serious cardiac adverse effects.

Pomalidomide is an analogue of lenalidomide and thalidomide approved for the treatment of relapsed refractory MM. It has significant activity in relapsed refractory MM, even in patients in whom lenalidomide[106,107] or lenalidomide plus bortezomib[58,108] has been ineffective. In a randomized trial of 302 patients with refractory

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MM, PD was superior to high-dose dexamethasone (median PFS, 4.0 vs 1.9 months, respectively; $P<.0001$).[109] As with Rd, the doublet regimen of PD is a reasonable option for patients with indolent relapse. More often, however, pomalidomide must be administered in combinations such as pomalidomide, cyclophosphamide, and prednisone; pomalidomide, bortezomib, and dexamethasone; or carfilzomib, pomalidomide, and dexamethasone.

Panobinostat. Panobinostat is a pan-deacetylase inhibitor approved in 2015 for the treatment of relapsed and refractory MM.[110] It is the first agent from a new class of drugs with meaningful clinical activity in MM in nearly 15 years. Its putative mechanism of action is to block the aggresome pathway, an alternative route for cells to bypass the lethal effects of proteasome inhibition. By combining bortezomib and panobinostat, there is simultaneous blockade of both proteasome and aggresome pathways.[111,112] In a randomized trial of 768 patients, bortezomib-dexamethasone plus panobinostat was associated with superior PFS compared with bortezomib-dexamethasone plus placebo (median PFS, 12 vs 8.1 months, respectively; $P<.0001$).[110] However, panobinostat therapy was associated with grade 3 diarrhea in approximately 25% of patients, and care should be exercised when using this drug. We recommend a lower dose than the approved starting dose. We also recommend that bortezomib be used in the once-weekly subcutaneous schedule rather than the twice-weekly regimen used in the pivotal trial.[47,48,65]

Liposomal Doxorubicin. Anthracyclines have marginal single-agent activity in MM. A phase 3 randomized trial found that median time to progression was superior with bortezomib plus pegylated liposomal doxorubicin compared with bortezomib alone (9.3 vs 6.5 months, respectively; $P<.001$).[113] Overall survival at 15 months was also superior (76% compared with 65%, respectively; $P=.03$). Despite these results, liposomal doxorubicin is infrequently used in the treatment of relapsed MM given the availability of other active agents.

Monoclonal Antibodies. Two monoclonal antibodies (daratumumab and SAR650984) targeting CD38 have shown promise in relapsed refractory MM. In a phase 2 trial, daratumumab as a single agent produced a response rate of approximately 30% in heavily pretreated patients.[114] These results are very encouraging, and daratumumab has been recently approved in the United States for use in relapsed refractory MM on the basis of these data.

Elotuzumab, a monoclonal antibody targeting the signaling lymphocytic activation molecule F7, also has activity in relapsed MM.[115] Unlike anti-CD38 antibodies, elotuzumab does not appear to have any single-agent activity. However, it seems to have synergistic activity when combined with Rd. In a phase 3 trial of 646 patients, elotuzumab plus Rd was superior to Rd in terms of PFS (median PFS, 19.4 vs 14.9 months, respectively; $P<.001$). Elotuzumab is also well tolerated and has been approved in the United States for the treatment of relapsed MM based on these data.

Ixazomib. Ixazomib is an oral proteasome inhibitor that is active in both the relapsed refractory setting and in newly diagnosed MM. In a randomized controlled trial in relapsed MM, ixazomib, lenalidomide, and dexamethasone was reported to improve PFS compared

TABLE 10. Criteria for High-Risk Smoldering Multiple Myeloma[a,b]

Bone marrow clonal plasma cells ≥10% and any one or more of the following:
Serum M protein ≥30 g/L
IgA SMM
Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes
Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)
Progressive increase in M-protein level (evolving type of SMM)[c]
Bone marrow clonal plasma cells 50%-60%
Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
t(4;14) or del(17p) or gain(1q)
Increased circulating plasma cells
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

[a]FLC = free light chain; MRI = magnetic resonance imaging; PET-CT = positron emission tomography–computed tomography; SMM = smoldering multiple myeloma.

[b]Note that the term *smoldering multiple myeloma* excludes patients without end-organ damage who meet revised definition of multiple myeloma, namely clonal bone marrow plasma cells ≥60% or serum FLC ratio ≥100 (plus measurable involved FLC level ≥100 mg/L) or more than one focal lesion on MRI. The risk factors listed in this table are not meant to be indications for therapy; they are variables associated with a high risk of progression of SMM and identify patients who need close follow-up and consideration for clinical trials.

[c]Increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period.

From *Blood*.[128]

with Rd.[116] On the basis of these results, ixazomib has now been approved for the treatment of relapsed MM in the United States. It has the advantage of once-weekly oral administration. Compared with bortezomib, it has more gastrointestinal adverse events but lower risk of neurotoxicity.

Other Emerging Options. Other promising agents include marizomib (a new proteasome inhibitor), oprozomib (an oral proteasome inhibitor related to carfilzomib), filanesib (a kinesin spindle protein inhibitor), dinaciclib (a cyclin-dependent kinase inhibitor), ABT-199 (a selective BCL-2 inhibitor), and LGH-447 (pan-PIM kinase inhibitor). Each of these agents has single-agent activity in relapsed MM.

Supportive Care

Hypercalcemia. The mainstay of therapy for hypercalcemia is hydration, corticosteroids, and bisphosphonates (pamidronate or zoledronic acid). Pamidronate at 60 to 90 mg intravenously over 2 to 4 hours or zoledronic acid at 4 mg intravenously over 15 minutes will normalize the calcium levels within 24 to 72 hours in most patients.[117,118] In patients with refractory disease, salmon calcitonin can be used.

Skeletal Lesions. The most important element in supportive care is the use of bisphosphonates to prevent or reduce the number of skeletal lesions.[119-121] Zoledronic acid or pamidronate once monthly at least for the first 1 to 2 years is recommended for almost all patients with MM who have evidence of MM bone disease.[120,122] Data from a randomized trial revealed that in such patients, there is also a favorable effect on OS.[123]

In patients with osteolytic bone disease, the use of local radiation should be limited to those with spinal cord compression from extramedullary tumor extension and to patients with bone pain refractory to analgesics and systemic therapy. Vertebroplasty (injection of methylmethacrylate into a collapsed vertebral body) or kyphoplasty (introduction of an inflatable bone tamp into the vertebral body and after inflation the injection of methylmethacrylate into the cavity) can be used to decrease pain from vertebral fractures.[124] Some patients with impending fracture may need prophylactic surgical intervention.

Prevention of Infections. Patients with MM should receive pneumococcal and influenza vaccinations. Intravenously administered gamma globulin every 3 to 4 weeks is indicated if patients have recurrent serious infections associated with severe hypogammaglobulinemia. The role of prophylactic antibiotics in patients receiving chemotherapy for MM has not been settled. Randomized trials have not found significant benefit.[125] We do recommend acyclovir for all patients receiving bortezomib or carfilzomib to prevent herpes zoster activation. Prophylaxis against *Pneumocystis jiroveci* should be considered in all patients receiving long-term corticosteroids.[126] However, there is a risk of serious skin toxicity in patients receiving an immunomodulatory agent (thalidomide, lenalidomide) and trimethoprim-sulfamethoxazole. In such patients, alternative antibiotics (such as levofloxacin) and alternative agents for *Pneumocystis* prophylaxis should be considered.

Hyperviscosity Syndrome. A small proportion of patients with MM, especially of the IgA subtype, have development of hyperviscosity syndrome. Plasmapheresis promptly relieves the symptoms and should be performed regardless of the viscosity level if the patient has signs or symptoms of hyperviscosity.[127]

SMOLDERING MM

Smoldering MM is a stage that is clinically positioned between MGUS and MM.[128] It comprises a heterogeneous group of patients, some of whom have MM that has not yet manifested with myeloma-defining events and some who have premalignant MGUS. Patients with SMM have a risk of progression of approximately 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% per year thereafter.[11] Patients with the highest risk of progression (ultrahigh risk) have now been reclassified as having MM by the new International Myeloma Working Group criteria.[1] Within the current definition of SMM (Table 1), there are 2 groups of patients: high risk (25% per year risk of progression in the first 2 years) and low risk (~5% per year risk of progression).[128] Criteria for high-risk SMM are presented in Table 10. The presence of one or more of these factors is

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associated with a median time to progression to MM of approximately 2 years. Early studies in SMM failed to document an advantage for early intervention but were limited by lack of power, safe and effective drugs, and a risk-adapted strategy.[129,130] A recent randomized trial conducted in Spain found that patients with high-risk SMM had an OS benefit when treated with Rd compared with observation (3-year survival rate, 94% vs 80%, respectively; $P=.03$).[131] These are very promising results, and further confirmatory studies are ongoing. Observation is still the standard of care for SMM; however, selected high-risk patients with SMM and multiple risk factors can be considered for therapy. They are also candidates for clinical trials testing early intervention.

CONCLUSION

Major advances in the diagnosis and treatment of MM have occurred in the past decade. Future trials should address the optimal sequencing of the various treatment regimens available, the incorporation of monoclonal antibodies to existing regimens in a cost-effective and safe manner, the role of MRD as a goal of therapy, optimal treatment of high-risk MM and EMD, and early intervention toward a cure of the disease.

Abbreviations and Acronyms: ASCT = autologous stem cell transplant; **EMD** = extramedullary disease; **FLC** = free light chain; **ISS** = International Staging System; **KRD** = carfilzomib, lenalidomide, and dexamethasone; **MGUS** = monoclonal gammopathy of undetermined significance; **MM** = multiple myeloma; **MPR** = melphalan, prednisone, and lenalidomide; **MRD** = minimal residual disease; **OS** = overall survival; **PD** = pomalidomide plus low-dose dexamethasone; **PFS** = progression-free survival; **Rd** = lenalidomide plus dexamethasone; **SMM** = smoldering MM; **TRM** = treatment-related mortality; **VCD** = bortezomib, cyclophosphamide, and dexamethasone; **VGPR** = very good partial response; **VRD** = bortezomib, lenalidomide, and dexamethasone; **VTD** = bortezomib, thalidomide, and dexamethasone

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