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ONCOLOGY BOARD REVIEW MANUAL

Management of Plasma Cell Disorders

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INTRODUCTION

The plasma cell disorders are a spectrum of conditions that include asymptomatic precursor conditions—monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM)—as well as symptomatic multiple myeloma (MM) and solitary plasmacytoma.[1] Other plasma cell disorders include immunoglobulin light chain amyloidosis and POEMS syndrome, which are characterized by a unique set of end-organ manifestations. There are other related plasma cell and B-cell proliferations, such as light chain deposition disease and cryoglobulinemia, that are beyond the scope of this review but are relevant to the hematologist/oncologist and have been reviewed in detail elsewhere.[2]

MM is the second most common hematologic malignancy, with approximately 20,000 patients diagnosed annually in the United States.[3] The median age at presentation is 72 years, and it is more common in men and in African Americans. In fact, MM is the most common hematologic malignancy in African Americans.

The precursor states MGUS and SMM are asymptomatic without end-organ manifestations. MM is characterized by the accumulation of clonal bone marrow plasma cells and production of monoclonal immunoglobulins leading to the cardinal end-organ manifestations known by the acronym CRAB: hypercalcemia, renal failure, anemia, and bone disease.[4] Hypercalcemia occurs as a result of bone destruction from increased osteoclast activity stimulated by malignant plasma cells. Renal failure may be associated with hypercalcemia, light chain cast nephropathy, or light chain deposition. Anemia is generally due to the expansion of plasma cells in the bone marrow, which may also lead to leukopenia and thrombocytopenia. Myeloma-related bone disease includes osteoporosis, osteolytic bone lesions, fractures, and bone pain. Additional, less common manifestations of symptomatic MM include hypogammaglobulinemia with frequent infections, susceptibility to bleeding, plasmacytomas either extending from bone or in soft tissue sites, and amyloidosis.

Immunoglobulin light chain amyloidosis (AL) may be a primary disorder or may be seen in association with frank MM. Features of amyloidosis are rare in newly diagnosed MM, but may occur in up to 10% of patients in the relapsed and refrac-
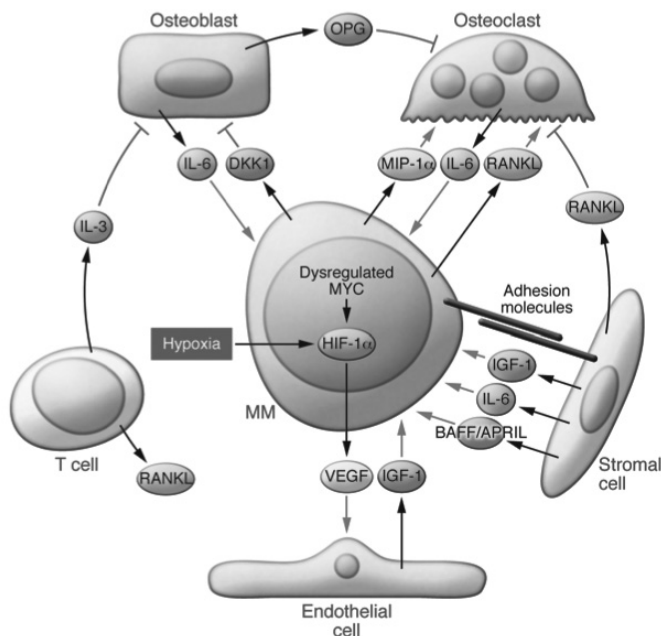
Figure 1. Myeloma is dependent on interactions with the bone marrow microenvironment. Interleukin (IL)-6 is a critical growth factor secreted by multiple cells. Hypoxia and increased *MYC* expression stimulate HIF1a and VEGF secretion and consequent IGF-1 secretion from the endothelium. There is increased osteoclast activity and decreased osteoblast activity mediated by RANKL/RANK, osteoprotegerin, and MIP-1a, a cardinal feature of myeloma. (Adapted with permission from Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. J Clin Invest 2012;122:3456-63.)

tory state. AL is characterized by organ dysfunction mediated by the deposition of insoluble amyloid fibrils that are derived from immunoglobulin light chains.[5] The manifestations of AL include cardiomyopathy, nephrotic syndrome, peripheral and autonomic neuropathy, macroglossia, and many others.

This article reviews the diagnostic approach to plasma cell disorders, describes the management of newly diagnosed and relapsed MM, and describes the management of the rare plasma cell disorders AL and POEMS syndrome.

PATHOGENESIS

MM is a malignancy of bone marrow plasma cells. MM cells rely heavily on the bone marrow microenvironment (the extracellular matrix, stromal cells, osteoclasts, osteoblasts, and immune cells) for essential survival and growth factors, such as interleukin-6 (IL-6).[4] These interactions between the tumor and the microenvironment result in several important biologic features of the pathogenesis of myeloma, including homing of MM plasma cells to the bone marrow, spread to secondary sites via the peripheral blood, generation of paracrine factors (IL-6, insulin-like growth factor 1, APRIL), angiogenesis, osteoclastogenesis, inhibition of osteogenesis, resistance to therapeutic agents, immunodeficiency, and cytopenias (**Figure 1**).[6] The novel agents, immunomodulatory drugs and proteasome inhibitors, are thought to directly target the tumor cell as well as its interaction with the bone marrow micro-environment.

Our understanding of the multistep pathogenesis of MM and its precursor states, MGUS and SMM, have undergone significant advances over the past 20 years. Studies utilizing metaphase cytogenetics, fluorescence in situ hybridization (FISH), and gene expression profiling in MGUS, SMM, active MM, extramedullary MM, and human MM cell lines have clarified these critical steps (**Figure 2**). The initial transition (TR1) involves immunoglobulin heavy chain (IgH) translocations or multiple trisomies, which are generally nonoverlapping events. Universal dysregulation of cyclin D expression is seen in MGUS. The transition from MGUS to MM (TR2) is associated with increased *MYC* expression and activating mutations of *K-RAS*. Additional early and late progression events and their approximate timing are depicted in Figure 2.

MULTIPLE MYELOMA

CASE PRESENTATION

A 60-year-old man who works as a carpenter presents to his primary care physician with worsening low back pain. He has had chronic low back pain for years with many acute exacerbations; the current episode has been more prolonged and severe. His primary physician obtains the following: hemoglobin 14.5 g/dL, serum IgG kappa monoclonal immunoglobulin 1.8 g/dL, and normal creatinine and calcium levels. Serum free light chain (FLC) analysis shows a kappa FLC of 405.0 mg/L, lambda FLC of 15.5, and a kappa:lambda ratio of 26.1. A skeletal survey is negative for osteolytic lesions. A bone marrow biopsy shows 40% kappa-restricted plasma cells.

- **Does the patient have MM requiring therapy?**

DIAGNOSIS

It is essential to establish a diagnosis of symptomatic MM in need of therapy. It has been shown that MM always arises from asymptomatic precursor states, either MGUS or SMM.[7,8] MGUS is present in approximately 4% of whites over the age of 50 years, and the risk of progression to symptomatic MM is approximately 1% per year.[9,10] The average rate of progression in SMM to MM is variable, but on average is approximately 10% for the first 5 years.[11] Patients with MGUS and SMM should be followed carefully for the development of myeloma-related end-organ manifestations (CRAB, see Introduction).

The tests needed for the evaluation of monoclonal gammopathies are outlined in **Table 1**. Utilizing serum and urine electrophoresis with immunofixation along with serum FLC analysis, a monoclonal gammopathy is detectable in nearly all patients
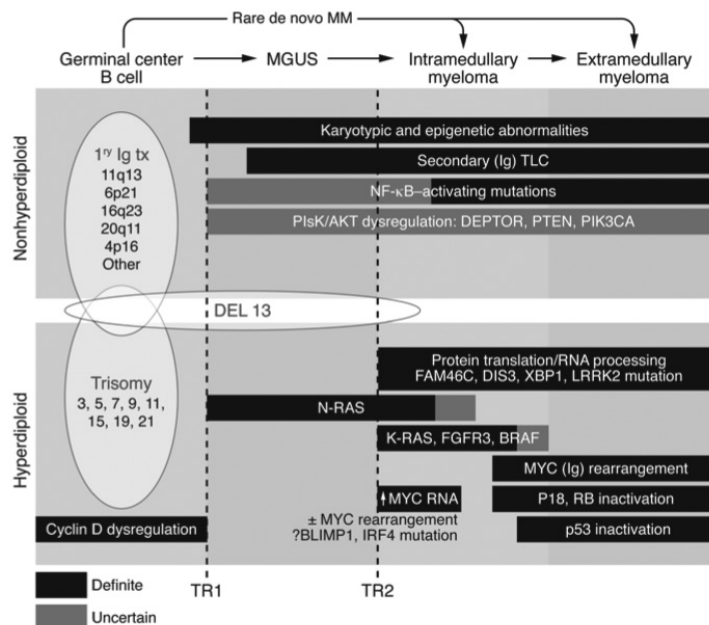

Figure 2. A model for the pathogenesis of multiple myeloma (MM). The multistep process and approximate timing of events are depicted. The initial transition (TR1) to malignancy involves 2 pathways: immunoglobulin heavy chain (IgH) translocations (nonhyperdiploid) and multiple trisomies (hyperdiploid). The transition from monoclonal gammopathy of undetermined significance (MGUS) to active MM (TR2) is associated with increased *MYC* expression. (Adapted with permission from Kuehl WM, Bergsagel PL. Molecular pathogenesis of multiple myeloma and its premalignant precursor. J Clin Invest 2012;122:3456-63.)

with MM. There are very rare cases of IgD and IgE myeloma, and specific immunofixation for these should be requested if suspicion exists. Serum FLC analysis is able to measure the 20% of MM that is light chain secreting; thus, nonsecretory MM is exceedingly rare. Serum chemistries and beta-2 microglobulin assay are necessary for detection of organ damage and staging.

The current standard for detection of osteolytic bone disease is skeletal survey, but magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are

Table 1. Diagnostic Tests Used in the Evaluation of Monoclonal Gammopathies

Essential diagnostic tests

Complete blood count with leukocyte differential

Complete metabolic panel

Serum protein electrophoresis with immunofixation

Quantitative immunoglobulins

24-hour urine protein electrophoresis with immunofixation

Skeletal survey

Serum free light chain analysis

Serum beta-2 microglobulin

Serum albumin

Bone marrow aspirate and biopsy

Bone marrow cytogenetics

Bone marrow fluorescence in situ hybridization (FISH) panel

Useful in selected situations

Magnetic resonance imaging

Positron emission tomography/computed tomography

useful in selected circumstances.[12,13] MRI is specifically useful for evaluation of paraspinal masses or spinal cord compression. PET/CT is useful in the evaluation of solitary plasmacytomas to detect additional sites of bone marrow FDG-avid lesions and osteolytic disease. This has become a critical modality in the modern evaluation of solitary plasmacytomas.[14] A bone marrow aspiration and biopsy is necessary to quantify bone marrow PC infiltration and obtain molecular studies for prognosis.

The International Myeloma Working Group (IMWG) criteria for the diagnosis of MM requires the presence of end-organ manifestations; patients without these manifestations are classified as either MGUS or SMM (**Table 2**).[15] The distinction between MGUS and SMM is made on the basis of the monoclonal immunoglobulin concentration and degree of bone marrow plasmacytosis, but the diagnosis of symptomatic MM can be made at any level of M-protein or bone marrow plasma cell

infiltration. Again, it is imperative that the clinician establishes that these manifestations are related to MM. There are numerous examples of falsely attributing these manifestations to MM when in fact other conditions are present, such as primary hyperparathyroidism accounting for hypercalcemia or anemia secondary to iron deficiency. Patients should *not* be treated in the absence of MM-related end-organ dysfunction.

The IMWG has developed guidelines for the management of MGUS and SMM and has recommended observation based on the risk of progression to MM.[16] Factors that increase the risk of progression from MGUS to MM are monoclonal immunoglobulin concentration $\geq$1.5 g/dL, abnormal serum FLC ratio, and a non-IgG isotype.[17] Patients with a monoclonal gammopathy and the absence of high-risk features for progression can be observed every 2 to 3 years. For patients with a single adverse feature, additional testing including a bone marrow biopsy and skeletal survey is recommended. Patients with MGUS should return initially in 3 to 6 months to assess for evidence of progression to active MM and then follow-up annually if not low risk. Patients with SMM should be evaluated every 3 to 6 months depending on risk. Features that increase the risk of progression from SMM to MM are monoclonal immunoglobulin concentration $\geq$3 g/dL, bone marrow plasma cells $\geq$10%, and a widely skewed serum FLC ratio ($\leq$0.125 or $\geq$8).[18] During surveillance, patients should have a directed history and physical examination with focus on evidence of MM, lymphoma, or amyloidosis along with standard laboratory tests.

Patients with SMM represent a highly heterogeneous group of patients—some are progressing to MM at a slow rate similar to high-risk MGUS, and others are early MM patients who have a very high risk of progression to MM in 2 years.[11] Identi-

Table 2. Diagnostic Criteria for Monoclonal Gammopathies

	Monoclonal Gammopathy of Undetermined Significance	Smoldering Multiple Myeloma	Multiple Myeloma	Solitary Plasmacytoma
Monoclonal immunoglobulin concentration	<3.0 g/dL	≥3.0 g/dL	Any	Any
	and/or	**and/or**	**or**	
Bone marrow plasma cells (%)	<10	≥10	Any	Any
Myeloma-related organ or tissue impairment*	Absent	Absent	Present	A single bone or extraosseous plasmacytoma, but no CRAB

*CRAB features: calcium >11.0 mg/dL, creatinine >2 mg/dL, hemoglobin 2 g below the lower limit of normal or <10.0 g/dL, osteolytic bone lesions or osteoporosis with compression fractures. Other: symptomatic hyperviscosity, recurrent bacterial infections.

fying these patients with ultra-high risk SMM who would benefit from earlier intervention prior to the onset of end-organ damage may have substantial benefit for patients.[19] The PETHEMA performed a landmark randomized trial of lenalidomide and dexamethasone versus observation in high-risk SMM using the Mayo Clinic and/or PETHEMA bone marrow flow cytometry criteria.[20] This study demonstrated both a progression-free and overall survival benefit of lenalidomide and dexamethasone therapy. At a median follow-up of 40 months, the median time to progression was not reached in the treatment group and was 21 months for observation. Overall survival was also significantly prolonged (hazard ratio for death 0.33, *P* = 0.03). However, this study has been criticized and has not changed practice for the following reasons: the definition of high-risk SMM using the flow cytometry criteria is not widely available and is technically complex, the treatment arm had intensification of treatment at signs of biochemical progression, outcomes on the observation arm were quite poor, and the treatment at progression was not uniform in the experimental arm. Furthermore, lenalidomide was not given at the time of progression.

CASE CONTINUED

The patient's back pain resolves with analgesics and physical therapy in 6 weeks. He is diagnosed with SMM and is observed with evaluations every 3 months. Two years after initial consultation, he reports dyspnea and fatigue; he can barely finish a half day of work as a carpenter. He also has a new site of pain in his upper back. Laboratory studies show the following: hemoglobin 7.2 g/dL, creatinine 2.1 mg/dL, IgG kappa 3.8 g/dL, serum kappa FLC 835.5 mg/L, lambda FLC 9.0, kappa:lambda ratio 92.8, beta-2 microglobulin 8.2 µg/mL, albumin 3.2 g/dL. A bone marrow biopsy demonstrates 70% kappa-restricted plasma cells with normal cytogenetics and FISH testing shows t(14;16) and del(17). A skeletal survey reveals a vertebral compression fracture at T6.

- **What is the appropriate management of newly diagnosed MM?**

MANAGEMENT

The patient has symptomatic MM based on the presence of anemia, renal failure, and osteolytic bone disease and requires therapy. MM remains incurable, but outcomes have markedly improved

Table 3. Induction Regimens

	Regimen	CRR (%)	Common Toxicities (>10%)
Transplant eligible	Bortezomib-dexamethasone (Vd)	21	Infection, peripheral neuropathy
	Cyclophosphamide, bortezomib, dexamethasone (CyBorD)	46	Thombocytopenia, neutropenia, anemia
	Lenalidomide, bortezomib, dexamethasone (RVD)	29	Lymphopenia
	Lenalidomide, dexamethasone (Rd)	24	Neutropenia, venous thrombosis
Transplant ineligible	Melphalan, prednisone, thalidomide (MPT)	13	Neutropenia, venous thrombosis, peripheral neuropathy, infection
	Melphalan, prednisone, bortezomib (VMP)	24	Neutropenia, thrombocytopenia, anemia, peripheral neuropathy
	Melphalan, prednisone, lenalidomide (MPR)	16	Neutropenia, anemia, thrombocytopenia, infection

CRR = complete response rate.

in the past 20 years.[21] In the mid 1990s, high-dose therapy and autologous stem cell transplantation (HDT/autoSCT) was shown to improve survival compared to conventional chemotherapy. This represented the first major advance in MM since the development of melphalan and prednisone in the 1960s. Subsequently, the development of immunomodulatory drugs (IMiDs: thalidomide, lenalidomide, and pomalidomide) and proteasome inhibitors (bortezomib and carfilzomib) has resulted in improved outcomes. Several epidemiologic studies have shown dramatic survival gains.[22,23] Based on SEER data, 5-year relative survival in MM has increased from 29% to 35% from the time period 1990–1992 to 2002–2004.[24]

There are 3 phases in the current approach to treatment of newly diagnosed MM: induction, consolidation, and maintenance.[1] The approach to each phase of therapy is individualized based on the features of the myeloma, age, comorbidities, and personal preferences. There are several general considerations for all patients at initial diagnosis. Renal failure at presentation should prompt urgent chemotherapy. In MM patients with renal failure, it is important to maintain volume status and avoid nephrotoxic drugs. The benefit of plasmapheresis in the management of myeloma-related renal failure remains unclear.[25,26] Analgesia and bisphosphonates for painful bone lesions should be started. Consultation with an orthopedic oncologist may be necessary if there are lesions at high risk for pathologic fracture. Hypercalcemia should be managed with aggressive intravenous fluids and bisphosphonates.

Another critically important decision to be made early in the course of therapy is the patient's candidacy for HDT/autoSCT. Generally, patients under the age of 70 without significant comorbidities are candidates for HDT/autoSCT. Melphalan-based induction regimens and extensive radiation therapy to bone marrow should be avoided to preserve the option of autologous stem cell collection. Prolonged therapy with lenalidomide-based induction regimens may also impact stem cell collection and should be done with caution.[27,28]

Induction regimens contain drugs from 4 classes: corticosteroids, IMiDs, proteasome inhibitors, and alkylating agents. The most common regimens employed and their response rates are shown in **Table 3**. The choice of regimen is individualized. The intent of induction therapy is to achieve a hematologic response, improve symptoms, and allow

for stem cell collection. Two- or 3-drug induction regimens from the above 4 classes are usually employed. Although 3-drug regimens result in higher response rates, they are associated with increased toxicity. Low-dose dexamethasone is now the standard of care based on a randomized controlled trial comparing lenalidomide with high-dose dexamethasone (480 mg per month) to lenalidomide and low-dose dexamethasone (160 mg per month).[29] The low-dose dexamethasone arm achieved better overall survival and lower toxicity, including a significantly lower rate of mortality within 4 months of therapy.

Patients who are not candidates for HDT/autoSCT have several options for induction therapy. Randomized trials have shown that the addition of a novel agent to melphalan and prednisone results in improved outcomes. Melphalan, prednisone, and thalidomide (MPT) has been compared to melphalan and prednisone (MP).[4,30] Patients received 6 cycles of MPT followed by maintenance thalidomide until progression versus MP for 6 cycles. MPT was superior, with an event-free survival at 2 years of 54% for MPT compared to 27% for MP (P = 0.0006). The combination of melphalan, prednisone, and bortezomib (VMP) was compared to MP, both administered for 9 cycles without maintenance therapy.[6,31] The partial response rates for VMP and MP were 71% and 35%, respectively. The hazard ratio for overall survival favored bortezomib (0.61, P = 0.008).

• **How is prognosis defined in MM?**

PROGNOSIS

Prognosis in MM is based on both molecular features of MM and the International Staging System (ISS) (**Table 4**). The ISS uses 2 biomarkers, serum beta-2 microglobulin and serum albumin, and is simple and more useful than the Durie-Salmon system.[7,8,32] Collectively, beta-2 microglobulin and albumin reflect myeloma tumor burden, renal failure (long known to be an independent prognostic factor), and host fitness. Molecular features of MM that have prognostic value include bone marrow karyotype, translocations, chromosome content, and gene expression profiling.[9,10,33] There continues to be debate on the molecular classification of MM because the significance of the individual markers changes with the introduction of new therapies. Standard risk molecular features include t(11;14) and hyperdiploidy. High-risk features include del(17), t(14;16), and chromosome 1 gain. Translocation (4;14) is considered intermediate risk. The presence of del(13) is no longer considered an adverse prognostic feature unless it is seen on bone marrow karyotype. Several groups have developed gene expression–based prognostic systems, but they are not widely used in clinical practice.[34] The IMWG have analyzed outcomes with ISS staging and FISH and have been able to show that the combination of these factors provides robust prognostic information.[35] The patients were stratified by ISS stage and the presence of either t(4;14), del(17), or chromosome 1 gain into 3 groups: (a) low risk: ISS I or II and negative FISH; (b) standard risk: ISS III and negative FISH or ISS 1 and positive FISH; and (c) high risk: ISS II/III and positive FISH.[11,36] The median survivals for these 3 groups are more than 10 years, 7 years, and 2 years, respectively. At present, there are no specific therapies for specific molecular subgroups of myeloma.

CASE CONTINUED

The patient has ISS III myeloma with high-risk molecular features. He begins therapy with cyclophosphamide, bortezomib, and dexamethasone

Table 4. Staging and Prognosis in Multiple Myeloma

International Staging System (ISS)		Median OS (mo)
Stage I	Beta-2 microglobulin < 3.5 mg/L and albumin ≥3.5 g/dL	62
Stage II	Neither stage I or III	44
Stage III	Beta-2 microglobulin ≥5.5 mg/L	29
Combined ISS-Genetic Prognostic System		**Median OS (yr)**
Low risk	ISS I or II and absence of t(4:14), del(17), and chromosome 1 gain, age <55 yr	>10
Standard risk	Others	7
High risk	ISS II or III plus t(4;14) or del(17)	2

OS = overall survival.

and has a partial response to therapy after 2 cycles. He continues to take narcotics for bone pain. He is started on zoledronic acid with the first cycle of chemotherapy.

- **What is the best approach to management of myeloma-related bone disease?**

Osteolysis is fundamental to the pathophysiology of MM and begins early in the pathogenesis of MM in the MGUS state.[37] In fact, patients with MGUS have been shown to have altered bone microarchitecture and are at increased risk of fracture.[38] Bone pain and fractures are a significant problem in a majority of MM patients. Intravenous bisphosphonates, both pamidronate and zoledronic acid, have been shown to reduce skeletal-related events (SREs) in MM.[15,39,40] The UK MRC IX trial randomly assigned patients to zoledronic acid or clodronate (an oral bisphosphonate available in the UK) regardless of the presence of radiographically detected bone disease. Zoledronic acid was superior in terms of reduction in SREs, 27% versus 35% (P = 0.0004).[16,41] Notably in this trial the patients receiving zoledronic acid had a 5.5-month survival benefit. The overall survival benefit was observed only in those with bone disease at baseline (hazard ratio 0.82, P = 0.017). The current National Comprehensive Cancer Network (NCCN) and IMWG guidelines support the use of bisphosphonates (either pamidronate or zoledronic acid) in patients with active MM regardless of the presence of osteolytic bone lesions on conventional radiography.[11,42]

The dose and duration of bisphosphonates remain an open question. In practice and in the guidelines at least 2 years of monthly bisphosphonate therapy is recommended as long as disease is in remission and not progressing. The Nordic Myeloma Group performed a randomized trial of pamidronate 30 mg versus 90 mg intravenously monthly, with the primary end point being quality of life, not SREs.[19,43] These arms were equivalent. There is a randomized trial of zoledronic every month versus every 3 months being performed (NCT00622505).

Serious toxicities of bisphosphonates requiring preventive strategies include nephrotoxicity and osteonecrosis of the jaw (ONJ).[20,44] Patients should have careful monitoring of renal function, intravenous hydration, and dose reductions when creatinine clearance is between 30 and 60 mL/min. Lengthening the infusion time of pamidronate to more than

4 hours can reduce nephrotoxicity. Changes in renal function during therapy should prompt discontinuation. The rate of ONJ in the MRC IX trial was approximately 1% per year, but preventive dental care was not mandatory. Preventive dental care reduces the rate of ONJ and is recommended prior to starting bisphosphonates as is avoidance of invasive dental procedures.[22,23,45]

Denosumab, a monoclonal antibody to RANK-ligand approved for use in breast and prostate cancer metastatic to bone, is contraindicated in MM. A subset of MM patients treated with denosumab had inferior survival compared to the zoledronic acid patients.[46] A prospective trial in MM is ongoing.

CASE CONTINUED

The patient continues therapy with cyclophosphamide, bortezomib, and dexamethasone. During the last cycle of therapy he develops mild, nonpainful paresthesias in his feet. He is now in a very good partial remission. The patient returns with questions regarding the role of HDT/autoSCT.

• **How are the toxicities of induction therapy managed?**

Toxicities of MM induction that require specific management include peripheral neuropathy, venous thromboembolism, and infection. Peripheral neuropathy is common with both bortezomib and thalidomide.[47] Bortezomib neuropathy is related to dose, schedule, and mode of administration and is generally reversible. Peripheral neuropathy from thalidomide is cumulative and dose-dependent and is often permanent. Prompt dose reductions are required with development of neuropathy of any grade with thalidomide. In patients with grade 1 or 2 bortezomib-related neuropathy, dose reduction to 1.0 mg/m^2 is suggested, or weekly admin-

istration should be considered. For patients who develop grade 3 neuropathy, bortezomib should be held and resumed at 0.7 mg/m^2 when the neuropathy has resolved to grade 1 or better. A randomized trial of subcutaneous administration compared to intravenous administration of bortezomib showed a dramatic decrease in peripheral neuropathy of all grades (38% vs 53%) and grade 3 (6% vs 16%) peripheral neuropathy.[48]

There is an increased risk of venous thromboembolism (VTE) when IMiDs are combined with steroids or anthracyclines.[49] The rate of VTE ranges from 20% to 40% without prophylaxis; the highest rates are with combinations that include anthracyclines. A randomized trial comparing aspirin (100 mg/day), mini-dose warfarin (1.25 mg/day), and enoxaparin (40 mg subcutaneously daily) in patients receiving thalidomide-based regimens demonstrated equivalence between aspirin and mini-dose warfarin.[50] Therefore, all patients receiving IMiDs in combination with steroids or anthracyclines should receive VTE prophylaxis with aspirin. For patients with additional risk factors for VTE, one should consider low-molecular-weight heparin at either prophylactic or therapeutic doses.

MM patients are at increased risk of infection due to the underlying disease and therapy. High-dose dexamethasone regimens have a higher risk of infection compared to low-dose regimens.[29] Therefore, prophylaxis for opportunistic infection and bacterial infections is less commonly used now that low-dose dexamethasone regimens are standard. Bortezomib is associated with varicella zoster reactivation rates of over 10%, making antiviral prophylaxis mandatory.[51] For patients with recurrent bacterial infections, intravenous immune globulin is an option, although this practice is based on a study done before the advent of more effective novel agents.[52]

• What is the current role of HDT/autoSCT?

The place of HDT/autoSCT in the management of MM continues to evolve in the era of novel drugs.[53] The Intergroupe Francophone du Myelome (IFM) first reported improved overall survival with HDT/autoSCT compared to conventional chemotherapy in 1996.[54] Several clinical trials comparing HDT/autoSCT to conventional therapy have demonstrated that HDT/autoSCT improves progression-free survival compared to conventional therapy, and in some trials there was an overall survival benefit.[55] Tandem HDT/autoSCT (2 planned courses of HDT/autoSCT with a 3-month interval) is not clearly superior to a single course of HDT/autoSCT, but this is the subject of ongoing studies.[56,57] The standard conditioning regimen is melphalan alone, as a randomized trial comparing melphalan 200 mg/m^2 to melphalan 140 mg/m^2 along with 8 Gy total body irradiation showed equivalent event-free survival but more toxicity in the irradiation regimen.[58] The timing of transplantation remains controversial, but overall survival is essentially the same whether it is performed early or at the time of relapse.[59] Early transplantation is associated with improved time without symptoms, treatment, and treatment-related adverse events and thus may be preferred in some patients.[60]

CASE CONTINUED

The patient undergoes HDT/autoSCT with melphalan 200 mg/m^2 for conditioning. His course is complicated by severe mucositis requiring parenteral narcotics and intravenous fluids and febrile neutropenia without source. He engrafts neutrophils and platelets on days 12 and 14, respectively. He is in a complete remission at day 100 following transplant.

• What is the role of maintenance therapy?

Due to the inevitable risk of relapse following induction therapy or transplant, there have been a series of studies over the years investigating the long-term use of therapy to maintain remission. Thalidomide increases progression free survival after conventional therapy and HDT/autoSCT, but toxicity is substantial and renders thalidomide intolerable for long-term use.[61] The toxicity profile of lenalidomide is more favorable, and this agent has been tested as maintenance therapy following both conventional therapy and HDT/autoSCT. A randomized trial of melphalan, prednisone, and lenalidomide followed by lenalidomide maintenance (MPR-R), MPR, and MP in transplant-ineligible patients was performed.[62] MPR-R demonstrated an improvement in progression-free survival from 14 and 13 months in the MPR and MP arms to 31 months with MPR-R. The IFM and Cancer and Leukemia Group B (CALGB) performed trials comparing lenalidomide to placebo following HDT/autoSCT.[63,64] Both trials showed improved progression-free survival from approximately 2 years to 4 years. The CALGB trial had an overall survival benefit. An updated analysis of the IFM trial presented at the American Society of Hematology annual meeting in 2013 still showed no overall survival benefit.[65] In the IFM trial, there was poor survival following progression in the lenalidomide maintenance group, which suggests the possibility of drug resistance. There are important differences in the IFM trial, notably, only half of patients received a novel agent during induction, one-quarter of patients received additional cytotoxic (DCEP) induction, and 2 cycles of consolidation full-dose lenalidomide-dexamethasone post transplant were included. Lenalidomide maintenance was continued for a median of 24 months in the IFM trial,

Table 5. Regimens for Relapsed Multiple Myeloma

Regimen	Study	Outcomes
Bortezomib	Bortezomib vs high-dose dexamethasone[51]	ORR: 43% vs 16% 1-year OS: 80% vs 67%
Bortezomib–pegylated doxorubicin	Bortezomib and pegylated doxorubicin vs Bortezomib[68]	TTP: 9.3 mo vs 6.5 mo
Lenalidomide-dexamethasone	Lenalidomide-dexamethasone vs high-dose dexamethasone[69,70]	TTP: 11.1 mo vs 4.7 mo Median OS: 29.6 vs 20.2 mo
Carfilzomib	Carfilzomib single agent[72]	DOR: 7.8 mo Median OS: 15.6 mo
Pomalidomide-dexamethasone	Pomalidomide-dexamethasone vs high-dose dexamethasone[73,74]	PFS: 4.0 vs 1.9 mo Median OS: 13.1 vs 8.1 mo

DOR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTP = time to progression.

whereas it was continued indefinitely in the CALGB trial.

Maintenance therapy likely prolongs progression-free survival, but it remains unclear if there is an overall survival benefit. The patient subset that is most likely to benefit from maintenance therapy remains unclear. A concerning toxicity in both studies was the increased risk of second primary malignancies. The NCCN recommends discussing these findings with patients prior to deciding on maintenance therapy, whereas the IMWG recommends against maintenance therapy.[66] Bortezomib during induction and maintenance compared to thalidomide has demonstrated improved progression-free and overall survival without any reported signal of second malignancies.[67]

CASE CONTINUED

The patient starts lenalidomide 10 mg daily and continues zoledronic acid monthly for another 18 months. Approximately 2 years following transplantation he fractures his right humerus while lifting a toolbox and undergoes surgical repair. Pertinent laboratory data show: hemoglobin 10.5 g/dL, creatinine 1.7 mg/dL, IgG kappa 1.8 g/dL, kappa FLC 325.0, lambda FLC 18.0, and kappa:lambda ratio 18.1.

• What is the approach to relapsed MM?

The approach to relapsed MM is based on the features of the clinical relapse and the patient's response and toxicity to prior regimens. A critical decision is when to consider treatment for relapse. Patients with asymptomatic rises in monoclonal protein can be observed carefully for the tempo and nature of relapse prior to treatment. However, patients with disease that has been known to behave aggressively or has other high-risk features should be considered for therapy even with biochemical relapse. It is appropriate to repeat a regimen that the patient previously responded to, particularly if the duration of response was greater than 6 months. It is advisable to change to a different drug class or different combination if the prior regimen did not provide a sufficient response, resulted in rapid relapse, or was intolerable. There are many regimens available for relapsed disease, but preferred regimens are listed in **Table 5**.

The APEX trial compared bortezomib to high-dose dexamethasone, which demonstrated a combined complete response and partial response rate of 38% compared to 18%.[51] Survival rates at 1 year were 80% versus 67% ($P = 0.0002$). These results include about two-thirds of patients crossing over to the bortezomib arm. Bortezomib has been combined with liposomal doxorubicin and compared to bortezomib alone, and this combination resulted in an extended time to progression compared to bortezomib alone (9.3 versus 6.5 months).[68] Lenalidomide is approved for patients who have relapsed following at least 1 prior line of therapy, based on a North American (MM-009) and International (MM-10) study of lenalidomide with high-dose dexamethasone compared to high-dose dexamethasone.[69,70] Both of these studies demonstrated improved median time to disease progression in the lenalidomide groups: MM-009 median time to progression was 11.1 months compared to 4.7 months ($P < 0.001$); MM-010 median time to progression was 11.3 versus 4.7 months ($P < 0.001$). Median overall survivals were also improved in the lenalidomide groups in both trials: 29.6 months versus 20.2 ($P < 0.001$) in MM-009, and in MM-010 the hazard ratio for death was 0.66 ($P = 0.03$).

Patients who have become refractory to both IMiDs and proteasome inhibitors have a very poor prognosis. The IMWG performed a retrospective study of patients refractory to current therapies including thalidomide, lenalidomide, and bortezomib.[71] The median overall and event-free survival in these patients was 9 and 5 months, respectively. Therefore, agents active in this population are urgently needed. The FDA has approved 2 agents, carfilzomib and pomalidomide, in this population.

Carfilzomib is a second-generation proteasome inhibitor with a potentially improved efficacy and toxicity profile compared to bortezomib. Carfilzomib primarily inhibits the chymotrypsin site of the proteasome, but in higher doses may inhibit the trypsin-like and caspase-like sites. Carfilzomib forms stable and irreversible adducts with the proteasome, unlike bortezomib, which is reversible. Optimal inhibition of the proteasome with carfilzomib requires consecutive daily dosing. Carfilzomib does not result in significant peripheral neuropathy, which is an advantage over bortezomib. The PX 171-003 trial enrolled 266 heavily pre-treated patients (more than 4 lines of therapy and 80% were double refractory).[72] Carfilzomib 20 mg/m^2 was given twice weekly on days 1 and 2 with dose escalation to 27 mg/m^2 on days 8, 9 and 15, 16. The overall response rate was 23.7%, with a median duration of response of 7.8 months, progression-free survival of 3.7 months, and overall survival of 15.6 months.

The toxicity profile of carfilzomib was notable for a low rate of treatment-emergent peripheral neuropathy (8.3%) despite baseline neuropathy in 77% of patients.[72] Severe acute renal failure occurred in 5 of 266 patients. There does appear to be significant cardiopulmonary toxicity with this agent. Five of 24 deaths during the study were considered carfilzomib-related, and 2 of these were cardiac arrests. In addition, one-third of patients experienced mild-moderate dyspnea without detectable lung injury. There is some thought that the dyspnea was related to aggressive hydration, but ongoing studies are evaluating the possibility of direct carfilzomib-related cardiopulmonary toxicity.

Pomalidomide is the third-in-class IMiD and has been approved by the FDA for MM patients treated with at least 2 prior therapies. In multiple phase 2 trials including lenalidomide- and bortezomib-refractory patients, pomalidomide at doses ranging from 2 to 4 mg either daily or daily for 21 days out of 28 days along with dexamethasone 40 mg weekly

demonstrated overall response rates of 25% to 63%.[73] A randomized phase 3 study compared pomalidomide 4 mg daily days 1 to 21 and dexamethasone 40 mg weekly to high-dose dexamethasone; pomalidomide/low-dose dexamethasone showed improved progression-free survival (4.0 vs 1.9 months, $P < 0.001$) and improved median overall survival (13.1 vs 8.1, $P = 0.009$).[74] This is notable even though approximately half of patients in the high-dose dexamethasone arm crossed over to pomalidomide. There was benefit even in patients with high-risk cytogenetics. Importantly, there did not appear to be any impact in the efficacy and toxicity in those with normal versus impaired renal function (creatinine clearance 30–60 mL/min).

RARE DISORDERS

IMMUNOGLOBULIN LIGHT CHAIN AMYLOIDOSIS

Case Evaluation

A 60-year-old woman presents with an unexplained weight loss of 20 pounds, lower extremity edema, dyspnea climbing a single flight of stairs, and several episodes of presyncope. She has seen several doctors without explanation. A nephrologist ordered a 24-hour urine study, which showed 7 g of protein and a small free lambda monoclonal protein.

- **What are the next steps in evaluation and management?**

The presence of nephrotic-range proteinuria that is mostly albumin and not monoclonal immunoglobulin light chain in the presence of additional systemic symptoms should raise suspicion for AL. Suspicion is a critical first step in the diagnosis of AL as many patients go undiagnosed until advanced organ dysfunction develops.[5] Clinical signs and symptoms that should raise suspicion for AL are unexplained fatigue, unintentional weight loss, cardiomyopathy, macroglossia, nephrotic syndrome, orthostatic hypotension, peripheral or autonomic neuropathy, carpal tunnel syndrome, unexplained bruising (especially periorbital purpura), and hepatomegaly.

The next step in diagnosis is to search for evidence of tissue amyloid deposition, which is based on demonstration of a positive Congo red stain in either the involved organ or a surrogate site.[75] The most easily accessible surrogate site is the abdominal fat, which is approximately 85% sensitive for detection of amyloid deposits. If suspicion remains high, biopsy of an involved organ (eg, heart or kidney) should be pursued. Accurate amyloid subtyping is necessary to direct therapy and avoid misdiagnosis with hereditary or other forms of amyloidosis due to the commonality of monoclonal gammopathies in the general population.[76] This may require submission of amyloid-bearing tissue to a reference lab for laser capture microdissection and mass spectrometry.[77]

Lastly, the extent of organ involvement needs to be assessed by clinical, laboratory, and imaging findings. The outcomes in AL are driven by the extent of cardiac involvement and the aggressiveness of the plasma cell clone. A staging system incorporating NT-pro-brain natriuretic peptide ($\geq$1800 pg/mL), cardiac troponin T ($\geq$0.025 ng/mL), and the serum FLC differential ($\geq$180 mg/dL) discriminates patients with very different median survivals: for stage I (no factors) 94.1 months, stage II (any 1 factor) 40.3 months, stage III (any 2 factors) 14 months, and stage IV (all 3 factors) 5.8 months.[78]

The fundamental treatment principle in AL is to obtain a complete hematologic remission, thereby removing the amyloidogenic precursor protein and allowing for reversal of organ dysfunction. Until the advent of novel drugs, HDT/autoSCT was the most potent anti-plasma cell therapy and was able to

Table 6. Diagnostic Criteria for POEMS Syndrome

	Feature
Mandatory major criteria (both required)	Polyradiculopathy (typically demyelinating)
	Monoclonal plasma cell disorder (almost always lambda)
Other major criteria (1 required)	Castleman's disease
	Sclerotic bone lesions
	Vascular endothelial growth factor (VEGF) elevation
Minor criteria (1 required)	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	Extravascular volume expansion (edema, pleural effusion, or ascites)
	Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)
	Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocyanosis, flushing, white nails)
	Papilledema
	Thrombocytosis/polycythemia
Other features	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombosis, diarrhea, low vitamin B_{12} levels

achieve complete hematologic remissions in approximately 40% of patients with variable rates of organ improvement.[79,80] However, a randomized trial of HDT/autoSCT compared to standard oral melphalan and dexamethasone performed by the IFM showed better survival in the melphalan-dexamethasone arm.[81] This has been attributed to a very high transplant-related mortality (TRM) of 24% due to poor patient selection. In the current era, careful selection of patients at experienced centers results in TRM of 5%. Most patients with AL are not fit enough for this procedure and are treated with conventional regimens. Fortunately, bortezomib-based regimens can achieve hematologic remission and organ improvement rates that are similar to HDT/autoSCT.[82–84]

POEMS SYNDROME

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a paraneoplastic disorder driven by a plasma cell clone or in some cases Castleman's disease.[85] The diagnostic criteria are complex, but all patients must have a polyneuropathy, osteosclerotic bone lesions, and a monoclonal gammopathy which is nearly always lambda (**Table 6**). Patients may have a solitary plasmacytoma and not a systemic plasma cell process, and these patients can be treated with radiation therapy alone; more than half of patients will have clinical improvement with this approach. Patients with systemic disease need to obtain a complete hematologic remission to have reversal of systemic manifestations. Defining a complete hematologic remission is difficult in POEMS syndrome because the plasma cell clone is usually small. Systemic therapy with either melphalan and dexamethasone or HDT/autoSCT leads to high rates of hematologic remission and clinical improvement, but HDT/autoSCT is the favored approach.

CONCLUSION

The plasma cell disorders represent a heterogeneous group of disorders. Careful diagnostic evalu-

ation is critical for accurate diagnosis and management. The outcomes for MM have improved greatly over the past 20 years with the introduction of HDT/autoSCT and 2 new classes of drugs, IMiDs and proteasome inhibitors.

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