Management of Multiple Myeloma

Introduction

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by aberrant expansion of plasma cells within the bone marrow, as well as in extramedullary sites.[McKenna 2008] The disease was first characterized in the 1840s with softening of bones and infiltrated bone marrow described in postmortem specimens of affected patients.[Solly 1844;Kyle 2000] Bence Jones[Bence Jones 1847; Bence Jones 1848] first described the unique physical characteristics of the urinary protein in MM patients that now bears his name. More than a century later, Edelman and Gally[Edelman 1962]demonstrated that the serum immunoglobulin light chain molecule and urine Bence Jones protein in MM patients share the identical amino acid sequence. Waldenström,[Waldenström 1961] meanwhile, played a pivotal role in the identification of a serum monoclonal protein in patients with MM and other plasma cell dyscrasias such as Waldenström macroglobulinemia.

Today, as in the past, MM is recognized as a source of significant morbidity and mortality. There were an estimated 20,180 new cases of MM in the United States in 2010 and 10,650 deaths attributable to the disease.[SEER 2011] The median age at diagnosis between 2004-2008 was 69 years, and fewer than 16% of cases occurred in persons younger than 55 years of age. The age-adjusted incidence rate for this period was 5.7/100,000 population. Overall, MM accounts for 1% of all malignant tumors and 10% to 15% of hematopoietic neoplasms.[McKenna 2008] MM is associated with a variety of well-known clinical manifestations, including osteolytic bone lesions, renal failure, anemia, hypercalcemia, recurrent infections, and neuropathy,[Kyle 2003] though physicians should be aware that the absence of this clinical constellation does not exclude the presence of MM. Treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation and/or surgery in selected cases associated with extramedullary disease.

The therapeutic landscape of MM has changed markedly in the past decade with the introduction of the novel immunomodulatory agents thalidomide and lenalidomide, as well as the first-in-class proteasome inhibitorbortezomib. Although MM remains an incurable malignancy, new approaches to therapy incorporating these agents have produced significantly higher response rates and improved intervals of both progression-free survival and overall survival in the context of randomized, controlled trials. In the aggregate, novel therapies in MM have been associated with substantial improvements in patient outcome.[Kumar 2008]

Etiology and Risk Factors

Normal B-cell differentiation occurs in early (antigen-independent) and late (antigen-dependent) stages, culminating in the development of plasma cells and memory B cells.[Hagman 2006; Fairfax 2008; Clark 2005] During the antigen-dependent stage of B-cell development, B cells that have encountered and bound antigen to the surface immunoglobulin receptor aggregate in germinal centers and undergo 2 forms of genetic modification—somatic hypermutation and immunoglobulin class switch—that result in higher affinity IgG or IgA antibodies.[MacLennan 1990]

A high degree of immunoglobulin heavy chain gene hypermutation is present in multiple myeloma (MM) cells, suggesting that the tumor cell derives from a post–germinal center B cell.[Bakkus 1992] Chromosomal abnormalities are detected in approximately one third of MM tumors by metaphase karyotype analysis[Sawyer 1995] and in a significantly higher percentage of tumors by fluorescence in situ hybridization analysis.[Avet-Loiseau 2007] Primary translocations in MM frequently involve the immunoglobulin heavy chain locus on chromosome 14q32 and partner genes such as cyclin D1 (chromosome 11q13), cyclin D3 (chromosome 6p21), and FGFR3/MMSET (chromosome 4p16.3), and C-MAF (chromosome 16q23).[Fonseca 2003; Hideshima 2004] Other common genetic abnormalities that are believed to occur as early events in the pathogenesis of MM include monosomy or partial deletion of chromosome 13 (13q14)[Fonseca 2004] and hyperdiploidy, with gains most often of odd-numbered chromosomes 3, 5, 6, 9, 11, 15, 19, and 21.[Chng 2007] At the level of the bone marrow microenvironment, interaction between MM cells and surrounding extracellular matrix and bone marrow stromal cells triggers secretion of cytokines such as interleukin-6 and insulin-like growth factor-1, which foster tumor proliferation and resistance to chemotherapy.[Hideshima 2001a; Damiano 2000;Mitsiades 2007]

Several risk factors for the development of MM have been identified, although the specific mechanisms by which they contribute to MM pathogenesis are not yet known. MM primarily affects older individuals, and the average age at diagnosis is 65 years. The disease is twice as common among blacks as among whites.[Ries 2007] Occurrences of familial MM have been reported,[Lynch 2001; Lynch 2008; Jain 2009] and, moreover, an increased incidence of monoclonal gammopathy of undetermined significance (MGUS) is seen among first-degree relatives of MM patients than among the general population.[Vachon 2009] An association exists between MM and exposure to ionizing radiation,[Linet 1987] as well as exposure to chemicals such as benzene, Agent Orange, and pesticides/herbicides.[Kyle 2007; Brown 2008]

Presentation and Diagnosis

Common presenting symptoms associated with multiple myeloma (MM) include bone pain, fatigue, and weight loss.[Kyle 2003] Recurrent infections can occur as a result of impaired immunoglobulin production or function, and in some instances, a diagnosis of MM is uncovered through evaluation of recurrent infection.[Jacobsen 1986; Broder 1975]Peripheral neuropathy develops in some patients as a result of the disease-related monoclonal paraproteinemia through mechanisms that have not been fully characterized.[Silberman 2008; Ropper

1998] Although infrequent in MM, sequelae of hyperviscosity, such as headache, dizziness, and bleeding, may be present at the time of diagnosis.[Preston 1978]

The diagnosis of MM is based on the presence of a monoclonal protein (M-protein) or significant (≥ 10%) involvement of the cellular bone marrow, along with evidence of end organ damage as manifested by either elevated serum calcium (≥ 11.5 g/dL), renal insufficiency (serum creatinine ≥ 2 mg/dL), anemia (hemoglobin ≤ 10 g/dL or 2 g below normal), or lytic bone lesions (Management Guidelines).[NCCN 2012; IMWG 2003] In some instances, plasmacytomas of the bone or extraosseous organs are the primary sites of disease involvement. Symptomatic MM must be differentiated from monoclonal gammopathy of undetermined significance (MGUS), asymptomatic (smoldering) MM, and either solitary or diffuse extramedullary MM (Table 1).[IMWG 2003] The presence of secondary amyloidosis and/or hyperviscosity may be suggested by symptoms and signs; in such circumstances, these should be assessed as part of the diagnostic workup.

Table 1. Criteria for the Classification of MGUS, MM, and Related Disorders: A Report of the International Myeloma Working Group [IMWG. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Copyright © 2003. Reproduced with permission of John Wiley & Sons, Inc.]

MGUS
M-protein in serum < 30 g/L
Bone marrow clonal plasma cells < 10% and low level of plasma cell infiltration in a trephine biopsy (if done)
No evidence of other B-cell proliferative disorders
No related organ or tissue impairment (no end organ damage, including bone lesions).
Myeloma-Related Organ or Tissue Impairment (End Organ Damage) due to the Plasma Cell Proliferative Process ("CRAB")
Calcium levels increased: serum calcium > 0.25 mmol/L above the upper limit of normal or > 2.75 mmol/L
Renal insufficiency: creatinine > 173 mmol/L
Anemia: hemoglobin 2 g/dL below the lower limit of normal or hemoglobin < 10 g/dL
Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)
Asymptomatic Myeloma (Smoldering Myeloma)
M-protein in serum ≥ 30 g/L and/or bone marrow clonal plasma cells >10%
No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms
Symptomatic MM
M-protein in serum and/or urine
Bone marrow (clonal) plasma cells or plasmacytoma
Related organ or tissue impairment (end organ damage, including bone lesions)

CRAB, calcium, renal insufficiency, anemia, or bone lesions; CT, computed tomography; MRI, magnetic resonance imaging.

Laboratory studies recommended in the evaluation of a patient with suspected MM include serum and urine protein electrophoresis with immunofixation, complete blood count with differential, comprehensive metabolic panel, $ß_2$-microglobulin, quantitative immunoglobulins, and serum free light chain quantification (Table 2).[Piehler 2008] Other laboratory studies, such as the test for serum C-reactive protein and lactate dehydrogenase, are useful although not required. Serum viscosity is measured when symptoms suggest hyperviscosity may be present. The skeletal bone survey is used to assess for lytic bone lesions and osteopenia/osteoporosis associated with MM. However, it is important to note that detection of osteolytic lesions requires 30% loss of bone density.[Resnick 1996] As such, more sensitive imaging modalities such as CT and/or MRI should be employed when there is suspicion of bone abnormalities despite a normal skeletal bone survey. MRI is also particularly useful in evaluating for paraspinal and epidural MM involvement.[Mulligan 2005]

A bone marrow aspiration and biopsy is essential for the diagnosis of MM and provides useful prognostic information as well. Morphological assessment of tumor cells, immunohistochemical analysis, flow cytometry, and cytogenetic analysis using both metaphase karyotype and fluorescence in situ hybridization are mainstays in the evaluation of a patient with suspected MM. The diagnosis of extramedullary plasmacytoma is made through biopsy of affected bone or soft tissue demonstrating a collection of plasma cells.

Table 2. Recommended Laboratory Tests in the Evaluation of Suspected MM

Hemoglobin, white blood cell with differential count, platelets
Serum creatinine, Ca2+, uric acid, $β_2$-microglobulin, albumin
Serum C-reactive protein, lactate dehydrogenase values (useful, but not required for formal diagnosis)
Serum protein electrophoresis with immunofixation
Quantification of immunoglobulins
Serum free light chain determination
Bone marrow aspirate and biopsy
Urinalysis
Electrophoresis and immunofixation of an adequately concentrated aliquot from a 24-hour urine specimen
If available, cytogenetics, fluorescence in situ hybridization from bone marrow specimen

Staging and Risk Stratification

Once a diagnosis of multiple myeloma (MM) has been established, patients are classified according to 2 staging systems: Durie-Salmon and the International Staging System (ISS). The Durie-Salmon system measures myeloma-related bone lesions on x-ray as well as concentrations of serum calcium, serum monoclonal protein, and urine Bence Jones protein to classify patients as having stage I, II, or III disease (Table 3).[Durie 1975]

Table 3. Durie-Salmon Myeloma Staging System Criteria **A clinical staging system for multiple myeloma. Correlation of measured cell mass with presenting clinical features, response to treatment and survival. Durie BGM, Salmon SE, copyright © 1975. Reproduced with permission of John Wiley & Sons, Inc.**

Stage I	Stage II	Stage III
All of the following: Hb > 10 g/L Serum Ca2+ normal (<12 mg/dL) X-rays: normal bone structure or solitary bone plasmacytoma only Low M-component production rates IgG value < 5 g/dL IgA value < 3 g/dL Urine light chain M-component on electrophoresis < 4 g/24 hrs	Overall data are minimally abnormal as shown for stage I and no single value as abnormal as defined for stage III	One or more of the following: Hb < 8.5 g/L Serum Ca2+ > 12 mg/dL Advanced lytic bone lesions (scale 3) High M-component production rates IgG value > 7 g/dL IgA value > 5 g/dL Urine light chain M-component on electrophoresis > 12 g/24 hrs
Subclassification: A = relatively normal renal function (serum creatinine value < 2.0 mg/dL) B = abnormal renal function (serum creatinine > 2.0 mg/dL)		

Ca2+, calcium; Hb, hemoglobin.

Thus, the Durie-Salmon stage reflects overall tumor burden. The ISS, on the other hand, provides both an aggregate measure of proliferative state and (through its β_2-microglobulin component) renal function as well as prognostic information.[Greipp 2005] Derived through multivariate analysis of clinical features present at the time of treatment initiation, the ISS uses serum β_2-microglobulin and serum albumin to categorize patients as having stage I (median survival: 62 months), stage II (median survival: 44 months), or stage III (median survival: 29 months) disease.

By ISS criteria, patients with β_2-microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL are stage I, whereas those with β_2-microglobulin ≥ 5.5 mg/L are stage III. The remaining patients are stage II, described as "neither stage I nor III," or more precisely, those who either have a serum albumin < 3.5 g/dL (ie, not meeting stage I criteria) or those with a stage I, or a β_2-microglobulin > 3.5 but < 5.5 mg/L, irrespective of serum albumin level (ie, not meeting stage III criteria).[Greipp 2005]

In addition to the ISS, genetic analysis of malignant plasma cells obtained from bone marrow aspirate samples provides important prognostic information in MM. Fluorescence in situ hybridization (FISH) analysis should target the previously discussed gene mutations that commonly occur in MM, including monosomy or del(13q), del(17p), t(4;14), t(11;14), and t(14;16).[NCCN 2012] Immunohistochemical staining of bone marrow samples at diagnosis can be used to determine expression of proteins partnered with specific genetic abnormalities in MM, such as fibroblast growth factor receptor 3, cyclin D1, c-maf, and p-53. Hyperdiploidy has been associated with a favorable prognosis, t(11;14) with an intermediate prognosis, and hypodiploidy, such as t(4;14), t(14;16), t(14;20), and del(17p), with a poor prognosis.[Stewart 2007; Yeung 2008; Gertz 2005; Chang 2005] Deletion 13 detected by metaphase karyotype, although not necessarily by interphase FISH analysis, is consistently associated with a poor prognosis in MM.[Avet-Loiseau 2007;Stewart 2007] It is important to note that almost all of these studies which documented the prognostic significance of the aforementioned markers involved treatment of patients with regimens that did not contain at least one of the novel agents (thalidomide, bortezomib, lenalidomide) recently developed for myeloma therapy. Consequently, the prognostic significance of some of these markers may not apply anymore with some of these new therapies. For instance, bortezomib-based treatments have been shown to overcome the adverse prognostic significance of chromosome 13 deletion.[Jagannath 2007; Sagaster 2007]

Gene expression profiling based on microarray analysis of mRNA derived from CD138-enriched plasma cells has recently been used to classify patients with MM.[Zhan 2007; Shaughnessy 2007] In one example of this approach, a group performed unsupervised hierarchical clustering of mRNA expression profiles on 414 newly diagnosed MM patients and identified 7 subgroups with unique molecular and phenotypic features.[Zhan 2006] Although gene expression profiling is still considered investigational in MM, it is likely that with additional study and refinement, the technique will be incorporated into the prognostic and therapeutic management of patients.

General Management Principles and Response Criteria

Patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (MM), and asymptomatic early-stage MM can be managed by observation alone. There is no evidence to suggest that early systemic MM therapy will benefit patients

at this stage of disease. Bisphosphonate therapy can be considered in this setting, particularly for patients with either smoldering or asymptomatic early phase disease who may have mild bone abnormalities or decreased bone density.

For patients with symptomatic MM, determinants of initial therapy are: eligibility for autologous stem cell transplantation (ASCT), comorbid conditions, performance score, the ability to participate in a clinical trial, patient preference regarding oral or intravenous therapy, and unique characteristics of the underlying plasma cell neoplasm. Eligibility for ASCT is established primarily on age and comorbidities, with an age limit of 65-70 years serving as a somewhat arbitrary cutoff for ASCT eligibility in MM. The procedure can be considered in older individuals who are otherwise fit at the discretion of the treating physician. Coexisting cardiovascular, pulmonary, hepatic, and renal disease are considered carefully in assessing patient fitness before proceeding with ASCT. Impaired renal function at the time of ASCT (creatinine clearance > 2 mg/mL) is associated with inferior survival among patients who undergo the procedure.[Blade 1998]
Patients ineligible for ASCT typically receive regimens combining novel drugs with conventional agents such as corticosteroids and alkylating agents. Patients eligible for ASCT receive induction therapy with a nonalkylator-containing regimen before peripheral blood stem cell mobilization, since alkylating agents such as melphalan are known to impair collection of healthy stem cells.
Levels of the serum and/or urine monoclonal protein (M-protein) before and after therapy are the basis for response assessment in MM. The most commonly used response criteria are those developed by the European Group for Blood and Marrow Transplantation (Table 4),[Blade 1998] commonly known as the EBMT criteria, and the more recent International Myeloma Working Group criteria.[Durie 2006] The serum free light chain assay can be a useful adjunct in monitoring response to therapy, particularly for patients with either oligo- or hyposecretory disease.[Bradwell 2003]Radiographic monitoring using skeletal bone survey, computed tomography, or magnetic resonance imaging plays an important role in the assessment of patients with significant extramedullary disease.
The aforementioned EBMT criteria are summarized below:

Table 4. EBMT Criteria for Response

Response	Criteria for Response
CR	Requires all of the following: ▪ Disappearance of the original M-protein from the blood and urine on at least 2 determinations for a minimum of 6 wks by immunofixation studies ▪ < 5% plasma cells in the bone marrow on at least 2 determinations for a minimum of 6 wks ▪ No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response) ▪ Disappearance of soft tissue plasmacytomas for at least 6 wks
PR	PR includes patients in whom some, but not all, criteria for CR are fulfilled providing the remaining criteria satisfy the requirements for PR. Requires all of the following: ▪ 50% reduction in the level of serum M-protein for at least 2 determinations 6 wks apart ▪ If present, reduction in 24-hr urinary light chain excretion by either > 90% or to < 200 mg for at least 2 determinations 6 wks apart ▪ ≥ 50% reduction in the size of soft tissue plasmacytomas (by clinical or applicable radiographic examination, ie, 2-dimensional magnetic resonance imaging or computed tomography scan) ▪ No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
MR	MR includes patients in whom some, but not all, criteria for PR are fulfilled providing the remaining criteria satisfy the requirement for MR. Requires all of the following: ▪ ≥ 25% to < 50% reduction in the level of serum M-protein for at least 2 determinations ▪ If present a 50 to 89% reduction in 24-hr light chain excretion, which still exceeds 200 mg/24 hrs for at least 2 determination 6 weeks apart. ▪ 25% to 49% reduction in the size of plasmacytomas (by clinical or applicable radiographic examination, ie, 2-dimensional magnetic resonance imaging or CT scan). ▪ No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
NC	Not meeting the criteria for MR or PD
PD for patients not in CR	Requires one or more of the following: ▪ > 25% increase in the level of monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on repeat investigation 1-3 wks later ▪ > 25% increase in 24-hr urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hrs and confirmed on a repeat investigation 1-3 wks ▪ > 25% increase in plasma cells in a bone marrow aspiration or on trephine biopsy, which must also be an absolute increase of at least 10% ▪ Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas ▪ Development of new bone lesions or soft tissue plasmacytomas (not including compression fractures) ▪ Development of hypercalcemia (corrected serum Ca2+ > 11.5 mg/dL or 2.8 mmol/L, not attributable to

Response	Criteria for Response
	other causes)
Relapse from CR	Requires at least 1 of the following: ▪ Reappearance of monoclonal paraprotein on immunofixation or routine electrophoresis to an absolute value > 5 g/L confirmed by at least 1 follow-up 6 wks later and excluding oligoclonal immune reconstitution ▪ > 5% plasma cells in a bone marrow aspirate or biopsy ▪ Development of new lytic bone lesions or soft tissue plasmacytomas, or definite increase in the size of residual bone lesions (not including compression fractures) ▪ Development of hypercalcemia (corrected serum Ca2+ >11.5 mg/dL or 2.8 mmol/L, not attributable to other causes)

CR, complete response; CT, computed tomography; MR, minimal response; NC, no change; PD, progressive disease; PR, partial response.

Several factors have led to the development of the International Response Criteria,[Durie 2006] including the need for more refined criteria by which to compare levels of response; the need to subclassify complete responders based on the presence or absence of clonal plasma cells within the bone marrow; and the intention to better assess response in patients with nonsecretory or oligosecretory disease.
In the International Myeloma Working Group Uniform Response Criteria, **complete response (CR)** is identified by negative immunofixation on urine and serum, the absence of plasmacytomas, and bone marrow with fewer than 5% plasma cells. Patients are considered to have a **stringent complete response (sCR)** if, in addition to meeting criteria for CR, they have a normal serum free light chain (FLC) ratio and an absence of clonal cells in bone marrow as assessed by immunohistochemistry or immunofluorescence. In contrast, **very good partial response (VGPR)** is defined as either the presence of serum/urine M-protein by immunofixation but not electrophoresis, or as a ≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 hours. A **partial response (PR)** is defined as a reduction in the serum M-protein of at least 50%, and a reduction in the 24-hour urine M-protein by at least 90% or < 200 mg/24 hours. If the serum and urine M-protein are unmeasurable, a decrease in the difference between involved/uninvolved FLC levels of 50% is required to meet criteria for PR, and if FLC is also unmeasurable, a reduction in plasma cells of at least 50% is required (as long as the bone marrow plasma cell percentage was at least 30% at baseline). Finally, if soft tissue plasmacytomas were present at baseline, they must be reduced by at least 50%.

Novel Therapies in the Treatment of Multiple Myeloma

Regimens built upon novel therapies now constitute first-line therapy for both transplantation-eligible and transplantation-ineligible patients with relapsed multiple myeloma and newly diagnosed disease. In addition, maintenance therapy following autologous stem cell transplantation using novel therapies can be considered in selected patients.

Thalidomide

Thalidomide-containing regimens can be employed as salvage therapy in the setting of relapsed disease, primary induction therapy for transplant candidates and nontransplantation candidates, and maintenance therapy following autologous stem cell transplantation. This agent exhibits, through its liver-derived metabolites, various anti–multiple myeloma properties, including direct anti–multiple myeloma activity, inhibition of angiogenesis through effects on vascular endothelial growth factor and basic fibroblast growth factor,[D'Amato 1994] enhancement of T-cell and natural killer cell–mediated immunologic response,[Davies 2001] disruption of multiple myeloma stromal cell adhesion,[Geitz 1996] and induction of caspase-8 mediated apoptosis.[Mitsiades 2002]

Thalidomide in Relapsed and Refractory Multiple Myeloma

The activity of thalidomide in multiple myeloma (MM) was first demonstrated in a phase II trial by Singhal and colleagues[Singhal 1999] in which 84 patients with relapsed and relapsed/refractory MM received thalidomidemonotherapy at doses ranging from 200-800 mg/day. In this heavily pretreated group, the overall response rate was 32%. In 169 patients who ultimately enrolled in the trial, the 2-year event-free survival and overall survival rates were 20% and 48%, respectively,[Barlogie 2001] with 10-year event-free survival and overall survival rates of 6% and 10%, respectively.[van Rhee 2008] These impressive results were corroborated by other clinical trials involving thalidomide. In a systematic review of 42 phase II trials involving 1674 patients with relapsed and refractory MM, thalidomidemonotherapy produced an overall response rate of 29.4% and a median overall survival of 14 months.[Glasmacher 2006]

Thalidomide in Newly Diagnosed Multiple Myeloma

As has been demonstrated in several phase III trials, thalidomide in combination with melphalan (MP) andprednisone (MPT) is an effective regimen for patients with newly diagnosed MM who are ineligible for autologous stem cell transplantation (ASCT). In a randomized phase III trial by Palumbo and colleagues,[Palumbo 2006] MPT was compared with MP in 255 previously untreated patients aged 60 years or older. The overall response and near complete response plus complete response rates among patients who received MPT were 76.0% and 27.9%, respectively, compared with 47.6% and 7.2%, respectively, in the MP group. In addition, MPT was superior to MP in terms of both 2-year event-free survival (54% vs 27%, respectively) and 3-year overall survival (80% vs 64%, respectively).

In another phase III trial by Facon and colleagues,[Facon 2007] 447 individuals between 65 and 75 years of age with previously untreated MM were randomly assigned to receive either MP, MPT, or 2 courses of VAD (vincristine,doxorubicin, and dexamethasone) followed by reduced-intensity ASCT using melphalan 100 mg/m^2. A partial response or better was achieved in 35% of patients treated with MP, 76% of those treated with MPT, and 65% of those who received VAD followed by ASCT. Complete response rates were 2%, 13%, and 18% in the MP, MPT, and VAD followed by melphalan-ASCT arms, respectively. Although response rates in the MPT and melphalan-ASCT arms were similar, after a median follow-up of 51.5 months, MPT produced superior progression-free survival compared with melphalan-ASCT (27.5 vs 19.4 months, respectively) and median overall survival (51.6 vs 38.3 months, respectively).

However, results of studies comparing MP with MPT are conflicting, and a recent meta-analysis of 5 prospective randomized trials (N = 1568) found that the addition of thalidomide to MP improved response rates and progression-free survival and was associated with a trend toward improved overall survival vs MP alone, but at a cost of greater toxicity.[Kapoor 2011] The odds ratio for a response to therapy with MPT vs MP was 3.39 (P < .001), indicating MPT was superior to MP. The hazard ratio for progression-free survival was 0.68 (P < .001) and for 0.8 for overall survival (P = .07), respectively, in favor of MPT.

The efficacy of thalidomide and dexamethasone (TD) in transplantation-eligible patients with newly diagnosed MM is well documented. In a retrospective, case-control analysis, TD and VAD induction were compared in 200 patients, and TD yielded higher rates of overall response (76% vs 52% for VAD).[Cavo 2005] Patients in both treatment groups successfully underwent stem cell collection, and more than 90% of study participants received ASCT.

In a phase III study, Rajkumar and colleagues[Rajkumar 2006] randomized 207 individuals with newly diagnosed MM to either dexamethasone alone or TD. The TD arm compared with the dexamethasone arm achieved superior overall response (63% vs 41%, respectively; P = .0017) and complete response (4% vs 0%, respectively) rates. Risk of early grade 4/5 toxicity was significantly greater with the combination regimen. In a second, larger phase III trial also led by Rajkumar and colleagues,[Rajkumar 2008] 470 transplantation-eligible, newly diagnosed MM patients were randomized to either dexamethasone plus placebo or TD. Combination therapy yielded an overall response rate of 64%, whereasdexamethasone alone produced an overall response rate of 46%. Time to progression was longer in patients who received the combination (median: 22.6 vs 6.5 months, respectively). Grade 4 adverse events were more frequent in the TD arm than in the group treated with dexamethasone alone (30.3% vs 22.8%, respectively).

Thalidomide Maintenance Therapy Following Autologous Stem Cell Transplantation

Along with its role in patients with newly diagnosed and relapsed multiple myeloma (MM), thalidomide has also been evaluated as maintenance therapy following autologous stem cell transplantation (ASCT). The basis for this approach stems from the recognition that although many patients achieve a complete response following ASCT, others do not. Patients who do not achieve a complete response may gain further reduction in tumor burden with additional therapy. Moreover, even patients in complete response following ASCT ultimately relapse. Maintenance therapy could thus theoretically improve clinical outcomes in such patients by suppressing a small, clinically undetectable clonal population of MM cells.

Several randomized clinical trials have addressed the role of thalidomide maintenance following ASCT. In a study by Attal and colleagues,[Attal 2006] 597 patients with MM were randomized after induction therapy and ASCT to either observation, pamidronate, or pamidronate plus thalidomide 400 mg daily. The rate of response, 3-year event-free survival, and 4-year overall survival were significantly better among patients who received pamidronate plusthalidomide than in the other treatment groups. In another study of thalidomide maintenance, Spencer and colleagues[Spencer 2009] randomized 243 patients with MM who had previously undergone induction therapy followed by ASCT to either prednisolone 50 mg every other day maintenance alone or the same dose and schedule ofprednisolone plus thalidomide (initial dose of 100 mg daily, with an increase to 200 mg daily after 2 weeks if well tolerated). Use of thalidomide-based maintenance resulted in superior 3-year progression-free survival (42% vs 23%) and overall survival (86% vs 75%) rates. Of note, the 12-month rate of survival following disease progression was similar in the 2 treatment groups.

Thalidomide has also been assessed as part the intensive Total Therapy 2 program developed at the University of Arkansas-Little Rock. In a study by Barlogie and colleagues,[Barlogie 2006] 668 patients with newly diagnosed MM received the Total Therapy regimen, consisting of induction with vincristine, doxorubicin, and dexamethasone (VAD);dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP); and cyclophosphamide, doxorubicin, anddexamethasone (CAD); tandem ASCT using high-dose melphalan; consolidation with dexamethasone, cisplatin,doxorubicin, cyclophosphamide, and etoposide (DPACE); and maintenance with interferon alfa-2b anddexamethasone. Study participants were randomized to either placebo or thalidomide as part of induction, consolidation, and maintenance. The incorporation of thalidomide within the treatment regimen resulted in higher rates of complete response (62% vs 43%, respectively) and 5-year event-free survival (56% vs 44%, respectively). However, the 5-year overall survival was equivalent in the two treatment groups at 65%, and median survival after relapse was shorter in the thalidomide group than in the control group (1.1 vs 2.7 years, respectively). However, the apparent lack of overall survival benefit in the thalidomide cohort should be interpreted with caution, since 83% of patients in the control arm received thalidomide after relapse. The longer postrelapse survival of patients in the control arm may represent benefit derived by thalidomide administration late in the course of treatment. Conversely, 77% of relapsed patients in the thalidomide arm

continued on thalidomide-based salvage therapy in spite of acquiredthalidomide resistance. Therefore, this particular study may indicate comparable benefit of early vs late thalidomidetreatment on overall survival, rather than lack of efficacy of thalidomide overall.

Thalidomide-Associated Toxicities

Because of the teratogenic effects associated with thalidomide, access to the drug is restricted in most countries to patients who participate in the System for Thalidomide Education and Prescription Safety (STEPS) program. Sedation, fatigue, and constipation should be anticipated in patients who receive thalidomide. These toxicities can be cumulative as well as dose dependent.[Richardson 2004] Peripheral neuropathy is a dose-dependent and time-dependent toxicity associated with thalidomide,[Mileshkin 2006] resulting from axonal injury and loss of large-diameter myelinated nerve fibers.[Dimopoulos 2004] The incidence of venous thromboembolism with thalidomide plus eitherdexamethasone or chemotherapy ranges from 3% to 34% among patients with newly diagnosed multiple myeloma, and from 2% to 15% among those with relapsed and refractory disease.[Palumbo 2008] As a result, anticoagulation with either full-dose warfarin targeting an international normalized ratio of 2.0-3.0 or a prophylactic dose of low molecular-weight heparin is generally preferred for individuals who receive thalidomide in combination with eitherdexamethasone or chemotherapy,[Rajkumar 2005] whereas aspirin is appropriate for patients intolerant of or unwilling to receive anticoagulation. Other infrequent but important thalidomide-associated toxicities include bradycardia,[Kaur 2003] hypothyroidism,[Badros 2002] hepatotoxicity,[Trojan 2003] pulmonary hypertension, and skin reactions that can range from a mild macular-papular rash[Grover 2002] to life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis.[Rajkumar 2000]

Lenalidomide

Lenalidomide is a thalidomide analogue modified by elimination of a carbonyl group and addition of an amine.Lenalidomide exerts its anti–multiple myeloma (MM) activity via several mechanisms, including upregulation ofinterferon gamma-1b and interleukin-2, with a resulting increase in natural killer activity, inhibition of angiogenesis, direct anti-MM effect leading to induction of apoptosis, and modulation of binding of multiple myeloma cells to bone marrow stromal cells.[Davies 2001; Mitsiades 2002; Chang 2006; Dredge 2005] Lenalidomide also modulates bone metabolism by potently inhibiting osteoclastogenesis.[Breitkreutz 2008]

Lenalidomide in Relapsed and Refractory Multiple Myeloma

In phase I and II investigations, lenalidomide was shown to be active and well tolerated, with or withoutdexamethasone, in patients with relapsed or refractory multiple myeloma (MM).[Richardson 2002; Richardson 2006c]Subsequently, two large, randomized phase III clinical trials in relapsed MM—the MM-009 North American study and the MM-010 European/Israeli/Australian study—confirmed the efficacy of lenalidomide in combination withdexamethasone for relapsed MM.[Weber 2007; Dimopoulos 2007] Study participants in both MM-009 and MM-010 were randomized to either placebo or lenalidomide, with dexamethasone administered to both treatment groups.Lenalidomide and dexamethasone yielded superior overall response rates compared with placebo in both MM-009 (61.0% vs 19.9%, respectively) and MM-010 (60% vs 24%, respectively). Median time to progression, the primary endpoint of the trials, was significantly longer in both MM-009 (11.1 vs 4.7 months, respectively) and MM-010 (11.3 vs 4.7 months, respectively).

As dexamethasone toxicities can be dose-limiting, investigators have further studied single-agent lenalidomide 30 mg/day once daily in 222 patients with relapsed and refractory MM, and found it to be safe and effective with acceptable grade 3 or 4 toxicities (the most common being neutropenia in 60%); the results support the use of this dosing regimen alone or in steroid-sparing combination regimens.[Richardson 2009a] Early-phase clinical trials indicate that lenalidomide is also effective in combination with both alkylating agents and anthracyclines in relapsed and refractory MM. The combinations of lenalidomide, doxorubicin, and dexamethasone (RAD) as well as lenalidomide,cyclophosphamide, and dexamethasone (RCD) yielded promising results in these studies.[Morgan 2007] A phase II trial of lenalidomide and dexamethasone in combination with elotuzumab, an investigational humanized monoclonal IgG1 antibody directed against the CS1 antigen, reported an overall response rate of 85% among 59 patients with relapsed/refractory MM.[Richardson 2010a] A phase I study of bendamustine combined with lenalidomide anddexamethasone in 26 patients with relapsed/refractory MM found 63% of patients achieved at least a partial response.[Lentzsch 2010]

Bortezomib in combination with lenalidomide and dexamethasone (RVD) also appears to be very effective in the treatment of both newly diagnosed and relapsed MM. In a phase II study, 64 patients with relapsed and refractory MM were treated with RVD for up to eight 21-day cycles.[Richardson 2008] When reported, the overall response rate (complete/near complete response plus very good partial response plus partial response plus minimal response) in this study was 86%, with 24% of study participants achieving a complete/near complete response and 67% achieving a partial response or better. Patients who responded to therapy experienced a median duration of response of 21 weeks. Of note, response rates in this study were equivalent among patients with standard- and high-risk disease features, including advanced International Staging System score and cytogenetic abnormalities. Toxicities associated with RVD in this study included grade 1/2 myelosuppression and only 2 cases of deep vein thrombosis, with minimal significant peripheral neuropathy.

Lenalidomide in Newly Diagnosed Multiple Myeloma

Lenalidomide-containing regimens have also been used successfully in the management of individuals with newly diagnosed multiple myeloma (MM). In a phase II study, Lacy and colleagues[Lacy 2007] treated 34 previously untreated MM patients with lenalidomide and dexamethasone. After 4 cycles, patients continued lenalidomide anddexamethasone, proceeded to autologous stem

cell transplantation (ASCT), or were observed without therapy. The overall response rate was 91%, with partial response, very good partial response, and complete response rates of 35%, 38%, and 18%, respectively. The 2-year progression-free survival rates for patients who underwent ASCT and those who remained on lenalidomide and dexamethasone were 83% and 59%, respectively. The 3-year overall survival rate for those who underwent ASCT was 92% and 85% for those who remained on lenalidomide anddexamethasone.

In a large phase III ECOG E4A03 trial led by Rajkumar and colleagues,[Rajkumar 2010] 445 patients with newly diagnosed MM were randomized to lenalidomide and either high-dose dexamethasone (RD) (40 mg/day on Days 1-4, 9-12, and 17-20) or low-dose dexamethasone (Rd) (40 mg/day on Days 1, 8, 15, and 22). RD was superior to Rd regarding overall response (79% vs 69%, respectively; odds ratio: 1.75; 80% confidence interval: 1.30-2.32; $P = .008$). However, Rd produced superior overall survival rates compared with RD (96% vs 87%, respectively; $P = .0001$ at 1 year). Grade ≥ 3 toxicity occurred in 50% of RD-treated patients as opposed to 30% of the Rd arm, which in part explains the inferior outcomes seen with higher-dose dexamethasone.

Richardson and colleagues[Richardson 2010b] conducted a phase I/II prospective evaluation oflenalidomide/bortezomib/dexamethasone (RVD) as frontline therapy for newly diagnosed MM patients (N = 66). Phase II dosing comprised eight 3-week cycles of bortezomib 1.3 mg/m^2 on Days 1, 4, 8, and 11 plus lenalidomide 25 mg on Days 1-14 with dexamethasone 20 mg on Days 1, 2, 3, 4, 8, 9, 11, and 12. Responders received transplantation or maintenance therapy. In both the phase I and II populations, 100% of patients responded to the RVD regimen, including 74% of the phase II population achieving a very good partial response or better. At a median follow-up of 21 months, the estimated 18-month progression-free survival and overall survival rates were 75% and 97%, respectively. Complete or near complete responses were achieved by 57% of the phase II population. This high overall extent and frequency of response now is allowing for a large (planned N = 1000) randomized trial of RVD, with or without transplantation and high-dose therapy, as first-line therapy in myeloma patients (Clinical Trial: NCT01208662).

Similarly, Kumar and colleagues[Kumar 2009a] are conducting the randomized phase II EVOLUTION study, which is evaluating induction therapy with either RVD, bortezomib/dexamethasone/cyclophosphamide (VDC), or lenalidomideplus VDC (VDCR). All patients received bortezomib maintenance therapy, and eligible patients could choose ASCT as well. In results presented at the 2008 annual meeting of the American Society of Hematology, the overall response rates for RVD, VDC, and VDCR were similar (90%, 97%, and 94%, respectively). However, the complete response rate was substantially lower in the VDC arm compared with the VDR and VDCR arms (6% vs 12% and 15%, respectively). In addition, higher rates of serious adverse events were seen in the VDCR arm compared with VDR and VDC (37% vs 24% and 13%, respectively). Ongoing attempts are comparing clinical and molecular (polymerase chain reaction negative) complete responses achieved by RVD vs VDC vs VDR.

Palumbo and colleagues[Palumbo 2010a] conducted a randomized phase III study comparing melphalan andprednisone (MP) vs MP plus lenalidomide (MPR) vs MPR with lenalidomide maintenance (MPR-R) in newly diagnosed elderly myeloma patients (N = 459) (Capsule Summary). Results showed that overall response rates were significantly higher with MPR-R vs MPR or MP. After a median follow-up of 25 months, risk of disease progression was reduced 60% in the MPR-R arm vs MP (hazard ratio: 0.398; $P < .0000001$). Median progression-free survival was 31 months in the MPR-R arm vs 13-14 months in the remaining arms.

Importantly, 2 recent randomized phase III trials investigated lenalidomide maintenance therapy after transplantation. In the CALGB 100104 trial (N = 568), lenalidomide 10 mg/day was associated with a significant prolongation in median time to progression vs placebo (42.3 vs 21.8 months, respectively; $P < .0001$), with a 60% reduction in the risk of progression or death vs placebo (Capsule Summary).[McCarthy 2010] In this trial, 12% of patients discontinuedlenalidomide because of adverse events. Similar findings were reported from the phase III IFM 2005-02 trial (N = 614) (Capsule Summary).[Attal 2010] In this study, investigators compared lenalidomide 10-15 mg/day maintenance therapy (n = 307) with placebo (n = 307), each continued until relapse, in patients with at least stable disease ≤ 6 months following first-line ASCT. Before randomization, all patients received consolidation lenalidomide 25 mg/day on Days 1-21 of two 28-day cycles. Lenalidomide maintenance therapy was associated with a 50% reduction in the risk of disease progression or death relative to placebo, and a 21% rate of discontinuation for adverse events compared with 15% in the placebo group. The overall survival rate at 5 years postdiagnosis was 81% in both treatment arms. Although overall survival data from CALGB 100104 and IFM 2005-02 are not yet mature, these landmark studies have set the stage for the routine use of maintenance therapy with lenalidomide in MM.

Increased secondary cancers have been observed in patients receiving lenalidomide maintenance after transplantation. These observations are potentially related to prior DNA damaging agent therapies; however, the benefit of maintenance lenalidomide far outweighs this risk.

The combination of lenalidomide and dexamethasone with the novel proteasome inhibitor carfilzomib has reported efficacy as a first-line treatment for MM in phase I/II study.[Jakubowiak 2010]

Lenalidomide-Associated Toxicities

Although the teratogenic effects of lenalidomide in humans are unknown, access to the drug is restricted to individuals who participate in the RevAssist program, which aims to prevent fetal exposure to lenalidomide and minimize the risk of birth defects.

Unlike thalidomide, lenalidomide is rarely associated with peripheral neuropathy. In the MM-009 and MM-010 clinical trials, myelosuppression was the most common high-grade toxicity.[Weber 2007;Dimopoulos 2007] Analysis of elderly patients receiving lenalidomide-containing therapy for newly diagnosed multiple myeloma suggests that overall risk for secondary primary

malignancies is low (Capsule Summary).[Palumbo 2011]Although lenalidomide as a single agent has not been associated with a markedly increased risk of venous thromboembolism,[Richardson 2002] the lenalidomide and dexamethasone combination was associated with venous thromboembolism rates of 14.7% and 8.5% in the MM-009 and MM-010 studies, respectively.[Weber 2007; Dimopoulos 2007] A rash, which may be morbilliform, urticarial, dermatitic, or acneiform, develops in up to 30% of patients who receive lenalidomide.[Sviggum 2006] Other rare toxicities associated with lenalidomide-based therapy include hepatotoxicity[Hussain 2007] and hypersensitivity pneumonitis.[Thornburg 2007] Progressive azotemia has been reported in patients with preexisting renal dysfunction who received lenalidomide and dexamethasone.[Batts 2008] Several groups have demonstrated that exposure to lenalidomide impairs stem cell collection.[Kumar 2007; Mazumder 2008;Paripati 2008] Mobilization with cyclophosphamide and filgrastim, rather than filgrastim alone, however, appears to overcome the inhibitory effect lenalidomide exposure has on stem cell mobilization.[Mark 2008]

Bortezomib

Bortezomib is a boronic acid dipeptide small molecule that reversibly inhibits the chymotrypsin-like activity of the 20S proteasome. Various mechanisms account for the agent's anti–multiple myeloma activity. Bortezomib inhibits NK-kB, induces caspase-8/9 mediated apoptosis, cleaves DNA repair enzymes, and disrupts interleukin-6–induced activation of the ERK, STAT3, and AKT pathways.[Hideshima 2001b; Hideshima 2002; Mitsiades 2003; Hideshima 2003a;Hideshima 2003b] In addition, bortezomib influences bone metabolism by both inhibiting osteoclast activity and promoting osteoblast differentiation and proliferation.[von Metzler 2007; Mukherjee 2008]

Bortezomib in Relapsed and Refractory Multiple Myeloma

After encouraging results from early phase clinical trials,[Orlowski 2002; Richardson 2003; Jagannath 2004] the efficacy ofbortezomib in relapsed multiple myeloma (MM) was confirmed by a phase III study in which 669 patients with relapsed MM were randomized to either bortezomib or dexamethasone.[Richardson 2005] Bortezomib was superior to high-dose dexamethasone regarding rates of overall response (38% vs 18%, respectively), complete response (6% vs 1%, respectively), median time to progression (6.22 vs 3.49 months, respectively), and 1-year overall survival (80% vs 66%, respectively). Grade 3/4 treatment-related toxicities included thrombocytopenia (26%), neutropenia (14%), anemia (10%), peripheral neuropathy (7%), and diarrhea (7%). With extended follow-up, the overall and complete response rates among bortezomib-treated patients increased to 43% and 95%.[Richardson 2007] The median overall survival was 29.8 months in the bortezomib arm vs 23.7 months in the dexamethasone arm, despite crossover in more than 60% of patients. Importantly, activity was seen in patients with adverse features and advanced age, as well as poor-risk cytogenetics.[Richardson 2006a]

Several clinical trials have demonstrated the effectiveness of regimens combining bortezomib with both corticosteroids and anthracyclines. In a phase III trial by Orlowski and colleagues,[Orlowski 2007] for example, 646 patients with relapsed MM, 66% of whom had received 2 or more previous lines of therapy, received either bortezomibor bortezomib in combination with doxorubicin liposomal. The combination was superior to bortezomib alone in terms of median time to progression (9.3 vs 6.5 months, respectively) and 15-month overall survival (76% vs 65%, respectively). Although grade 3/4 toxicities, such as anorexia, vomiting, thrombocytopenia, neutropenia, and hand-foot syndrome, occurred more frequently with the doublet, cardiac toxicity was only moderately increased with the combination, and rates of peripheral neuropathy were equivalent in both arms.

Bortezomib has been combined with multiple other agents, based on preclinical rationale, to achieve responses in relapsed and refractory MM, including patients refractory to bortezomib alone. As was discussed in the lenalidomidesection, lenalidomide, bortezomib, dexamethasone (RVD) can achieve responses in nearly 60% of patients with relapsed and refractory MM.[Richardson 2008] Likewise, Ghobrial and colleagues[Ghobrial 2011] have shown, in a phase II trial conducted in 43 relapsed or refractory patients, that 33% achieved at least a minimal response with the addition of the mTOR inhibitor temsirolimus to bortezomib.

Based on preclinical studies showing that combining an Akt inhibitor, perifosine, with bortezomib mediates synergistic in vitro cytotoxicity,[Hideshima 2006] clinical trials are evaluating perifosine plus bortezomib in advanced MM. For example, sustained responses were observed in a phase I/II study of perifosine, bortezomib, anddexamethasone,[Richardson 2009b] and a phase III clinical trial is now comparing this combination vs bortezomib alone in relapsed MM (Clinical Trial: NCT01002248). Finally, preclinical studies show that the addition of a histone deacetylase (HDAC) inhibitor to bortezomib to block aggresomal and proteasomal degradation of proteins, respectively, mediates synergistic MM cytotoxicity.[Hideshima 2005] Already, phase I/II clinical trials have shown that the combination of bortezomib with either of the HDAC inhibitors vorinostat[Siegel 2010] or panobinostat[San Miguel 2010]can achieve responses in the majority of patients with bortezomib-refractory MM; phase III clinical trials of bortezomibplus vorinostat (Clinical Trial: NCT00773747) or panobinostat (Clinical Trial: NCT01023308) in advanced MM are ongoing.

Bortezomib in Newly Diagnosed Multiple Myeloma

Bortezomib is effective as a single agent in previously treated multiple myeloma[Richardson 2009c] but is especially active in combination with other agents. Indeed, bortezomib in combination with melphalan and prednisone was shown to be an effective regimen for patients with newly diagnosed multiple myeloma (MM) who are ineligible for autologous stem cell transplantation (ASCT). In a phase III trial by San Miguel and colleagues,[San Miguel 2008] 682 ASCT-ineligible patients with previously untreated MM were randomized to either bortezomib plus melphalan andprednisone (VMP) or melphalan and prednisone (MP) alone. VMP was superior to MP in terms of time to progression (24 vs 16.6 months, respectively), complete response rate (30% vs 4%, respectively) and duration of response (median: 19.9

vs 13.1 months, respectively). The hazard ratio for survival also favored VMP over MP (0.61). Grade 3 toxicities were more frequent with VMP than MP (53% vs 44%, respectively), whereas grade 4 toxicities were equivalent (28% vs 27%, respectively). Within the VMP arm, 13% of patients experienced grade 3 peripheral neuropathy.

The phase IIIb UPFRONT study compared 3 bortezomib-based induction regimens followed by bortezomibmaintenance therapy in transplantation-ineligible elderly patients with MM (Capsule Summary).[Niesvizky 2010] Three hundred patients were randomized to induction therapy comprising either bortezomib plus dexamethasone (VD);bortezomib, thalidomide, and dexamethasone (VTD); or bortezomib, melphalan, and prednisolone (VMP). High response rates were observed across treatment arms: 71% to 79% obtained a response after induction and maintenance. The highest frequency of adverse events was observed with VTD.

Palumbo and colleagues[Palumbo 2010b] conducted a randomized phase III study which compared VMP plusthalidomide (VMPT) plus bortezomib and thalidomide (VT) maintenance therapy with VMP induction and no maintenance therapy in 511 newly diagnosed transplantation-ineligible elderly patients with MM. The overall response rate, extent of response, and progression-free survival rate were superior with VMPT plus VT. The 3-year estimate of progression-free survival was 56% in patients receiving VMPT-VT and 41% in those receiving VMP (hazard ratio: 0.67; 95% confidence interval: 0.50-0.90; *P* = .008). However, overall survival was not improved. Importantly, this study showed that the use of bortezomib weekly rather than twice weekly markedly decreased neurotoxicity, risk of discontinuation, and prolonged time on therapy without compromising efficacy. Mateos and colleagues[Mateos 2010]studied VMP vs bortezomib, thalidomide, and prednisone (VTP) in this patient population, with randomization in each cohort to VT vs VP maintenance therapy. The majority of patients responded to either induction therapy (at least partial response: VTP 81% vs VMP 80%; *P* = .9), although VTP resulted in more serious adverse events (31% vs 15%; *P* = .01) and discontinuations (17% vs 12%; *P* = .03) than did treatment with VMP. Patients who received VT maintenance had were more likely to obtain complete remission than those receiving VP maintenance (44% vs 39%, respectively).

Bortezomib, thalidomide, and dexamethasone (VTD) is an effective regimen for patients with previously untreated MM who are eligible for autologous stem cell transplantation (ASCT). In a phase III study by Cavo and colleagues,[Cavo 2010a] 480 transplantation-eligible patients with newly diagnosed MM were randomized to VTD or thalidomide anddexamethasone (TD) as induction therapy before and maintenance therapy after double ASCT. After induction therapy, complete or near complete remission was obtained by 31% of patients receiving VTD vs 11% receiving TD (*P* < .0001). Grade 3/ 4 adverse events were significantly more common in patients on VTD than in those on TD (56% vs 33%; *P* < .0001), with a significantly higher occurrence of peripheral neuropathy in patients on VTD. Analysis of patients through consolidation during a median of 36 months' follow-up has been reported separately (Capsule Summary).[Cavo 2010b] Among patients who underwent double ASCT, those treated with VTD experienced higher posttransplantation rates of complete/near complete response vs TD (55% vs 41%, respectively; *P* = .0024), and higher rates of complete/near complete response following consolidation (62% vs 45%; *P* = .0002). Three-year progression-free survival was superior among patients who received VTD compared with TD (68% vs 56%, respectively; *P* = .0057). The 3-year overall survival rate was similar in both arms (87% vs 84%), although the study was not powered to detect a difference in this parameter.

For transplantation-eligible patients with newly diagnosed MM, regimens such as bortezomib and dexamethasone(VD) and bortezomib plus doxorubicin and dexamethasone (PAD) are effective.[Jagannath 2005; Oakervee 2005] In a study by Harousseau and colleagues,[Harousseau 2010] 482 patients with newly diagnosed MM were randomized to induction therapy with either 4 courses of vincristine, doxorubicin, and dexamethasone (VAD) or 4 courses of VD. Study participants then underwent a second randomization to 2 cycles of dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) consolidation or not prior to ASCT. VD was superior to VAD in rates of very good partial response or better (37.7% vs 15.1%, respectively; *P* < .0001) and complete/near complete response (14.8% vs 6.4%, respectively; *P* = .0035), even among patients with advanced International Staging System score and del(13). The clinical benefit associated with VD persisted post-ASCT (in those who actually had a first transplantation) in rates of both very good partial response or better (54.3% v 37.2%, respectively; *P* < .0001) and complete/near complete response (35.0% v 18.4%, respectively; *P* < .0001). Response rates were not improved in either treatment group by DCEP consolidation.

A phase III study by Sonneveld and colleagues[Sonneveld 2010] has demonstrated that PAD induction therapy plusbortezomib maintenance following ASCT is also effective for individuals with newly diagnosed MM. In this trial, 744 transplantation-eligible patients were randomized to either PAD or VAD followed by stem cell mobilization and either single or tandem ASCT (Capsule Summary). Patients treated with VAD then received maintenance therapy with dailythalidomide, whereas those in the PAD arm received bortezomib every other week as maintenance. Survival outcomes were significantly prolonged with PAD/bortezomib vs VAD/thalidomide (hazard ratio for overall survival: 0.73; 95% confidence interval: 0.56-0.96; *P* = .02). The bortezomib survival benefit was maintained in poor-risk subgroups, including those with elevated creatinine levels and high-risk cytogenetics. Maintenance bortezomib therapy was also better tolerated than thalidomide, with fewer discontinuations in the bortezomib group.

Bortezomib-Associated Toxicities

Important adverse effects associated with bortezomib include peripheral neuropathy, thrombocytopenia, and gastrointestinal symptoms. The incidence of bortezomib-associated peripheral neuropathy appears to be cumulative, with the incidence peaking at a dose of approximately

30 mg/m^2.[Richardson 2006b] In most cases, bortezomib-associated peripheral neuropathy is reversible with interruption of therapy or dose modification.[Richardson 2006b;Badros 2007; Richardson 2009c] Importantly, Palumbo and colleagues[Palumbo 2010b] have shown that the use of weeklybortezomib is associated with markedly less neurotoxicity and reduced likelihood of discontinuation than twice-weekly dosing with no loss of efficacy. Adverse events, including peripheral neuropathy, may be less frequent with subcutaneous rather than intravenous bortezomib according to data from the relapsed setting.[Moreau 2010]

Thrombocytopenia in the context of bortezomib therapy is usually cyclical, with a decline in the platelet count during the 2-week treatment period followed by recovery during the rest period and is only very rarely associated with bleeding.[Lonial 2005] Gastrointestinal adverse effects observed with bortezomib include diarrhea, nausea and emesis, constipation, anorexia, and abdominal pain. Attentive symptom-directed management is recommended, using stool softeners, laxatives, antidiarrheals, antiemetics, and either proton-pump inhibitors or H_2-receptor blockers, when appropriate. Bortezomib is associated with an increased risk of herpes zoster virus reactivation, and antiviral prophylaxis should be considered in patients with no contraindications to such therapy. Rare instances of lung injury have been reported in patients receiving bortezomib, including bronchiolitis obliterans with organizing pneumonia,[Zappasodi 2007] pulmonary fibrosis,[Duek 2007] and diffuse alveolar hemorrhage.[Miyakoshi 2006] These are typically managed with high-dose steroids and usually reversible with treatment cessation. Of potential interest to practices with high numbers of patients of Asian descent, pulmonary toxicities associated with bortezomib appear to be somewhat higher in MM patient populations in the Far East.[Ogawa 2008]

It should be noted that patients with moderate or severe hepatic impairment should be started on bortezomib at a reduced dose of 0.7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance.[Bortezomib PI]

Choice of Therapy

With the introduction of novel therapies in multiple myeloma (MM), clinicians now have a variety of treatment options for managing patients with newly diagnosed and relapsed MM. Lenalidomide-based or thalidomide-based therapies are used for patients who prefer or require oral therapy. Bortezomib-containing regimens are favored for patients with high International Staging System score or high-risk cytogenetic abnormalities, as the agent has consistently been shown to overcome the poor prognosis associated with these findings.[Richardson 2006a; Harousseau 2010]

Renal dysfunction, which is observed in 20% to 40% of individuals with newly diagnosed MM, also influences choice of therapy in certain circumstances.[Kyle 2003] Lenalidomide is rapidly absorbed following oral administration and is excreted unchanged in urine. The half-life of lenalidomide increases with declines in creatinine clearance[Chen 2007] ; because of that, lenalidomide-containing therapy in MM patients with renal insufficiency has been associated with myelosuppression,[Roussou 2008] and specific lenalidomide dose adjustments are recommended for patients with varying degrees of renal dysfunction.[Lenalidomide PI]

Bortezomib is not renally cleared, and therefore, dose adjustment is not necessary in patients with renal dysfunction. The anti-MM activity of bortezomib is preserved in patients with renal failure, and improvements in renal function following therapy have been seen in a significant number of patients.[Roussou 2008; Chanan-Khan 2007]

Decisions concerning 2-drug vs 3-drug regimens are influenced by individualized treatment goals. As previously discussed, 3-drug combinations such as bortezomib, thalidomide, and dexamethasone (VTD) and lenalidomide,bortezomib, dexamethasone (RVD) produce high overall response and complete response rates with manageable side effect profiles. Ongoing and forthcoming clinical trials will determine whether these regimens significantly prolong survival.

In the management of patients with relapsed MM, previous therapy and duration of response to previous therapy influence decisions regarding appropriate treatment. An immunomodulatory agent (IMiD)–containing regimen is recommended for patients who are refractory to or relapse after a short progression-free interval with bortezomib-based therapy. Similarly, bortezomib-based therapy is indicated for patients who are refractory to or experience a short progression-free interval with IMiD treatment.

It is important to emphasize, however, that relapse should not necessarily be interpreted as resistance to previously used drugs. In situations where a durable response to a particular agent or combination is achieved, retreatment at the time of relapse may be appropriate. Moreover, refractory disease can, in certain circumstances, be treated with a particular agent to which resistance has developed, if the agent is used in conjunction with other compounds that produce a synergistic anti-MM effect. Toxicities experienced during the course of previous therapies are also considered when choosing agents at time of relapse. For example, lenalidomide is preferred for patients who previously developed grade 2 peripheral neuropathy with pain or grade 3/4 peripheral neuropathy with eitherbortezomib or thalidomide.

Stem Cell Transplantation in Multiple Myeloma

Autologous stem cell transplantation (ASCT) has been an important treatment modality in the management of patients with multiple myeloma (MM) for more than 20 years. Barlogie and colleagues[Barlogie 1986; Barlogie 1987] first demonstrated that myeloablative doses of melphalan with autologous hematopoietic stem cell support could overcome resistance to conventional dose chemotherapy in patients with relapsed and refractory MM. ASCT was subsequently employed in the management of patients with newly diagnosed disease following

induction therapy, and a pivotal randomized trial by Attal and colleagues[Attal 1996] demonstrated that this approach increases event-free survival and overall survival.

It is important to emphasize that ASCT is not curative in MM. Moreover, a meta-analysis of 9 randomized, controlled trials of ASCT vs conventional therapy in 2411 patients suggested that ASCT performed early in MM confers benefit in terms of progression-free survival but not overall survival.[Koreth 2007]

Allogeneic stem cell transplantation (SCT) has also been used in the setting of relapsed and refractory MM. Retrospective analysis suggests that this approach appears to offer comparable progression-free survival and overall survival compared with ASCT, although at the cost of increased treatment-related morbidity and mortality.[Lee 2002]Allogeneic SCT is, therefore, recommended as an approach to treatment of patients with relapsed and refractory MM in the context of a clinical trial. BMT CTN 0102 was a phase III trial of ASCT followed by allogeneic SCT vs tandem ASCT in 625 patients with standard-risk MM (Capsule Summary).[Krishnan 2010] Similar 3-year survival outcomes were reported for the 2 transplant strategies, with any potential benefits of graft-vs-myeloma effect within the ASCT/allogeneic SCT arm counterbalanced by increased treatment-related mortality.

Typically performed after 4-6 cycles of initial therapy, mobilization of stem cells for ASCT is accomplished with either single-agent filgrastim or cyclophosphamide in conjunction with filgrastim (Management Guidelines).[Kumar 2009b;Giralt 2009] Although 2 million CD34+ cells/kg is considered the minimum threshold for a single ASCT, collection of 4 million CD34+ cells/kg for a single ASCT and 8-10 million CD34+ cells/kg is recommended for patients who may undergo 2 autografts during the overall disease course.[Giralt 2009] ASCT can be performed immediately following stem cell mobilization or deferred until time of relapse; whether outcomes are superior with early vs delayed ASCT is a matter of debate.[Bensinger 2009; Rotta 2009] Melphalan 200 mg/m^2 is the most widely used preparative regimen for ASCT.[Harousseau 2005]

Before the development of novel agents in MM, some MM experts recommended by that ASCT be avoided in patients with high-risk cytogenetic findings such as hypodiploidy and deletion 13 detected by metaphase cytogenetics or t(4;14), t(4;16), and del(17) because of short progression-free survival and overall survival times posttransplantation observed in this group.[Gertz 2005] There is emerging evidence, however, that bortezomib, in particular, can overcome the poor prognosis associated with unfavorable cytogenetics[Jagannath 2007] and, moreover, that bortezomib-containing induction therapy followed by ASCT leads to a progressive increase in complete response.[Harousseau 2010]

In addition, Harousseau and colleagues[Harousseau 2010] have shown that the achievement of a very good partial response or better with induction therapy portends improved outcome following autologous transplantation. Moreover, the achievement of a very good partial response or better decreased the need for a second transplantation. Importantly, the combination of bortezomib plus dexamethasone was effective in patients with high-risk MM, including those with International Staging System stage III disease and poor-risk cytogenetic abnormalities. The role of ASCT for patients with high-risk cytogenetic abnormalities is being reconsidered in light of these data and will be clarified by further study.

Finally, the role of ASCT in the era of novel therapies is being re-examined. Specifically, Palumbo and colleagues[Palumbo 2009] have compared induction with lenalidomide plus low-dose dexamethasone induction followed by randomization to melphalan, prednisone, and lenalidomide (MPR) vs tandem high-dose melphalan and ASCT in patients with newly diagnosed MM. In both arms, patients were further randomized to lenalidomide vs no maintenance therapy. Although follow-up is short in this interim analysis, there is at present no significant difference in progression-free survival or overall survival. In addition, the use of lenalidomide, bortezomib, and dexamethasone(RVD) as induction therapy in patients with newly diagnosed MM has been shown to produce a 100% response rate with 74% rate of very good partial response or better.[Richardson 2010b] This high rate and extent of response has set the stage for an international randomized phase III trial comparing RVD induction followed by randomization to high-dose therapy and ASCT vs continued RVD; each cohort will receive maintenance lenalidomide therapy (Clinical Trial: NCT01208662). This trial will assess the added value of high-dose therapy in patients who receive RVD, as well as the durability of responses to RVD, and further evaluate a transplantation paradigm incorporating novel therapies.

Supportive Care

Because multiple myeloma (MM) is associated with a range of metabolic, hematologic, infectious, and musculoskeletal complications, supportive care is critical in managing patients with this disease. Bone abnormalities are detected in approximately 80% of MM patients at the time of diagnosis.[Kyle 2003] Sequelae related to these bone abnormalities, such as pathologic fractures and vertebral body compression fractures, are a source of morbidity, and the pain associated with these events cannot be overstated. Bisphosphonates such as pamidronate and zoledronic acid are the mainstays of treatment for MM-related bone disease,[Berenson 1996; Berenson 2001] but preventive steps may be required to avoid the renal dysfunction and osteonecrosis of the jaw associated with these agents (Management Guidelines).[Terpos 2009] A recent large study did suggest a survival advantage for patients who receivezoledronic acid.[Morgan 2010] Conversely, another study found that compared with placebo, pamidronate reduced bone involvement at progression but did not increase overall survival nor decrease the risk of progression into overt myeloma.[DArena 2011] The existence of these toxicities underscores a

need for alternative approaches currently under investigation for the management of bone disease in MM, such as bortezomib, lenalidomide, the RANK ligand antagonist denosumab,[Roodman 2009] and DKK1 antagonists.[Fulciniti 2009]

Patients with MM are followed closely for metabolic abnormalities such as hypercalcemia and other electrolyte imbalances. Renal impairment occurs as a result of various disease-related phenomena, including distal tubular injury mediated by filtered light chains, hypercalcemia, dehydration, hyperuricemia, amyloid deposition, nonsteroidal antiinflammatory analgesia, and intravenous contrast agents used with imaging studies. Patients should be counseled to maintain a high level of fluid intake and advised to avoid exposure to nephrotoxic compounds such as nonsteroidal antiinflammatory drugs and intravenous contrast agents. Allopurinol is recommended in the setting of hyperuricemia.

Patients with MM are immunocompromised as a result of both the underlying disease and its multiple effects on immune function, as well as by therapies used to treat the disease such as corticosteroids, alkylating agents, the immunomodulatory agents, and bortezomib. Symptoms and signs of infection should prompt a timely evaluation for potential underlying causes and appropriate antibiotic therapy. In addition to the use of antimicrobial agents, immune globulin intravenous is an important adjunctive measure in the management of infection.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is an indolent yet incurable disorder that is characterized by production of serum monoclonal immunoglobulin M (IgM) and lymphoplasmacytic cell growth.[Ghobrial 2003] In recent years, important therapeutic advances have been made in this disease, including the development of regimens incorporating rituximab and bortezomib alone or in combination with other agents.[Vijay 2008] It is increasingly clear that combination regimens will yield responses as good or better than those that can be achieved with single agents.[Dimopoulos 2009]

The evaluation of patients with WM, indications for treatment, and primary treatment options have been summarized in National Comprehensive Cancer Network (NCCN) guidelines (Management Guidelines).[NCCN 2011] For patients who have indications for treatment (such as bulky adenopathy), currently recommended options for primary therapy include alkylating agents, nucleoside analogs, rituximab, thalidomide, and bortezomib. Clinical trial participation should be considered when feasible and in line with patient preferences. According to these guidelines, treatment should be discontinued after maximal response is achieved, and plasmapheresis should be used adjunctively for patients with symptomatic hyperviscosity. Treatment choices at the time of relapse depend in part on the type of initial therapy (eg, patients initially treated with rituximab would be considered for alkylating agents or nucleoside analogs upon disease progression). Patients who have rapidly progressive disease after follow-up treatment are candidates for clinical trials, including studies evaluating stem-cell transplantation.

In light of new treatments available for WM, an International Prognostic Scoring System has recently been developed.[Morel 2009] Based on a series of 587 patients, this scoring system is designed to optimize treatment based on prognostic groups, and facilitate comparisons between clinical trials. The median survival in this patient cohort was 87 months after treatment initiation, and a total of 5 adverse prognostic factors were identified:

- Older than 65 years of age
- Hemoglobin ≤ 11.5 g/dL
- Platelet count ≤ 100 x 10(9)/L
- β_2-microglobulin > 3 mg/L
- Serum monoclonal protein concentration > 7.0 g/dL

These covariates have been incorporated into the following scoring system (Table 5):

Table 5. International Prognostic Scoring System for WM

Patient Group	Adverse Covariates	Proportion of Patients (Out of Overall Series), %	5-Yr Survival, %
Low risk	0-1*	27	87
Intermediate risk	2†	38	68
High risk	> 2 adverse covariates	35	36

* Plus advanced age

†Or only advanced age

To access the CCO inPractice chapter on Waldenström Macroglobulinemia, click here.

Conclusion

Although multiple myeloma remains an incurable illness associated with significant morbidity and mortality, the introduction of novel therapies has improved outcomes for patients with the disease and, moreover, provided a paradigm for the development of new agents. It is expected that ongoing translational and clinical research will result in the further development of active, well-tolerated combination regimens

and at the same time inform the appropriate use of such regimens in conjunction with other treatment modalities such as autologous stem cell transplantation. Moreover, it is anticipated that the emergence of new compounds currently undergoing evaluation either alone or in combination with existing therapies will expand the repertoire of multiple myeloma therapies still further and, therefore, enhance the management of patients with this disease.

Tables and Figures

Table 1 | Table 2 | Table 3 | Table 4 | Table 5

Table 1. Criteria for the Classification of MGUS, MM, and Related Disorders: A Report of the International Myeloma Working Group [IMWG. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Copyright © 2003. Reproduced with permission of John Wiley & Sons, Inc.]

MGUS ▪ M-protein in serum < 30 g/L ▪ Bone marrow clonal plasma cells < 10% and low level of plasma cell infiltration in a trephine biopsy (if done) ▪ No evidence of other B-cell proliferative disorders ▪ No related organ or tissue impairment (no end organ damage, including bone lesions).
Myeloma-Related Organ or Tissue Impairment (End Organ Damage) due to the Plasma Cell Proliferative Process ("CRAB") ▪ ***C***alcium levels increased: serum calcium > 0.25 mmol/L above the upper limit of normal or > 2.75 mmol/L ▪ ***R***enal insufficiency: creatinine > 173 mmol/L ▪ ***A***nemia: hemoglobin 2 g/dL below the lower limit of normal or hemoglobin < 10 g/dL ▪ ***B***one lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify) ▪ Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)
Asymptomatic Myeloma (Smoldering Myeloma) ▪ M-protein in serum ≥ 30 g/L and/or bone marrow clonal plasma cells >10% ▪ No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms
Symptomatic MM ▪ M-protein in serum and/or urine ▪ Bone marrow (clonal) plasma cells or plasmacytoma ▪ Related organ or tissue impairment (end organ damage, including bone lesions)

CRAB, calcium, renal insufficiency, anemia, or bone lesions; CT, computed tomography; MRI, magnetic resonance imaging.

Table 2. Recommended Laboratory Tests in the Evaluation of Suspected MM

▪ Hemoglobin, white blood cell with differential count, platelets ▪ Serum creatinine, Ca2+, uric acid, β_2-microglobulin, albumin ▪ Serum C-reactive protein, lactate dehydrogenase values (useful, but not required for formal diagnosis) ▪ Serum protein electrophoresis with immunofixation ▪ Quantification of immunoglobulins ▪ Serum free light chain determination ▪ Bone marrow aspirate and biopsy ▪ Urinalysis ▪ Electrophoresis and immunofixation of an adequately concentrated aliquot from a 24-hour urine specimen ▪ If available, cytogenetics, fluorescence in situ hybridization from bone marrow specimen

Table 3. Durie-Salmon Myeloma Staging System Criteria [A clinical staging system for multiple myeloma. Correlation of measured cell mass with presenting clinical features, response to treatment and survival. Durie BGM, Salmon SE, copyright © 1975. Reproduced with permission of John Wiley & Sons, Inc.]

Stage I	Stage II	Stage III
All of the following: ▪ Hb > 10 g/L ▪ Serum Ca2+ normal (<12 mg/dL) ▪ X-rays: normal bone structure or solitary bone plasmacytoma only	Overall data are minimally abnormal as shown for stage I and no single value as abnormal as defined for stage III	One or more of the following: ▪ Hb < 8.5 g/L ▪ Serum Ca2+ > 12 mg/dL ▪ Advanced lytic bone lesions (scale 3)

Stage I	Stage II	Stage III
▪ Low M-component production rates ▪ IgG value < 5 g/dL ▪ IgA value < 3 g/dL ▪ Urine light chain M-component on electrophoresis < 4 g/24 hrs		▪ High M-component production rates ▪ IgG value > 7 g/dL ▪ IgA value > 5 g/dL ▪ Urine light chain M-component on electrophoresis > 12 g/24 hrs
Subclassification: A = relatively normal renal function (serum creatinine value < 2.0 mg/dL) B = abnormal renal function (serum creatinine > 2.0 mg/dL)		

Ca2+, calcium; Hb, hemoglobin.

Table 4. EBMT Criteria for Response

Response	Criteria for Response
CR	Requires all of the following: ▪ Disappearance of the original M-protein from the blood and urine on at least 2 determinations for a minimum of 6 wks by immunofixation studies ▪ < 5% plasma cells in the bone marrow on at least 2 determinations for a minimum of 6 wks ▪ No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response) ▪ Disappearance of soft tissue plasmacytomas for at least 6 wks
PR	PR includes patients in whom some, but not all, criteria for CR are fulfilled providing the remaining criteria satisfy the requirements for PR. Requires all of the following: ▪ 50% reduction in the level of serum M-protein for at least 2 determinations 6 wks apart ▪ If present, reduction in 24-hr urinary light chain excretion by either > 90% or to < 200 mg for at least 2 determinations 6 wks apart ▪ ≥ 50% reduction in the size of soft tissue plasmacytomas (by clinical or applicable radiographic examination, ie, 2-dimensional magnetic resonance imaging or computed tomography scan) ▪ No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
MR	MR includes patients in whom some, but not all, criteria for PR are fulfilled providing the remaining criteria satisfy the requirement for MR. Requires all of the following: ▪ ≥ 25% to < 50% reduction in the level of serum M-protein for at least 2 determinations ▪ If present a 50 to 89% reduction in 24-hr light chain excretion, which still exceeds 200 mg/24 hrs for at least 2 determination 6 weeks apart. ▪ 25% to 49% reduction in the size of plasmacytomas (by clinical or applicable radiographic examination, ie, 2-dimensional magnetic resonance imaging or CT scan). ▪ No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
NC	Not meeting the criteria for MR or PD
PD for patients not in CR	Requires one or more of the following: ▪ > 25% increase in the level of monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on repeat investigation 1-3 wks later ▪ > 25% increase in 24-hr urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hrs and confirmed on a repeat investigation 1-3 wks ▪ > 25% increase in plasma cells in a bone marrow aspiration or on trephine biopsy, which must also be an absolute increase of at least 10% ▪ Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas ▪ Development of new bone lesions or soft tissue plasmacytomas (not including compression fractures) ▪ Development of hypercalcemia (corrected serum Ca2+ > 11.5 mg/dL or 2.8 mmol/L, not attributable to other causes)
Relapse from CR	Requires at least 1 of the following: ▪ Reappearance of monoclonal paraprotein on immunofixation or routine electrophoresis to an absolute value > 5 g/L confirmed by at least 1 follow-up 6 wks later and excluding oligoclonal immune reconstitution ▪ > 5% plasma cells in a bone marrow aspirate or biopsy

Response	Criteria for Response
	Development of new lytic bone lesions or soft tissue plasmacytomas, or definite increase in the size of residual bone lesions (not including compression fractures) Development of hypercalcemia (corrected serum Ca2+ >11.5 mg/dL or 2.8 mmol/L, not attributable to other causes)

CR, complete response; CT, computed tomography; MR, minimal response; NC, no change; PD, progressive disease; PR, partial response.

Table 5. International Prognostic Scoring System for WM

Patient Group	Adverse Covariates	Proportion of Patients (Out of Overall Series), %	5-Yr Survival, %
Low risk	0-1*	27	87
Intermediate risk	2†	38	68
High risk	> 2 adverse covariates	35	36

* Plus advanced age

†Or only advanced age

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