Management of Multiple Myeloma and Serious Side Effects

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Author's disclosures of potential conflicts of interest are found on page 4 and at the end of this article.

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Abstract

Multiple myeloma (MM) is a B-cell malignancy arising from neoplastic proliferation of monoclonal plasma cells. The majority of patients are men, and the median age at diagnosis is 71 years. Information provided by laboratory and radiologic assessments and bone marrow biopsy and aspirate is used for diagnosis, staging, risk stratification, and prognostication. The International Staging System is used to determine disease stage. Plasma cell neoplasms progress from monoclonal gammopathy of undetermined significance to asymptomatic/smoldering MM to symptomatic MM. Treatment is indicated only for symptomatic MM. Selection of initial therapy depends on whether the patient is a candidate for autologous stem-cell transplantation. Combination regimens are generally used, and excellent overall response rates have been achieved with incorporation of the novel agents bortezomib, lenalidomide, and thalidomide. Several new therapies for MM are also being investigated in clinical trials. Treatment-emergent toxicity, such as peripheral neuropathy and thrombosis, is a frequent reason for discontinuation of therapy. Early detection of side effects, prompt intervention, and education of patients and health-care providers can improve adherence to therapy and quality of life. Disease-related complications, particularly renal dysfunction and bone destruction, occur in a large percentage of patients and are important considerations in management.

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Multiple myeloma (MM) is a B-cell malignancy arising from the neoplastic proliferation of monoclonal plasma cells that results in the overproduction of a monoclonal protein (Munshi & Anderson, 2005). The protein produced is typically an intact immunoglobulin (Ig), most commonly IgG or IgA. Up to 16% of patients produce excess light chains, with fewer than 3% having nonsecretory MM (Rajkumar & Kyle, 2005).

In 2010, 20,180 new cases of MM were diagnosed and 10,650 deaths were reported in the United States (Jemal, Siegel, Xu, & Ward, 2010). Multiple myeloma accounts for 1% of all malignancies and 10% of hematologic malignancies. It is more prevalent in men, and the incidence is twice as high in African Americans compared with whites (Rajkumar & Kyle, 2005). The median age at diagnosis is 71 years (Munshi & Anderson, 2005).

The monoclonal protein associated

with the MM diagnosis is responsible for numerous clinical manifestations. Up to 70% of patients will have bone destruction, often associated with pain and immobility, and anywhere from 15% to 20% will have associated hypercalcemia. Anemia, which contributes to complaints of fatigue, is seen in up to 70% of patients at the time of diagnosis, and up to 30% of patients exhibit signs of renal impairment (Kyle & Rajkumar, 2009).

The diagnostic assessment for a suspected plasma cell–associated diagnosis is comprehensive and includes numerous laboratory and radiologic assessments as well as a diagnostic, unilateral bone marrow biopsy and aspirate (Table 1) (Dimopoulos et al., 2011). The assessments not only help establish a diagnosis, but will also provide information that is vital for staging, risk stratification, and prognostication.

Numerous diagnostic imaging methods, including conventional radiographs, computed tomography (CT), magnetic resonance imaging, and positron emission tomography, are useful in characterizing bone involvement in patients with MM (Table 2). These methods are useful for evaluating skeletal integrity and soft-tissue extension or involvement as well as for diagnosing medical emergencies such as cord compression (Dimopoulos et al., 2009).

The bone marrow biopsy and aspirate provides information regarding the degree of plasmacytosis; specialized molecular tests, such as cytogenetics and fluorescence in situ hybridization (FISH), aid in risk stratification. According to Kumar et al. (2009), patients can be stratified into three categories: standard, intermediate, or high risk, according to the Mayo Stratification of Myeloma and Risk Adapted Therapy (mSMART) 2.0 classification system (Table 3). The tests used to determine risk category include FISH analysis, gene expression profile (GEP), and plasma cell labeling index (PCLI). Cytogenetics evaluate for hyper/hypodiploid karyotypes and deletion 13, while FISH specifically assesses for translocations of multiple chromosomes (Kumar et al., 2009).

Risk stratification can be useful when deciding on therapeutic options. Avet-Loiseau et al. (2007) assessed the impact of chromosomal abnormalities on overall survival (OS) in MM and found a statistically significant difference in OS at 4 years when there was a genetic abnormality. Furthermore, they found that when the genetic abnormality was combined with International Staging System (ISS) stage, there was a positive correlation with decreased OS in patients with higher-stage disease.

Plasma cell neoplasms are a spectrum of diseases along a continuum that begins with a prema-

Table 1. Diagnostic Assessment for Multiple Myeloma

Test	Finding(s) with myeloma
CBC with differential	↓ Hgb, ↓ WBC, ↓ platelets
Chemistry	↑ creatinine, ↑ Ca+, ↑ uric acid, ↓ albumin
Serum electrophoresis with quantitative immunoglobulins	↑ M protein in serum, may have ↓ levels of normal immunoglobulins
Immunofixation	Identifies light/heavy chain types of M protein
$Beta_2$-microglobulin	↑ levels (measures tumor burden)
24-hour urine electrophoresis	↑ monoclonal protein (Bence Jones)
Serum free light chain	↑ free light chains
Bone marrow biopsy with FISH and cytogenetics	≥ 10% plasma cells
Skeletal survey	Osteolytic lesions, osteoporosis
MRI	Focal lesions, bone marrow involvement

Note. CBC = complete blood count; FISH = fluorescence in situ hybridization; Hgb = hemoglobin; MRI = magnetic resonance imaging; WBC = white blood count.
Information from Dimopoulos et al. (2011).

Table 2. Imaging Modalities for Evaluating Bone Disease in Multiple Myeloma

Type of imaging	Findings	Recommended use
Conventional radiography (x-rays)	• Lytic lesions • Diffuse osteopenia	• Durie-Salmon staging at the time of diagnosis • Further imaging needed during follow-up
Computed tomography	• Lytic lesions (too small to detect on x-ray)	• Evaluating patients who are symptomatic despite having no evidence of osteolysis on skeletal survey • Evaluating extent of associated soft-tissue masses • Superior to x-ray at estimating fracture risk and instability
Magnetic resonance imaging	• Degree of multiple myeloma cell infiltration before bone destruction visible on x-ray (focal disease vs. diffuse infiltration) • Amyloid deposition (soft tissue and cardiac)	• Evaluating for cord compression • Determining % loss of vertebral height prior to vertebroplasty and/or kyphoplasty
Positron emission tomography	• Persistent or recurrent osseous disease • Localizing extramedullary sites of disease	• Monitoring patients with nonsecretory myeloma • Evaluating for other areas of involvement in patients with suspected solitary plasmacytoma

Note. Information from Dimopoulos et al. (2009).

lignant process termed monoclonal gammopathy of undetermined significance (MGUS), followed by asymptomatic/smoldering MM, culminating in a diagnosis of symptomatic MM; see Table 4 for details regarding diagnostic criteria for each (Dimopoulos et al., 2011). Symptomatic MM is the only indication for the initiation of systemic therapy; the other forms require monitoring at differing intervals at the discretion of the clinician.

The risk of progression to MM from MGUS was described by Kyle et al. (2010). They described a model to predict progression that included the relative serum paraprotein level (> 1.5 g/dL), the presence of an abnormal free light chain ratio, or a non-IgG subtype. The relative risk of progression was 1, 5.4, and 10.1 in patients with one, two, and three factors, respectively.

Once a decision has been made to initiate systemic therapy based on one or more CRAB criteria (i.e., hypercalcemia, renal insufficiency, anemia, or bone lesions), the patient should be staged. The Durie-Salmon staging system (Table 5), although still in use, has been superseded by the ISS, which takes into account the pretreatment serum albumin and serum beta$_2$-microglobulin levels. An evaluation of nearly 12,000 patients across North America, Europe, and Asia found that regardless of therapeutic intervention, pretreatment levels of serum albumin and serum beta$_2$-microglobulin were two of the most significant prognostic factors (Greipp et al., 2005).

Table 3. mSMART 2.0 Risk Classification System

High risk	Intermediate risk[a]	Standard risk[a,b]
FISH Del 17p t(14:16) t(14;20) GEP High-risk signature	FISH[c] t(4;14) Cytogenetic deletion 13 or hypodiploidy PCLI > 3%	All others Hyperdiploidy t(11;14)[d] t(6:14)

Note. del = deletion; FISH = fluorescence in situ hybridization; GEP = gene expression profile; mSMART = Mayo Stratification of Myeloma and Risk Adapted Therapy; PCLI = plasma cell labeling index.
Information from Kumar et al. (2009).
[a]A subset of patients with these features will be defined as high risk by GEP.
[b]Lactate dehydrogenase > upper limit of normal and beta$_2$-microglobulin > 5.5 may indicate worse prognosis.
[c]Prognosis is worse when associated with high beta$_2$-microglobulin and anemia.
[d]t(11;14) may be associated with plasma cell leukemia.

Table 4. Classifications of Monoclonal Gammopathies

Disease classification	Definition
Monoclonal gammopathy of undetermined significance	Serum monoclonal protein < 3 g/dL Bone marrow plasmacytosis < 10% (clonal) Absence of CRAB criteria (hypercalcemia, renal insufficiency, anemia, bone disease)
Asymptomatic myeloma	Serum monoclonal protein ≥ 3 g/dL Bone marrow plasmacytosis >10% (clonal) Absence of CRAB criteria
Symptomatic myeloma	Bone marrow plasmacytosis ≥ 3 g/dL (clonal) Presence of serum/urine monoclonal protein Evidence of at least one CRAB criteria attributable to the underlying plasma cell proliferative disorder

Note. C = serum calcium ≥ 11.5 mg/dL; R = serum creatinine > 2 mg/dL; A = normochromic, normocytic anemia with hemoglobin > 2 g/dL below the lower limit of normal or hemoglobin < 10 g/dL; B = lytic lesions, severe osteopenia, or pathologic fractures.
Information from Dimopoulos et al. (2011).

Table 5. Staging Systems for Multiple Myeloma

ISS stage	Description	DS stage	Description
Stage I	Serum beta$_2$-microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL	Stage I	All of the following: • Hemoglobin > 10 g/dL • Serum calcium value normal or < 10.5 mg/dL • Bone radiograph, normal bone structure (scale 0), or solitary bone plasmacytoma only • Low M-component production rate: IgG < 5 g/dL; IgA value < 3 g/dL • Urine light chain M-component on electrophoresis < 4 g/24 h
Stage II	Not stage I or III	Stage II	Fitting neither stage I nor stage III
Stage III	Serum beta$_2$-microglobulin ≥ 5.5 g/dL	Stage III	One or more of the following: • Hemoglobin < 8.5 g/dL • Serum calcium > 12 mg/dL • Advanced lytic bone disease (scale 3) • High M-component production rate: IgG > 7 g/dL; IgA value > 5 g/dL • Bence Jones protein > 12 g/24 h
		Substage	A: Relatively normal renal function: serum creatinine < 2 mg/dL B: Abnormal renal function: serum creatinine > 2 mg/dL

Note. DS = Durie-Salmon; Ig = immunoglobulin; ISS = International Staging System.
Information from Greipp et al. (2005).

Treatment Overview

In the past decade, the US Food and Drug Administration (FDA) has approved four agents for the treatment of MM, all of which have added significantly to our treatment armamentarium for this disease.

Before initiating therapy, the decision must be made whether the patient is a potential candidate for autologous stem-cell transplantation, based on age, performance status, and comorbid conditions. If so, alkylators should be avoided during induction therapy so that collection of hematopoietic progenitor cells is not impaired. Once that decision has been made, the therapeutic options are quite broad. Based on the treatment advancements that have been made over

the past decade, it is now possible to prescribe personalized treatment plans for patients, taking into consideration factors such as risk stratification, comorbidities, access to care, prescription drug coverage, and side-effect profiles of the various agents. The trend has been toward combination therapy in doublets, triplets, and quadruplets with an excellent overall response rate (ORR) of ≥ 80% using the novel agents bortezomib (Velcade), lenalidomide (Revlimid), and thalidomide (Thalomid); see Figure 1 (Stewart, Richardson, & San-Miguel, 2009). The agents currently approved for use in MM are summarized in Table 6.

The National Comprehensive Cancer Network (NCCN) evidence-based guidelines (2007) can help in selection of treatment options for the MM disease continuum and can be accessed on their website (www.nccn.org); see Tables 7 and 8.

It is important to remember that treatment on a clinical trial is a consideration throughout all phases of the disease, from the time of diagnosis until patients become treatment refractory. The primary exclusion criteria that may preclude participation in a clinical trial are renal insufficiency and bone marrow suppression.

Treatment-Related Toxicities

Treatment-related toxicity is often a reason for early discontinuation of therapy, regardless of response. Since advanced practitioners are vital members of the health-care team and have frequent interactions with patients and caregivers, they are in a unique position to help identify early signs and symptoms of treatment-related toxicities as well as collaborate with physician colleagues to help maintain patients on optimal therapeutic regimens.

PERIPHERAL NEUROPATHY

Peripheral neuropathy (PN), one of the toxicities associated with agents used to treat MM, can lead to significant pain, loss of independence, and functional ability. Early detection and prompt intervention can minimize the severity and progression of neuropathic symptoms, and it begins with education of both health-care professionals and patients.

There are numerous reasons why PN or underlying risk factors for its development may be present at baseline. Peripheral neuropathy may be present at diagnosis due to mechanical factors such as spinal cord compression; radiculopathy, such as nerve-root compression or carpal tunnel syndrome; or underlying plasma cell proliferative disorders such as

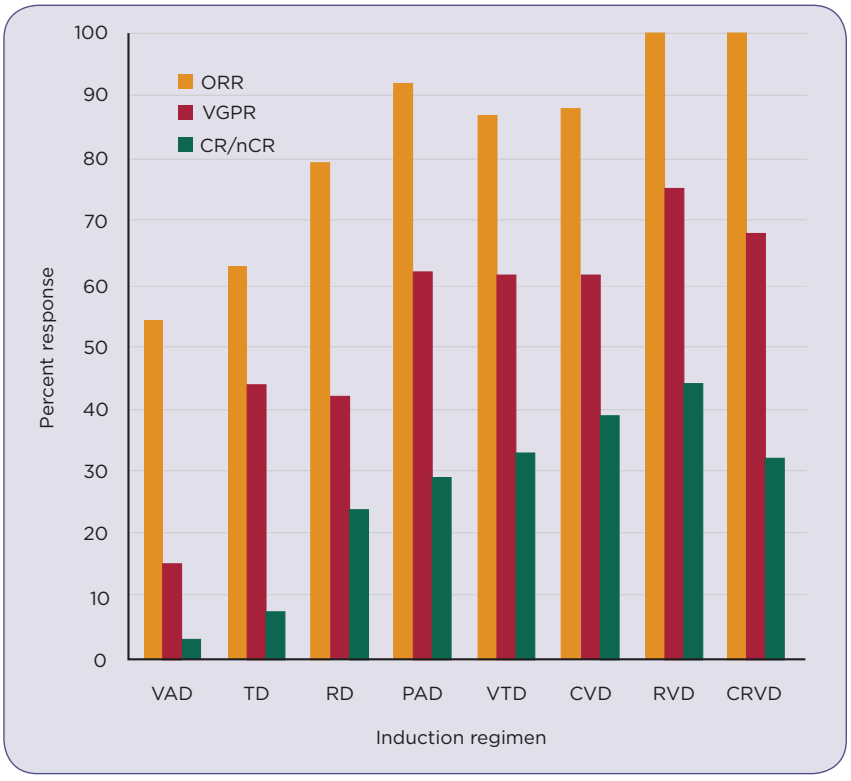

Figure 1. Reported response rates to induction regimens. CR/nCR = complete response/near complete response; CRVD = cyclophosphamide/lenalidomide/bortezomib/dexamethasone; CVD = cyclophosphamide/bortezomib/dexamethasone; ORR = overall response rate; PAD = bortezomib/doxorubicin/dexamethasone; RD = lenalidomide/high-dose dexamethasone; RVD = lenalidomide/bortezomib/dexamethasone; TD = thalidomide/dexamethasone; VAD = vincristine/doxorubicin/dexamethasone; VGPR = very good partial response; VTD = bortezomib/thalidomide/dexamethasone. Reprinted, with permission, from Stewart, Richardson, & San-Miguel (2009). Permission conveyed through Copyright Clearance Center, Inc.

Table 6. Agents Used in the Treatment of Multiple Myeloma

Drug	Indication
Bortezomib	Patients with multiple myeloma
Dexamethasone	Palliative management of leukemia and lymphomas
Lenalidomide	In combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least 1 line of therapy
Pegylated liposomal doxorubicin	In combination with bortezomib in patients who have not previously received bortezomib and have received at least 1 prior therapy
Prednisone	Palliative management of leukemia and lymphomas in adults
Thalidomide	In combination with dexamethasone for the treatment of patients with newly diagnosed myeloma

Note. Information from Celgene (2010a, 2010b), Centocor Ortho Biotech Products (2011), GlaxoSmithKline (2004), Merck (2007), Millennium Pharmaceuticals (2010), Pfizer (2007).

MGUS or MM. Factors that may increase the risk of developing treatment-emergent PN include comorbidities such as diabetes mellitus or obesity, prior exposure to neurotoxic agents, vitamin deficiencies, and alcohol or other addictions.

Peripheral neuropathy is identified on routine physical examination at the time of diagnosis in approximately 3% to 13% of patients (Dispenzieri & Kyle, 2005), the incidence being as high as 60% when a more sensitive diagnostic assessment is used (Richardson et al., 2005).

The drugs known to increase the risk of treatment-related PN include the cytostatic agents vincristine and cisplatin, the immunomodulatory agent thalidomide, and the proteasome inhibitor bortezomib (Wickham, 2007). The risk of PN is minimal with lenalidomide, pomolidomide, and carfilzomib. The neuropathy may present as sensory (e.g., paresthesia, pain), motor (e.g., weakness), or autonomic (e.g., hypotension, bradycardia). Sensory changes are common with both thalidomide and bortezomib but motor neuropathy is rarely reported.

Neuropathic pain is more prevalent with bortezomib but in rare instances is seen with thalidomide. The autonomic symptoms commonly seen with bortezomib include constipation and orthostatic hypotension; with thalidomide, constipation, impotence, and bradycardia are common (Tariman, Love, McCullagh, & Sandifer, 2008). Development of neuropathy with both bortezomib and lenalidomide appears to be dose dependent. In patients treated with thalidomide, neuropathy onset is typically slow, with the incidence doubling between 6 and 12 months of therapy (Mileshkin et al., 2006), whereas in patients treated with bortezomib, onset may be slow or subacute, with a peak around cycle 5 (Berenson et al., 2005). Approximately 70% of patients who experience bortezomib-related PN will see either resolution or improvement within 2 to 3 months of onset, whereas with thalidomide, reversal of PN is minimal if at all, and it may take years to see an appreciable difference (Richardson et al., 2006).

Although bortezomib is approved for IV administration, a recent phase III, prospective, randomized, open-label trial compared SC with IV bortezomib dosing for patients with relapsed MM. Peripheral neuropathy (all grades) was observed in 38% of patients in the SC arm and 53% in the IV arm (p = .04). For grades 3/4 PN, the incidence was 6% (SC) and 16% (IV) (p = .03). Most events were peripheral sensory neuropathies; 62% in the SC arm and 67% in the IV arm resolved in a median of 2.8 months (SC) and 1.5 months (IV) (Moreau et al., 2011).

The key to managing treatment-related PN is early recognition and intervention. In addition to modifying the dose of the causative agent, numerous topical and systemic interventions as well as complementary approaches have been tried, although no randomized clinical trials have compared the efficacy of any of these regimens (Sonneveld & Jongen, 2010) Among the topical agents suggested for symptom management of neuropathic pain are lidocaine patches, capsaicin cream, cocoa butter,

Table 7. NCCN Recommendations for Primary Induction Therapy for Transplant and Nontransplant Candidates

Primary induction therapy for transplant candidates (category)	Primary induction therapy for nontransplant candidates (category)
Bortezomib/dexamethasone (1)	Bortezomib/dexamethasone
Bortezomib/cyclophosphamide/dexamethasone	Dexamethasone (2B)
Bortezomib/doxorubicin/dexamethasone (1)	Lenalidomide/low-dose dexamethasone (1)
Bortezomib/lenalidomide/dexamethasone (2B)	Liposomal doxorubicin/vincristine/dexamethasone (2B)
Bortezomib/thalidomide/dexamethasone (1)	Melphalan/prednisone
Dexamethasone (2B)	Melphalan/prednisone/bortezomib (1)
Lenalidomide/dexamethasone (1)	Melphalan/prednisone/lenalidomide
Liposomal doxorubicin/vincristine/dexamethasone (2B)	Melphalan/prednisone/thalidomide (1)
Thalidomide/dexamethasone (2B)	Thalidomide/dexamethasone (2B)
	Vincristine/doxorubicin/dexamethasone (2B)

Note. NCCN = National Comprehensive Cancer Network. Information from NCCN (2011).

and creams and ointments containing 0.5% menthol. Potential systemic therapies include the tricyclic antidepressants amitriptylene and nortriptyline; the anticonvulsants gabapentin and pregabalin; the opioids oxycodone, morphine, and fentanyl; and the serotonin/norepinephrine-reuptake inhibitors duloxetine and venlafaxine. Nutritional supplements such as glutamine, L-carnitine, and alpha-lipoic acid have also been suggested as management options.

Open communication encourages patients and caregivers to report treatment-related toxicities, which enables appropriate dose modifications to be made according to the product package inserts. Grading toxicities based on the Common Toxicity Criteria version 3 allows advanced practitioners to speak a common language when evaluating toxicities and is helpful when assessing patients to either continue therapy or to initiate appropriate interventions.

No randomized trials have provided guidance on a standard of care to manage treatment-related PN, and clinical trials are needed to determine both preventive and treatment measures to reduce the incidence and severity of this potentially painful and debilitating toxicity. Until then, prompt intervention at the first onset of symptoms may be beneficial.

THROMBOSIS

The diagnosis of MM is one of the risk factors associated with thromboembolic events (TEs), and many of the therapeutic options used to manage the disease are associated with a potential risk of TEs. Among the agents known to increase the risk of TE are the immunomodulatory agents lenalidomide and thalidomide, high-dose (pulse) dexamethasone, doxorubicin, and supportive care

Table 8. NCCN Recommendations for Salvage Therapy in Multiple Myeloma

Salvage therapy (category)
Repeat primary induction therapy (if relapse > 6 mo)
Bendamustine (2B)
Bortezomib (1)
Bortezomib/dexamethasone
Bortezomib/lenalidomide/dexamethasone (2B)
Bortezomib/liposomal doxorubicin (1)
Cyclophosphamide + VAD
Cyclophosphamide/bortezomib/dexamethasone
Cyclophosphamide/lenalidomide/dexamethasone
Dexamethasone
Dexamethasone, cyclophosphamide, etoposide, and cisplatin
Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide
High-dose cyclophosphamide
Lenalidomide/dexamethasone (1)
Lenalidomide
Thalidomide
Thalidomide/dexamethasone

Note. NCCN = National Comprehensive Cancer Network; VAD = vincristine/doxorubicin/dexamethasone. Information from NCCN (2011).

agents such as epoetin alfa (Epogen, Procrit) and darbopoetin alfa (Aranesp) (Palumbo et al., 2008).

Because of the increased risk of thrombosis associated with MM treatment options, it is important to provide thrombosis prophylaxis unless there is an absolute contraindication. Palumbo et al. (2008) provide both a risk assessment tool and therapeutic recommendations for thromboprophylaxis specific to the MM population. The risk factors are divided into myeloma-related, individual, and therapy-related (Table 9). Mechanical forms of prophylaxis may also be used and include sequential compression devices, antiembolism stockings, and exercise.

Inadequately managed treatment-related side effects may have far-reaching implications. Awareness, open communication, and education for prevention and early detection can help to optimize outcomes.

Disease-Related Complications

Aside from the complications that may arise from therapeutic interventions for the management of MM, some disease-related complications can also be challenging. Two of the more devastating ones are renal dysfunction and bone destruction. Renal dysfunction can make drug administration and diagnostic assessment difficult because of potential concerns regarding drug clearance. Bone destruction, on the other hand, leads to significant morbidity and can profoundly diminish quality of life if it is not well managed.

RENAL DYSFUNCTION

Renal dysfunction in patients with MM may be caused by either factors inherent to the diagnosis itself or outside factors. The causes directly related to MM include cast nephropathy, light chain deposition disease, acute tubular necrosis, and amyloidosis (Dimopoulos et al., 2008). Certain drugs or conditions may also affect renal function in patients with MM, including radiocontrast dyes or IV contrast agents (for CT scans), cyclooxygenase-2 inhibitors and other nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, hypercalcemia, dehydration, comorbidities such as diabetes and hypertension, and older age.

Education regarding renal protection is important for health-care providers, patients, and their caregivers. Patients must be advised to maintain adequate oral hydration and to avoid nephrotoxic agents when possible. Health-care providers need to avoid the use of contrast dye when performing diagnostic tests, aggressively manage hypercalcemia and disease progression, be aware of and appropriately dose medications requiring adjustments for renal impairment, and

Table 9. Risk Assessment for Thrombosis and Suggested Therapies

Category	Risk factors	Therapeutic recommendations
Individual	Age History of VTE Central venous catheter Diabetes Infection Cardiac disease Immobilization Surgery Inherited thrombophilia	0 or 1 individual risk factor present: once daily aspirin ≥ 2 individual or myeloma-related risk factors: LMWH (once daily enoxaparin) or full-dose warfarin
Myeloma-related	Diagnosis Hyperviscosity	≥ 2 individual or myeloma-related risk factors: LMWH (once daily enoxaparin) or full-dose warfarin
Therapy-related	High-dose dexamethasone Doxorubicin Multiagent chemotherapy incorporating thalidomide or lenalidomide	LMWH (enoxaparin) or full-dose warfarin in all patients regardless of additional risk factors

Note. LMWH = low molecular-weight heparin; VTE = venous thromboembolism.
Adapted from Palumbo et al. (2008).

work collaboratively with the other members of the patient's health-care team to manage comorbid conditions aggressively.

BONE DESTRUCTION

Bone destruction from MM is usually osteolytic. A viscous circle of osteoclast activation by tumor-derived osteoclast-activating factors and bone-derived tumor growth factors allowing for further osteoclast activation occurs in the setting of active MM, as shown in Figure 2 (Roodman, 2004). Bisphosphonates such as zoledronic acid (Zometa) and pamidronate (Aredia) can inhibit osteoclast activity, leading to a decrease in the extent of bone destruction. Bisphosphonates concentrate under osteoclasts and are released during osteoclast bone degradation, leading to apoptosis and osteoclast inhibition, thus allowing for normal bone anabolic function.

The benefits of bisphosphonate are widely recognized, yet there is no consensus on the frequency of administration. Both the American Society of Clinical Oncology (Kyle et al., 2007) and the International Myeloma Working Group (Durie, 2007) have created guidelines for bisphosphonate administration; the guidelines are compared in Table 10.

The risks of bisphosphonates include infusion-related reactions (flu-like symptoms), osteonecrosis of the jaw (ONJ), and renal-related toxicity. Pamidronate may cause glomerular damage, which can present as nephrotic-range proteinuria (> 3.5 g/day) while zoledronic acid may cause tubular damage. Both are dose- and infusion time–dependent, and continuous assessment of renal function by 24-hour urine collection and serum creatinine analysis is needed (Perazella & Markowitz, 2008).

Bisphosphonates can aid in the prevention of skeletal-related events and management of hypercalcemia, but surgical intervention may also be needed to prevent bone destruction. In the case of vertebral compression fractures, a minimally invasive procedure called kyphoplasty may be appropriate. A trochar is used to drill a channel in the affected vertebral body followed by the insertion of a balloon-like inflatable bone tamp. A space is created and the balloon is removed. A catheter is then inserted and a viscous bone void filler of the physician's choice may be inserted, allowing for height restoration, stabilization, and improvement in pain (Dudeney, Lieberman, Reinhardt, & Hussein, 2002).

Emerging Therapies

At the 2010 meeting of the American Society of Hematology, many new concepts as well

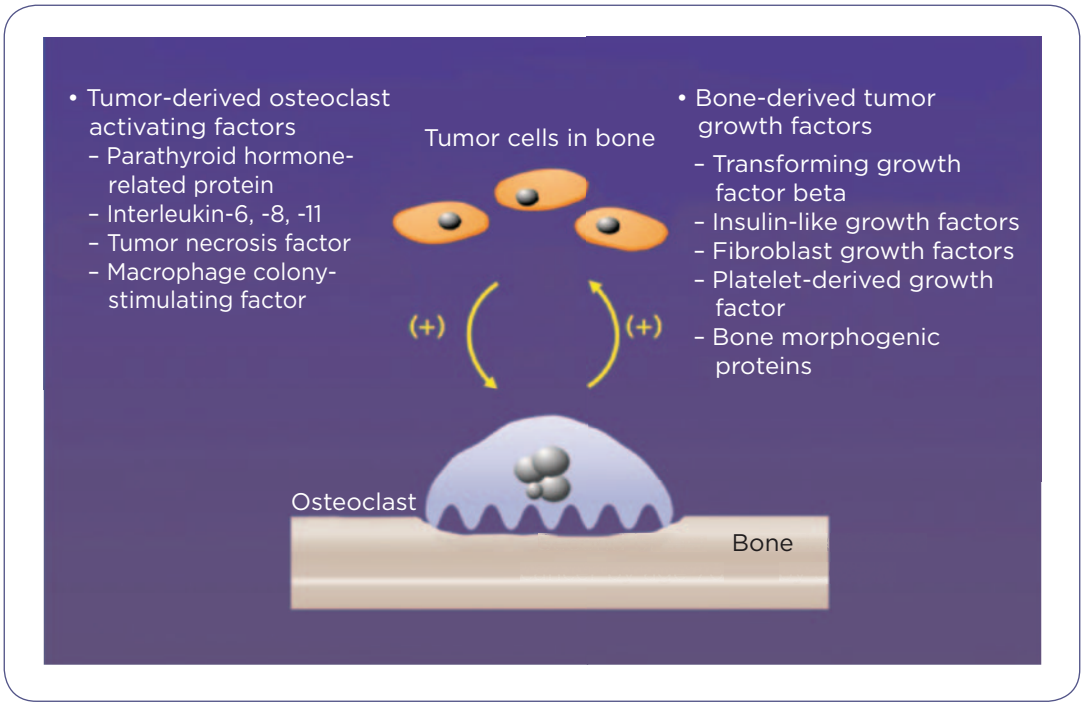

Figure 2. Pathogenesis of osteolytic bone metastases. Adapted, with permission, from Roodman (2004).

Table 10. Comparison of Bisphosphonate Administration Guidelines for Patients With Multiple Myeloma

ASCO guidelines	IMWG guidelines
Monthly bisphosphonate for 2 years	Monthly bisphosphonate for 1 year
After 2 years: • Consider stopping with responsive disease or stable disease • Further use at clinician's discretion • Resume treatment at relapse with new onset of skeletal events	After 1 year: • D/C if CR or VGPR occurs without evident bone disease • Continue if < VGPR or active bone disease evident After 2 years: • D/C if no active bone disease present • If active bone disease is present, further use is at clinician's discretion
Adequate dental hygiene	Need for adequate dental hygiene

Note. ASCO = American Society of Clinical Oncology; CR = complete response; D/C = discontinue; IMWG = International Myeloma Working Group; VGPR = very good partial response.
Information from Durie (2007), Kyle et al. (2007).

as emerging data on new agents for treating MM were presented. Pathways within the bone marrow microenvironment are being targeted. It is hoped that interfering with these pathways will block the ability of the plasma cell to proliferate and survive.

Two studies provided data regarding the use of lenalidomide maintenance in the posttransplant phase of therapy. The Intergroupe Francophone du Myélome (IFM) 2005-02 trial enrolled 614 patients and prescribed 2 months of consolidation with single-agent lenalidomide (25 mg once daily days 1–21 every 28 days) following high-dose melphalan transplantation with subsequent randomization to either placebo or lenalidomide (10–15 mg daily) until relapse. They reported a statistically significant difference in progression-free survival (PFS; 42 vs. 24 months, $p < 10^{-8}$) for those receiving lenalidomide maintenance (Attal et al., 2010). This was confirmed by the Cancer and Leukemia Group B (CALGB) 10014 study in which 568 patients were also randomized to either placebo or lenalidomide maintenance (10 mg daily) without consolidation following high-dose transplantation. In this study, the maintenance arm had a 42-month time to progression vs. 22 months in the control group ($p < .0001$) (McCarthy et al., 2010).

Table 11. Reported Toxicities With Selected Phase I/II Investigational Agents

Carfilzomib toxicity	Percentage	Pomalidomide toxicity	Percentage
Anemia	44%	Anemia	20%
Thrombocytopenia	38%	Thrombocytopenia	22%
Lymphopenia	23%	Neutropenia	42%
Fatigue	46%	Fatigue	12%
Upper respiratory infection	26%	Infection	31%
Pyrexia	29%		
Nausea	41%	Deep-vein thrombosis	1%
Diarrhea	29%		
Peripheral neuropathy	12% (0.8% grade 3/4)	Peripheral neuropathy	0%
Dyspnea	31%		
Headache	25%		

Note. Information from Richardson et al. (2010), Siegel et al. (2010).

The MM-002 study presented by Richardson et al. (2010) provided updated phase I clinical data regarding the use of pomalidomide (CC-4047) in a heavily pretreated population. The 38 patients received single-agent pomalidomide with the option to add dexamethasone at the time of progression or if there was no response after four cycles of treatment. The ORR in a population refractory to lenalidomide was 28%. Commonly reported toxicities in phase I/II trials of investigational agents are shown in Table 11 (Richardson et al., 2010).

Siegel et al. (2010) presented the 003-A1 data on the use of carfilzomib in relapsed-refrac-

tory MM patients who had previously received both a proteasome inhibitor and an immunomodulatory drug. All patients received single-agent carfilzomib (20–27 mg/m^2) for up to 12 cycles of 28 days each. The ORR was 24%, the clinical benefit rate (partial response plus minor response was 34%, and the duration of response was 8.3 months. Commonly reported toxicities are shown in Table 11.

Conclusion

The 5-year OS rate of patients diagnosed with MM has improved to approximately 42% (National Cancer Institute, 2011). This improvement in OS has been most apparent in those diagnosed since 2001. These improvements are largely due to the approval of new agents (bortezomib, lenalidomide, liposomal doxorubicin, and thalidomide) as well as advances in supportive care and new drug development.

DISCLOSURES

Elizabeth Bilotti, MSN, RN, APN, OCN®, reported a financial interest/relationship in the form of: Consulting Fees: Celgene, Merck, Millennium: The Takeda Oncology Company; Speaker's Bureau: Celgene, Millennium: The Takeda Oncology Company.

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