



# MULTIPLE MYELOMA: NURSING ROUNDTABLE DISCUSSIONS



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## Inside this issue ▶▶▶

Treatment of Multiple Myeloma:  
Exploring the Role of Novel Agents 1

Case Presentation: Newly  
Diagnosed Multiple Myeloma 5

Case Presentation:  
Relapsed/Refractory Multiple  
Myeloma 9

Case Presentation: Older Adult  
With Newly Diagnosed  
Multiple Myeloma 12

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### Target Audience

This activity has been designed to meet the educational needs of oncology nurses and nurse practitioners involved in the treatment of patients with multiple myeloma (MM).

### Purpose

To educate nurses on the latest treatment and nursing management strategies for patients with MM.

### Program Overview

A physician thought leader will provide an overview of current treatment standards and the role of novel agents used in the treatment of MM. This will be followed by a series of case studies, which will illustrate complex nursing management scenarios. MM standards of care based on disease stage, patient performance status, previous treatment exposure, and genetic factors will be discussed as they relate to the pertinent case.

### Learning Objectives

Upon completion of this program, participants should be better able to:

- Describe changes in the standard of care for patients with newly diagnosed MM
- Identify new combination therapies for patients who are not candidates for transplant
- Describe new options for treating patients with relapsed or refractory MM
- Describe toxicities of novel agents and novel combinations used to treat MM
- Outline treatment considerations for older adults with newly diagnosed and relapsed MM
- Identify the supportive care needs of older adults with MM
- Describe the role of clinical trials in the treatment schema of patients

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## TREATMENT OF MULTIPLE MYELOMA: EXPLORING THE ROLE OF NOVEL AGENTS

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Multiple myeloma (MM) is a plasma cell disorder characterized by an uncontrolled proliferation of bone marrow plasma cells, resulting in the destruction of bone and bone marrow failure. It is the second most common hematologic malignancy in the United States, and accounts for approximately 1% of all malignancies (Horner et al, 2008). According to the American Cancer Society, an estimated 19,920 new cases of MM and 10,690 related deaths occur annually (Jemal et al, 2008). The 5-year survival rate for patients with newly diagnosed disease is approximately 37% (Horner et al, 2008).

In the 1960s, the alkylating agent melphalan plus the corticosteroid prednisone (MP) was established as the standard of care for MM, producing a median survival of approximately 2.5 to 3 years (Facon et al, 2007). Combination chemotherapy was compared to MP regimen and failed to show superiority (Myeloma Trialists' Collaborative Group, 1998). In the 1990s, the use of high-dose chemotherapy and **autologous stem cell transplant** (ASCT) was shown to significantly increase 5-year survival compared to conventional care (52% vs. 12%;  $p = .03$ ; Attal et al, 1996). This was confirmed in a subsequent trial in which median survival was 54.1 months with high-dose chemotherapy compared to 42.3 months with conventional care (Child et al, 2003). More recently, advances in the understanding of signaling pathways and disease pathophysiology have led to the development of effective **targeted therapies**, including the proteasome inhibitor bortezomib and the **immunomodulatory** agents thalidomide and lenalidomide. It is now evident that MM differs from one patient to another and that some subsets of patients may derive greater benefit from a particular treatment than others (O'Shea et al, 2006).

### CYTOGENETIC SUBGROUPS AND RISK FACTORS

All patients may not benefit from high-dose chemotherapy or ASCT. There are subgroups

of patients with cytogenetic characteristics that are predictive of favorable outcomes, whereas others have characteristics that are suggestive of poorer outcomes (Kumar et al, 2007). Myeloma patients who are **hyperdiploid** do well, as do patients with low levels of beta-2-microglobulin (Stewart et al, 2007). In contrast, those with t(4;14) or (del)17p derive little or no benefit from high-dose therapy (Pant & Copelan, 2007).

An elevated beta-2-microglobulin (> 3 mg/dL) and chromosome 13 abnormalities are associated with a poorer survival risk (Hari et al, 2006). In one study of patients with MM receiving high-dose therapy, those with neither chromosome 13 abnormalities nor elevated beta-2-microglobulin had a median survival of 111 months compared to 47.3 months with either characteristic and 25.3 months with both (Facon et al, 2001). Beta-2-microglobulin is an essential component of the International Staging System, which is now being used in all new large, randomized **phase III trials** to identify good risk versus poor-risk patients (Palumbo et al, 2008).

Determining the risk profile of a patient with MM can help guide the choice of therapy. Del(13) is found in approximately 48% of patients with MM, t(11;14)(q13;q32) in 21%, t(4;14)(p16;q32) in 14%, hyperdiploidy in 39%, *MYC* translocations in 13%, and del(17p) in 11% (Avet-Loiseau et al, 2007). Patients with del(13) have an overall survival (OS) of 68% compared to 83% for those without the abnormality ( $p < .001$ ), whereas those with t(11;14)(q13;q32) have an OS of 80% compared to 74% for those without the abnormality ( $p = 0.28$ ). Patients with hyperdiploidy have an OS of 82% compared to 70% for those without ( $p = .006$ ). The hazard ratio (HR) for OS in patients with del(17p) of more than 60% is 3.93 ( $p < .001$ ), whereas in those with t(4;14) the OS HR is 2.78 ( $p < .001$ ), and in those with beta-2-microglobulin > 4 mg/L the OS HR is 2.83 ( $p < .001$ ; Avet-Loiseau et al, 2007). Evidence also suggests that the presence of

(del)13, as determined by **fluorescent in situ hybridization**, on its own may not be a negative risk factor; however, OS is significantly shortened when del(13) occurs in conjunction with other abnormalities such as t(4;14) or (del)17p (Avet-Loiseau et al, 2007).

### IMPROVING TRANSPLANT OUTCOMES

A number of strategies have been evaluated in an effort to improve the OS of transplant recipients. In a study comparing single versus double ASCT in 399 patients with previously untreated MM, double transplant resulted in a 7-year OS of 42% versus 21% with single transplant ( $p = .01$ ; Attal et al, 2003). However, among patients achieving at least a very good partial response (VGPR) after the first transplant, the second transplant did not increase survival. Therefore, the authors suggested that maintenance chemotherapy may be a more effective approach for this patient subset (Attal et al, 2003).

The addition of novel agents to the pretransplant regimen is also under investigation. In a phase I trial presented at American Society of Hematology's 2008 annual meeting, bortezomib was added at doses from 1.0 mg/m<sup>2</sup> to 1.6 m/m<sup>2</sup> to the pretransplant regimen either before (Arm A) or after (Arm B) treatment with melphalan 200 mg/m<sup>2</sup>, followed by ASCT. Of the 34 evaluable patients, 53% achieved a VGPR or better, and 94% had a **partial response** (PR), or better. No difference in toxicity was found between treatment arms. These results were very encouraging, demonstrating a near doubling of the  $\geq$  VGPR rate observed in previously high-dose melphalan trials by adding bortezomib (Lonial et al, 2008).

### RELAPSED/REFRACTORY DISEASE

Bortezomib received fast-track approval for refractory MM in 2003 based on phase II findings in which the agent produced a 35% overall response rate (ORR) and a complete or near-complete response (nCR) rate of 10% (Richardson et al, 2003). In the phase III Assessment of Proteasome Inhibition for Extending Remissions trial, the agent demonstrated superior overall and complete response rates compared to high-dose oral dexamethasone (Richardson et al, 2007). The

1-year survival rate was 80% with bortezomib and 66% with dexamethasone ( $p = .003$ ) — a 41% decrease in the risk of death during the first year. This analysis included data from 147 patients (44%) in the dexamethasone cohort who crossed over to receive bortezomib (Richardson et al, 2005). These findings led to the full approval of bortezomib for relapsed/refractory MM in 2005.

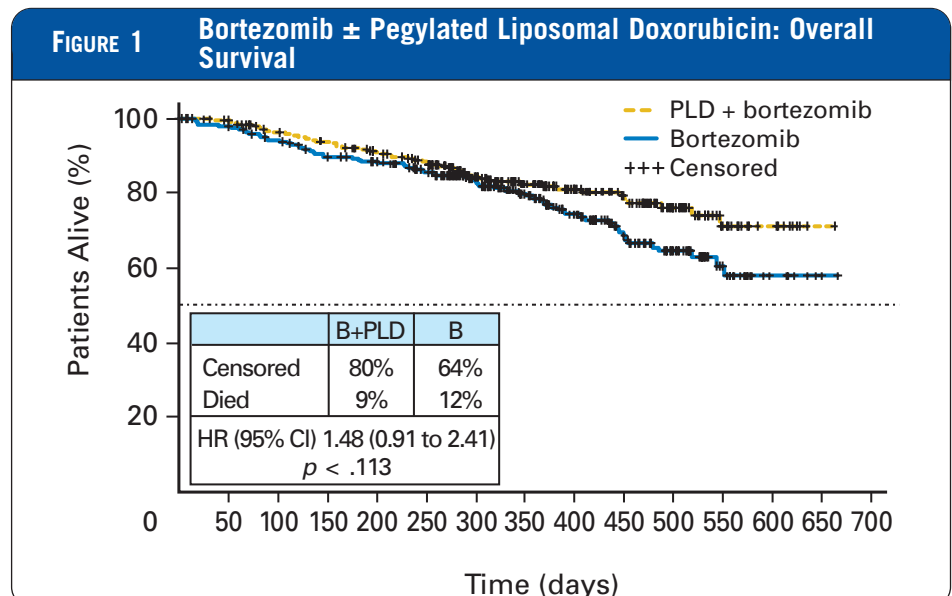
The addition of pegylated liposomal doxorubicin (PLD) to bortezomib is superior to bortezomib monotherapy in patients with relapsed/refractory disease (Harrousseau, Nagler, et al, 2007). In a trial involving 646 patients with relapsed or refractory MM, median time to progression (TTP) was 6.5 months in those who received bortezomib alone versus 9.3 months for those who received bortezomib plus PLD ( $p = .000004$ ; HR = 1.82). The ORR was 41% for bortezomib and 44% for combination treatment, and the 15-month survival rates were 65% and 76%, respectively. OS was significantly improved with bortezomib plus PLD ( $p < .113$ ; HR = 1.48; 95% confidence interval [CI]: 0.91–2.41; Harrousseau, Nagler, et al, 2007; Figure 1). The safety profile with combination treatment was consistent with known toxicities of each agent, with the most common adverse events being **neutropenia** (35%), **thrombocytopenia** (30%), fatigue (31%), and anemia (23%; Orłowski et al, 2007).

Bortezomib has also been investigat-

ed in combination with other agents, including lenalidomide plus dexamethasone, thalidomide plus dexamethasone, cyclophosphamide plus prednisone. The highest CR/nCR (52%) was achieved with bortezomib plus thalidomide, dexamethasone, and PLD, and the highest CR (17%) with bortezomib, melphalan, prednisone, and thalidomide (Richardson et al, 2006; Zangari et al, 2005; Reece et al, 2008; Ciolli et al, 2008; Palumbo et al, 2006).

In a study comparing lenalidomide plus dexamethasone with dexamethasone and placebo in patients with relapsed MM, the ORR (CR + nCR + PR) in the lenalidomide group was 61.0% versus 19.9% in the placebo group ( $p < .001$ ). A CR of 14.1% occurred in the lenalidomide group compared to 0.6% in the placebo group ( $p < .001$ ; Weber et al, 2007). The improvement in response translated into an OS benefit, and based on these results, lenalidomide in combination with dexamethasone was approved for relapsed myeloma (Figure 2).

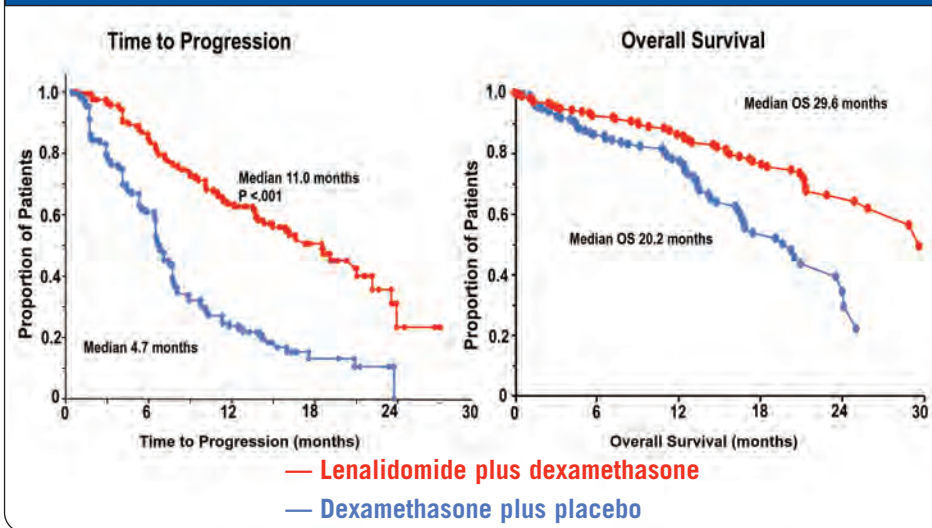
The combination of lenalidomide plus dexamethasone is effective regardless of prior thalidomide exposure. While lenalidomide and thalidomide are structurally similar, their mechanisms of action and associated toxicities differ (Weber et al, 2007). Lenalidomide is associated with improved potency and reduced toxicity (Wang et al, 2008). Emerging evidence indicates that the use of lenalidomide plus dexamethasone in patients previ-



(Harrousseau, Nagler, et al, 2007)

Overall survival was significantly improved in patients treated with bortezomib and pegylated liposomal doxorubicin. HR = hazard ratio; CI = confidence interval.

**FIGURE 2 Lenalidomide Plus Dexamethasone Versus Dexamethasone Plus Placebo in Relapsed Myeloma**



(Weber et al, 2006; Weber et al, 2007)

High response rates translate into benefit for both time to progression and overall survival in patients with relapsed multiple myeloma receiving lenalidomide plus dexamethasone.

ously treated with thalidomide still translates into superior ORR compared to those achieved with dexamethasone alone. An analysis of the safety and efficacy of lenalidomide + dexamethasone in patients with relapsed or refractory MM previously treated with thalidomide revealed that the combination led to higher ORR, longer TTP, and progression-free survival even in patients previously treated with thalidomide. ORR was higher in thalidomide-naïve patients versus thalidomide-exposed patients ( $p = .04$ ; Wang et al, 2008). Prior exposure to thalidomide did not affect survival in patients treated with lenalidomide + dexamethasone (36.1 vs. 33.3 months;  $p > .05$ ; Wang et al, 2008). Patients experienced similar toxicities regardless of prior thalidomide exposure (Wang et al, 2008).

### INDUCTION THERAPY

Recent studies have evaluated the use of novel agents as **induction** therapy. A trial involving patients with newly diagnosed MM showed that thalidomide/dexamethasone was associated with a significantly higher ORR compared to dexamethasone/placebo (63% vs. 46%, respectively; Rajkumar, Rasinol, et al, 2008). In addition, median TTP was significantly longer in the thalidomide group compared to the placebo group (22.6 vs. 6.5 months;  $p < .001$ ). A study comparing lenalidomide plus high-dose versus low-dose dexamethasone in newly diagnosed disease showed that OS was superior in

the low-dose dexamethasone group. Investigators evaluated a subset of the patients who went on to receive ASCT versus those who did not, and interestingly, the 1- and 2-year survival rates were identical in the two groups (99% and 94%, respectively; Rajkumar, Jacobus, et al, 2008). A phase I/II trial showed that induction therapy with bortezomib/dexamethasone/lenalidomide resulted in an ORR of 98% and a  $\geq$  VGPR of 71%—an unprecedented response rate (Richardson et al, 2008). Moreover, these rates were similar regardless of the presence or absence of (del)13q or t(4;14). The Eastern Cooperative Oncology Group and Southwest Oncology Group are conducting phase III trials investigating the bortezomib/dexamethasone/lenalidomide regimen.

Although historical data have suggested that the choice of induction therapy does not affect posttransplant outcomes, recent studies evaluating novel agents have indicated otherwise. A trial examining response to induction therapy in 482 newly diagnosed patients demonstrated a significantly superior CR (9.6% vs. 2.9%;  $p = .0023$ ), CR + nCR (21.3% vs. 8.3%;  $p < .0001$ ), and  $\geq$  VGPR (46.7% vs. 18.6%;  $p < .0001$ ) for bortezomib/dexamethasone compared to vincristine/doxorubicin/dexamethasone (VAD; Harousseau, Mathiot, et al, 2007; Harousseau, 2008). Importantly, these results held up after transplant. The post-ASCT CR + nCR rate

was 35.0% versus 23.6% for bortezomib/dexamethasone and VAD, respectively, whereas the  $\geq$  VGPR rate was 61.7% versus 41.7%, respectively (Harousseau, Mathiot, et al, 2007; Harousseau, 2008). The addition of thalidomide to bortezomib and dexamethasone (VTD) was shown to increase response rates even further in a trial that compared VTD to thalidomide plus dexamethasone (TD). Treatment with VTD was associated with a CR + nCR rate of 36% versus 9% for TD and a  $\geq$  VGPR rate of 60% versus 27% for TD ( $p < .001$  for both). Post-ASCT, VTD was associated with a CR + nCR of 57% vs. 28% for TD ( $p < .001$ ) and a  $\geq$  VGPR of 77% vs. 54% ( $p < .001$ ; Cavo et al, 2007; Harousseau, 2008).

### TREATMENT OF OLDER PATIENTS

Most older adults are not suitable candidates for ASCT. The melphalan/prednisone/thalidomide (MPT) regimen is an accepted standard for a large proportion of older patients. Newly diagnosed older patients with myeloma treated with MPT showed significantly higher response rate and longer progression-free survival than patients who received the MP combination (Palumbo et al, 2008). At a median follow-up of 38.1 months, median progression-free survival was 21.8 months for MPT and 14.5 months for MP ( $p = .004$ ). Median OS was 45.0 months for MPT and 47.6 months for MP ( $p = .79$ ). A phase III Eastern Cooperative Oncology Group trial is evaluating progression-free survival and OS in patients treated with MPT versus melphalan/prednisone/lenalidomide (US National Institutes of Health, 2008). Although MP has demonstrated efficacy in this population with an ORR of 50%, the long-term CR rate is less than 5% (Bladé & Rosiñol, 2006). Various combination therapies have been evaluated in an effort to improve response rates and duration of response. MP was compared to melphalan/dexamethasone in newly diagnosed patients aged 65 to 75 years. Response rates were significantly higher among those receiving melphalan/dexamethasone, and progression-free survival was superior as well ( $p < .001$ , for both); however, there was no difference in OS. Furthermore, dexamethasone-based therapy was associated with greater morbidity (Facon et al, 2006). A trial of

thalidomide/dexamethasone versus MP showed that while there was an increase in ORR and CR + nCR for thalidomide/dexamethasone, progression-free survival and OS were superior with MP (Ludwig et al, 2007). However, an effective alternative to MP has been demonstrated with the combination of melphalan/prednisone/bortezomib. This regimen demonstrated improvements in TTP, CR, and OS in the VISTA trial (San Miguel et al, 2007) and should be considered standard therapy for older patients and those not candidates for ASCT.

## CONCLUSION

The use of conventional care, novel agents, and combination therapies has resulted in marked improvement in the outcomes of patients with MM. Advances in cytogenetics will help to more accurately identify patients at highest risk for disease progression and aid clinicians in tailoring treatment regimens for particular myeloma subtypes. With the advent of more effective therapeutic regimens and genetic technologies, MM will continue its transformation from a terminal illness to a chronic disease with multiple treatment options associated with prolonged survival. ●

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# CASE STUDY

## CASE PRESENTATION: NEWLY DIAGNOSED MULTIPLE MYELOMA

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Mr. H is a 52-year-old electrician with no significant past medical history. He presents to the clinic complaining of excessive fatigue and lower back pain that began approximately 2 weeks ago. The pain has progressively worsened and Mr. H now rates it as a 10 on a scale of 0 (no pain) to 10 (worst pain possible). He has been taking ibuprofen 800 mg orally three times daily without benefit. Mr. H describes the pain as constant and indicates that he “has never experienced pain like this before.”

Mr. H's vital signs are as follows: blood pressure, 148/76 mm Hg; heart rate, 100 beats/min; temperature, 98.6° F; respiratory rate, 22 breaths/min. There is no evidence of lymphadenopathy or peripheral edema. His lungs are clear bilaterally, and his abdomen is soft and nontender. Neurological evaluation reveals normal deep tendon reflexes and normal strength and gait.

Laboratory studies reveal anemia (hemoglobin, 7.8 g/dL), hypercalcemia (calcium, 11.2 mg/dL), renal insufficiency (creatinine, 2.6 g/dL), and leukopenia (3,300/μL). Serum electrophoresis detects an elevated immunoglobulin (Ig) G lambda protein (4.8 g/dL). Urine electrophoresis with immunofixation shows an IgG lambda monoclonal spike. Serum beta-2-microglobulin is elevated at 5.9 mg/L (range, 0.3–1.9 mg/L). Bone marrow biopsy reveals 60% plasma cells in sheets and clusters. Fluorescent in situ hybridization is positive for (del)13.

### DIAGNOSTIC CRITERIA

A complete diagnostic evaluation in patients suspected of having multiple myeloma (MM) is essential as it not only confirms diagnosis but also provides baseline values for key measures that may help predict prognosis and response to therapy (National Comprehensive Cancer Network [NCCN], 2008b; Multiple Myeloma Research Foundation, 2008). Standard tests should include a complete blood

count (CBC) with differential, blood chemistry profile (including calcium, creatinine, lactate dehydrogenase, and albumin), bone marrow aspirate and biopsy, complete skeletal survey, serum and urine electrophoresis, serum beta-2-microglobulin, and serum immunofixation cytogenetics. Bone marrow aspiration or biopsy can be used to establish a diagnosis of MM. Skeletal imaging, either with radiography, magnetic resonance imaging (MRI), computed tomography (CT), or positron emission tomography (PET), can detect osteolytic lesions and osteoporosis (Durie et al, 2003). Both serum electrophoresis and urine electrophoresis can detect elevated M protein levels at the time of diagnosis. However if no M-component is detected, the Freelite test, which utilizes an ultrasensitive technique, may detect M protein through light chain assay (Durie et al, 2003). The level of beta-2-microglobulin reflects the tumor mass and is considered a standard measure of tumor burden. In patients with monoclonal gammopathy of undetermined significance, an abnormal serum free light chain ratio increases the likelihood of progression to malignancy (Rajkumar et al, 2005).

### STAGING

The International Staging System (ISS) has replaced the Durie-Salmon staging system in clinical practice, as it offers greater ease of use and more accurate prognostic information (Table

1). The ISS uses two criteria in determining a patient's disease stage: serum albumin and beta-2-microglobulin. Mr. H's serum beta-2-microglobulin level is higher than 5.5 gm/dL, and he is diagnosed with stage III IgG lambda MM, which is associated with a median survival of 29 months (Greipp et al, 2005).

### COMMON COMPLICATIONS OF MULTIPLE MYELOMA

#### ANEMIA

Anemia is a common complication of MM that may result as a side effect of therapy, an altered bone marrow environment, decreased erythropoiesis, renal insufficiency, and/or vitamin or iron deficiencies. Patients who develop symptomatic anemia may benefit from erythropoietin therapy to stimulate hematopoiesis in the bone marrow, which raises hemoglobin levels (NCCN, 2008a). Assessment for iron or B<sub>12</sub> deficiencies as a cause of anemia should also be performed (Birgegård, 2008).

#### HYPERCALCEMIA

Approximately 33% of patients with MM experience hypercalcemia (Oyajobi, 2007). Hypercalcemia related to bone destruction is generally treated with bisphosphonate therapy in the form of pamidronate or zoledronic acid and intravenous or aggressive oral hydration (He et al, 2008). If untreated, hypercalcemia may lead to a progressive decrease in renal function.

TABLE 1 International Staging System

Stage	Criteria	Median Survival (months)
I	Serum beta-2-microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III	44
III	Serum beta-2-microglobulin ≥ 5.5 mg/L	29

(Greipp et al, 2005)

The International Staging System, which uses two powerful predictors of survival (ie, beta-2-microglobulin and albumin) to determine stage and prognosis, has largely replaced the Durie-Salmon System.

Treatment of the underlying disease progression is imperative to overcoming hypercalcemia related to malignancy (Dimopoulos et al, 2008). Patients receiving bisphosphonates should be monitored for adequate renal function and for bisphosphonate-induced osteonecrosis of the jaw (BONJ; NCCN, 2008b). Jaw pain is the most common presenting symptom of BONJ. Treatment may consist of surgical sequestrectomy, antibiotics, and good oral hygiene. Most cases of BONJ are reversible or become asymptomatic (Katz et al, 2009).

**RENAL INSUFFICIENCY**

Renal insufficiency is present in approximately 15% of patients at diagnosis and occurs in up to 25% of patients during the course of their disease (Katzel et al, 2007). Immunoglobulin light chains may be noted in the serum or urine and may impair the ability of the kidneys' proximal tubules to absorb and process proteins. The light chains may then enter the distal tubules of the kidneys to form casts, ultimately causing nephron failure (Fentress et al, 2006). Thus, for patients who have developed renal insufficiency, a comprehensive assessment is necessary to determine whether the decline in renal function is due to the disease or other factors (such as nephrotoxic medications). Hypercalcemia results in significant volume depletion and should be corrected both with bisphosphonates and aggressive hydration (Trimarchi et al, 2006). Patients who present with renal insufficiency should be treated aggressively in an attempt to normalize renal function as quickly as possible. If a mild or moderate elevation in baseline creatinine is noted, aggressive oral or intravenous hydration should be considered as well as correction of the underlying cause of hypercalcemia. If moderate or severe renal dysfunction is present, serum plasmapheresis or hemodialysis may be indicated alone or with hydration (NCCN, 2008b). Treating the disease progression with appropriate therapies in addition to hydration may be critical in reversing renal dysfunction and preventing renal failure. Medications for MM may require dose modifications as a result of renal insufficiency. No standard treatment guidelines exist for dosage adjustments, but thalidomide and

**TABLE 2 Dose Modifications of Novel Agents for Renal Insufficiency**

<p><b>Thalidomide</b></p> <ul style="list-style-type: none"> <li>– Not renally excreted, no dosage adjustment recommended</li> </ul>
<p><b>Bortezomib</b></p> <ul style="list-style-type: none"> <li>– Safe alone or in combination in renally impaired patients (including dialysis patients); no dosage adjustment recommended</li> </ul>
<p><b>Lenalidomide</b></p> <ul style="list-style-type: none"> <li>– Excreted substantially by the kidney</li> <li>– Dose adjustments needed for moderate, severe, end-stage renal disease</li> <li>– Adverse effects may be greater in these patients</li> <li>– Dose reductions may be necessary and decrease the degree of myelosuppression</li> </ul>

(Eriksson et al, 2003; Fakhouri et al, 2004; Revlimid® prescribing information, 2009; Chanan-Khan et al, 2007) Medications for multiple myeloma may require dose modifications as a result of renal insufficiency. No standard treatment guidelines for dosage adjustments exist, but thalidomide and bortezomib are generally considered safe for patients with renal dysfunction.

bortezomib are generally considered safe for patients with renal dysfunction (Dimopoulos et al, 2008; Revlimid® prescribing information, 2009; Table 2).

**SKELETAL INVOLVEMENT**

Malignant cells produce osteoclast-activating factors that destroy bone cells (Mehrotra & Ruggiero, 2006). This may result in extensive osteolysis, severe bone pain, and pathologic fractures (Sonmez et al, 2008). Complications of MM may include spinal cord compression and plasmacytoma with significant bone destruction (NCCN, 2008b). Plain film radiograph, bone survey, MRI, and PET may be used to obtain a diagnosis. Treatment options for skeletal complications include radiotherapy, active treatment of underlying disease, analgesia, bisphosphonates, physical therapy, and orthopedic interventions (NCCN, 2008b).

**INFECTION**

Patients with MM are at increased risk for infections due to impaired production of normal immunoglobulins, which are key to immune system function (Paradisi et al, 2001). Patients with suspected infections should be cultured appropriately, undergo radiographic studies, and started on antibiotics (Mahany, 2008). While prophylaxis with the pneumococcal vaccine as well as the influenza vaccine may be effective at decreasing the risk of infection, vaccination with live attenuated zoster virus is not recommended, because it may cause patients with MM to have reactivation of the virus (NCCN,

2008c). Intravenous immunoglobulin and antibiotic prophylaxis for herpes zoster, pneumocystis, and fungal infections may also be considered. It is essential that oncology nurses instruct patients to promptly report the signs and symptoms of infection (NCCN, 2008c). Patients should also be educated about effective handwashing practices and to avoid people with infections.

**INDUCTION**

Patients presenting with stage III disease are initially treated with induction chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant. Factors to consider in choosing an optimal induction regimen include age, comorbidities, and transplant eligibility. Because **alkylating agents** such as melphalan may compromise stem cell reserves, they should be avoided in patients who are transplant candidates (NCCN, 2008b).

Studies have shown that a regimen of bortezomib, thalidomide, and dexamethasone as induction therapy for patients with newly diagnosed MM, with and without advanced renal failure, is highly active and well tolerated (Gladney et al, 2008). Because Mr. H has renal impairment and tests positive for del(13), he is started on bortezomib 1.3 mg/m<sup>2</sup> on Days 1, 4, 8, and 11, thalidomide 200 mg daily, and dexamethasone 40 mg on Days 1 to 4, 9 to 12, and 17 to 20. Bortezomib is approved for the treatment of patients with untreated and previously treated MM. Recent data indicate the agent is effective and well tolerated in patients

with renal impairment and in those with del(13) (Jaggonath et al, 2007; Chanan-Kahn et al, 2007). Furthermore, the novel combination of bortezomib plus thalidomide has been shown to be effective in patients with newly diagnosed MM (Table 3; Chen et al, 2007).

Common side effects of bortezomib are listed in Table 4 (Velcade® prescribing information, 2008). Asthenic conditions, such as fatigue and malaise, are often reported at the beginning of therapy, and are not usually dose limiting. Gastrointestinal side effects, such as nausea, vomiting, and diarrhea, may also be easily managed with antiemetics, antidiarrheals, oral or intravenous fluid, and electrolyte replacement if indicated.

Transient thrombocytopenia, which is one of the most common side effects of bortezomib, generally occurs during the dosing period (Days 1–11), with a return to baseline during the rest period (Days 12–21; Velcade® prescribing information, 2008). Oncology nurses should monitor platelet counts prior to each dose, and consider platelet transfusions, or if not available, holding bortezomib if the platelet count is less than 25,000/μL (Lonial, 2006; Lonial et al, 2008). Therapy may be reinitiated at a 25% reduced dose with acceptable platelet recovery (Velcade® prescribing information, 2008).

While baseline peripheral neuropathy (PN) is present in many patients with myeloma either due to the disease or prior therapies, patients receiving bortezomib may notice worsening symptoms with subsequent doses of chemotherapy. Bortezomib-associated PN tends to resolve or subside in the majority of patients following dose reduction or discontinuation, whereas thalidomide-related PN is less likely to resolve. The general character of the PN is sensory, and the small nerve fibers are often affected. Performing a baseline assessment prior to therapy, encouraging patients to report new onset or worsening symptoms, and utilizing tools such as the neuropathy questionnaire will aid in determining necessary dosage and schedule modifications (Table 5). Adjunct symptom control with medications such as pregabalin, duloxetine, or gabapentin with or without neurology referral may also be considered (Tariman et al, 2008).

**TABLE 3** Bortezomib Plus Thalidomide in Newly Diagnosed Multiple Myeloma

Cycles Completed	N	ORR	CR	nCR	PR	SD
2	26	25(96)	12(46)	4(15)	9(35)	1(4)
4	21	20(95)	6(29)	7(33)	7(33)	0(0)
6	18	16(89)	5(28)	4(22)	7(39)	2(11)

(Chen et al, 2007)

Treatment with bortezomib plus thalidomide in patients with newly diagnosed multiple myeloma was effective and well tolerated regardless of the number of cycles completed.

ORR = overall response rate; CR = complete response; nCR = near complete response; PR = partial response; SD = stable disease.

**TABLE 4** Management of Bortezomib Toxicities

SYMPTOM	DESCRIPTION	INTERVENTIONS
<b>Asthenic conditions</b> (fatigue, malaise, weakness)	Most often reported during Cycles 1/2; most patients are able to continue therapy	<ul style="list-style-type: none"> <li>• General supportive care at discretion of physician</li> </ul>
<b>Gastrointestinal events</b> (nausea, vomiting, constipation)	Majority of events are mild to moderate	<ul style="list-style-type: none"> <li>• Antiemetics and antidiarrheals</li> <li>• Fluid and electrolyte replacement</li> <li>• Hold bortezomib treatment at onset for any grade 3 adverse events; therapy may be reinitiated at 25% reduced dose when symptoms resolve</li> </ul>
<b>Hypotension</b>	Mild to moderate; may occur throughout therapy	<ul style="list-style-type: none"> <li>• Adjustment of antihypertensive medications, hydration, or administration of mineralocorticoids</li> </ul>
<b>Thrombocytopenia</b>	Transient thrombocytopenia generally occurs during dosing period (Days 1–11), with return to baseline, during rest period (Days 12–21)	<ul style="list-style-type: none"> <li>• Monitor platelet count prior to each dose</li> <li>• Platelet transfusions at discretion of physician</li> <li>• Hold bortezomib treatment at onset if platelet count &lt; 25,000/mL; therapy may be reinitiated at 25% reduced dose with acceptable platelet recovery</li> </ul>
<b>Peripheral neuropathy</b>	New onset or worsening of existing neuropathy may occur throughout cycles of treatment	<ul style="list-style-type: none"> <li>• Early detection and appropriate dose/schedule modification may result in symptom resolution</li> <li>• Instruct patients to contact physician if new or worsening symptoms occur</li> <li>• Use neuropathy questionnaire</li> <li>• Symptom control with medication</li> </ul>

(Velcade® prescribing information, 2008)

Common side effects associated with bortezomib include asthenia, gastrointestinal events, hypotension, thrombocytopenia, and peripheral neuropathy.

**TABLE 5 Neurotoxicity Assessment Tool**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I feel discomfort in my hands	0	1	2	3	4
I feel discomfort in my feet	0	1	2	3	4
I have joint pain or muscle cramps	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have trouble hearing	0	1	2	3	4
I get a ringing or buzzing in my ears	0	1	2	3	4
I have trouble buttoning	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
I have trouble walking	0	1	2	3	4

(Cella et al, 2003)

A neuropathy assessment tool may be useful in determining whether patients require dose-adjustments of novel agents.

**PATIENT OUTCOME**

Subsequent laboratory testing reveals the following: a barely detectable M spike; hemoglobin, 14.3 g/dL; calcium, 8.4 g/dL; and creatinine, 1.3 g/dL. Mr. H develops PN after four cycles. As a result, thalidomide is dose-reduced and then stopped as he achieves a near-complete response (Thalomid® prescribing information, 2007).

**CONCLUSION**

Novel agents such as bortezomib and thalidomide have been shown to be effective in patients with newly diagnosed MM, including those with complications such as anemia, hypercalcemia, renal insufficiency, and skeletal involvement. The choice of induction therapy is dependent upon age, comorbidities, and transplant eligibility. Oncology nurses play a key role in identifying the signs and symptoms of MM and the side effects of treatment and employing the appropriate interventions to optimize patient outcomes. ●

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# CASE STUDY

## CASE PRESENTATION: RELAPSED/REFRACTORY MULTIPLE MYELOMA

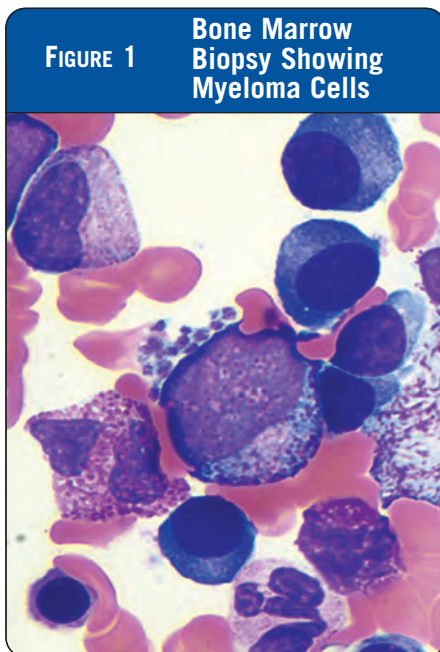
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 Joseph D. Tariman, PhD, RN, ARNP, BC, OCN®, University of Washington School of Nursing

Mr. C is a 55-year-old man who presented to his primary care provider for a routine examination. He was found to have elevated calcium (11.5 mg/dL) and total protein (10.6 g/dL) levels. He complained of worsening low back pain. He was referred to a cancer center and further laboratory studies revealed multiple myeloma (MM; Figure 1 and Table 1).

Mr. C was treated with thalidomide and dexamethasone and achieved a

partial response. He subsequently received high-dose chemotherapy and a stem cell transplant and achieved a complete response (National Comprehensive Cancer Network [NCCN], 2008). Maintenance therapy was not administered. Mr. C was followed for 2 years without incident. At the 2-year mark Mr. C developed lower back pain. At that time, laboratory testing revealed: immunoglobulin (Ig) A, 1,300 mg/dL; M protein, 0.9 g/dL; hemoglobin, 11.5 g/dL; **platelets**, 145,000/mm<sup>3</sup>; creatinine, 0.8 mg/dL. Bone marrow biopsy showed 45% monoclonal plasma cells. Bone survey detected a new lesion at L3, and magnetic resonance imaging (MRI) revealed a compression fracture at L2 (Figure 2).

includes radiation therapy, active treatment of the underlying disease, analgesia, and administration of bisphosphonates. In addition, minimally invasive surgical interventions such as vertebroplasty or balloon kyphoplasty may be effective at decreasing VCF-related pain (NCCN, 2008). Vertebroplasty reduces the fracture via inserting a needle into the collapsed vertebral body and filling the area with cement. With balloon kyphoplasty, an inflatable bone tamp is inserted percutaneously into the collapsed vertebral body, which creates a void (Fabeck, 2008). Cement (ie, polymethylmetacrylate) is instilled into the fractured body in an attempt to correct the fracture and restore the vertebral height (Figure 3). Both procedures are considered outpatient supportive care measures that may reduce pain scores, risk of infection, and risk of thrombosis due to pain and immobility, and may improve quality of life (Fabeck, 2008).



(Image courtesy of Tiffany Richards, MS, ANP, AOCNP®)

TABLE 1	Initial Diagnostic Workup
	Hgb = 11.0 g/dL
	IgA = 4,100 mg/dL
	M protein = 3.4 g/dL
	IFE = IgA lambda
	24-Hour UPEP = 300 mg lambda light chain
	Creatinine = 1.2 mg/dL
	Calcium = 11.5 mg/dL
	Bone survey: Multiple lytic lesions in the pelvis, femur, and thoracic spine

Mr. C's IgA, lambda light chain, and the presence of lytic lesions are indicative of multiple myeloma.

Hgb = hemoglobin; IgA = immunoglobulin A; IFE = immunofixation electrophoresis; UPEP = urine protein electrophoresis.

### VERTEBRAL COMPRESSION FRACTURE

The incidence of vertebral compression fracture (VCF) in patients with MM is approximately 70%, and if present, may lead to pain, increased infection, and impaired quality of life (International Myeloma Foundation, 2007). Medical management of VCF



(Image courtesy of Tiffany Richards, MS, ANP, AOCNP®)

### LENALIDOMIDE-INDUCED TOXICITIES

Mr. C agrees to a regimen of lenalidomide (25 mg once daily for 21 days) and pulsed dexamethasone (40 mg Days 1–4, 9–12, 17–20 with a 1-week break) after a discussion with his healthcare provider about lifestyle issues and potential treatment-related side effects. Although lenalidomide is an analog of thalidomide, each agent has a distinct toxicity profile (Revlimid® prescribing information, 2009; Tables 2 and 3). Patients receiving lenalidomide in combination with high-dose dexamethasone may be at increased risk for thrombosis (Merchionne, Perosa, & Dammacco, 2007). The American Society of Clinical Oncology recommends prophylaxis with LMWH or adjusted-dose warfarin (to an international normalized ratio ~1.5; in myeloma patients receiving thalidomide plus chemotherapy or dexamethasone; Lyman et al, 2007).

Patients receiving lenalidomide may also be at risk for gastrointestinal toxic-

ities, such as diarrhea or constipation, asthenia, and **myelosuppression**. Diarrhea and constipation are not often dose-limiting toxicities, and antidiarrheal agents and stool softeners may be effective at treating these symptoms. Although asthenic symptoms such as fatigue and malaise may be debilitating, they typically are not dose limiting. Limiting activities and allowing for periods of rest may help patients maintain optimal levels of functioning (Doss, 2006).

After starting lenalidomide, patients should be monitored for myelosuppression during the first 12 weeks of therapy. A complete blood count (CBC) should be obtained every 2 weeks and dose adjustments according to toxicity severity should be anticipated (Table 2; Sonneveld et al, 2007).

**TREATMENT COURSE**

Mr. C returns for follow-up after 1 month. He tolerated treatment well except for grade 1 diarrhea, which resolves with the administration of loperamide 2 mg every 4 hours or after each unformed stool (Smith et al, 2008). Laboratory studies reveal decreases in his M protein (0.4 g/dL) and IgA (600 mg/dL) levels.

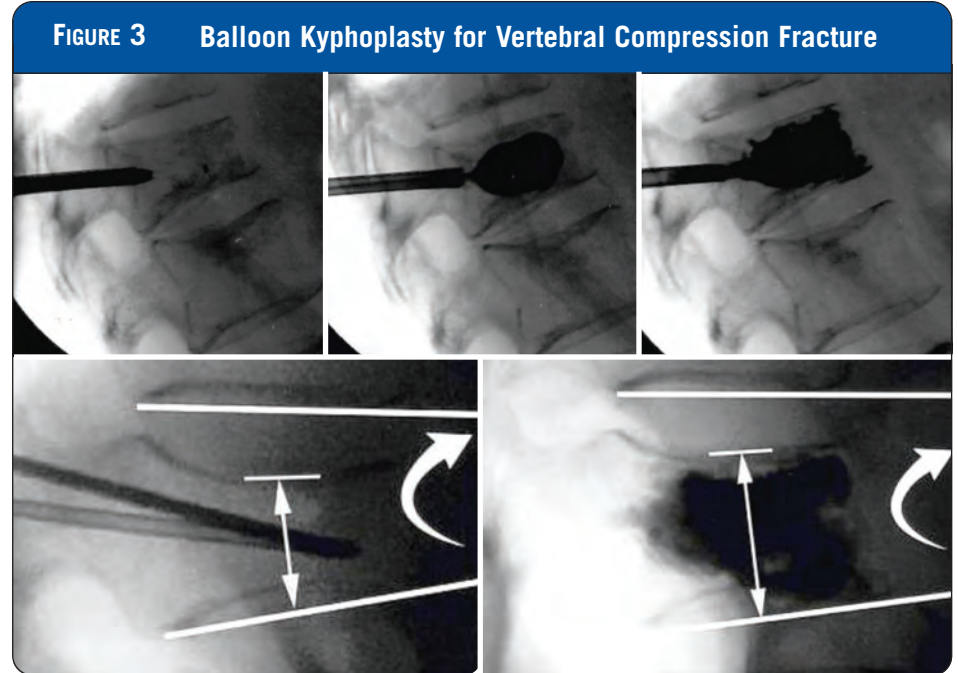
On Day 14, his bowel movements have improved to once daily; however, a CBC shows that his platelets measure 100,000/mm<sup>3</sup> and his absolute neutrophil count (ANC) measures 0.9/μL. In accordance with the prescribing information, lenalidomide is withheld and Mr. C is administered a granulocyte-colony stimulating factor. He resumes lenalidomide at a 25-mg dose after his ANC rises above 1,000/μL (Revlimid® prescribing information, 2009).

Mr. C returns for follow-up at the end of his third cycle of treatment. He achieves a near-complete response, with an M protein of 0 g/dL and an IgA of 134 mg/dL. During Cycle 4, Mr. C experiences mild constipation and grade 2 neuropathy. In addition, his platelets decrease to 25,000/mm<sup>3</sup>. Lenalidomide is withheld and Mr. C is followed with CBCs until his platelets rise above 30,000/mm<sup>3</sup>. The lenalidomide dose is then reduced by 5 mg to 20 mg once daily and the dexamethasone dose is reduced to 40 mg once weekly due to high blood sugar levels (Revlimid® prescribing information, 2009). Mr. C achieves a very good par-

tial response.

By Cycle 15, Mr. C progresses, with an M protein of 0.6 mg/dL and new back pain. Mr. C is given the combination of bortezomib plus pegylated liposomal doxorubicin (PLD), which is approved for the treatment of patients who have not previously received borte-

zomib and have received at least one prior therapy (Doxil® prescribing information, 2008; Velcade® prescribing information, 2007; NCCN, 2008; Orłowski et al, 2007). With the first PLD dose, an initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-



(Image courtesy of Tiffany Richards, MS, ANP, AOCNP®)  
An inflatable bone tamp is inserted percutaneously into the collapsed vertebral body, which creates a void. Cement (ie, polymethyl-metacrylate) is then instilled into the fractured body in an attempt to correct the fracture and restore the vertebral height.

TABLE 2 Management of Lenalidomide Toxicities		
SYMPTOM	DESCRIPTION	INTERVENTIONS
<b>Myelosuppression</b> (neutropenia, thrombocytopenia)	Predominant toxicity. Occurs most often with higher doses. More common in combination with dexamethasone.	<ul style="list-style-type: none"> <li>• Monitor CBC biweekly for first 12 weeks of treatment, monthly thereafter</li> <li>• Hold drug or reduce dose</li> <li>• Transfusions, growth factors</li> </ul>
<b>Thromboembolic events</b> (DVT, PE)	More common in combination with dexamethasone	<ul style="list-style-type: none"> <li>• Anticoagulation recommended</li> <li>• Monitor coagulation assays</li> </ul>
<b>Rash</b>	Usually resolves within 1 week	<ul style="list-style-type: none"> <li>• Antihistamine every 4–6 hours</li> <li>• Discontinue if any signs of toxic epidermal necrosis</li> </ul>
<b>GI complaints</b>	Usually mild/intermittent cramping and/or diarrhea; decreased appetite	<ul style="list-style-type: none"> <li>• Diet control</li> <li>• Dose reduction</li> </ul>

(Revlimid® prescribing information, 2009)  
Myelosuppression, thromboembolic events, rash, and GI complaints are associated with lenalidomide.  
DVT = deep vein thrombosis; PE = pulmonary embolism; GI = gastrointestinal; CBC = complete blood count.

related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over 1 hour. PLD should not be administered as a bolus or undiluted solution. Patients may be treated with up to eight cycles until disease progression or the occurrence of an unacceptable toxicity (there is potential for cardiac toxicity with PLD for a cumulative dose of 550 mg/m<sup>2</sup>).

**CONCLUSION**

With the availability of novel agents such as lenalidomide, thalidomide, PLD, and bortezomib, patients with MM can expect longer survival. Clinical trials are underway to further understand the effectiveness of novel combi-

nation therapies in the relapsed disease setting. Oncology nurses play a critical role in the vigilant monitoring and management of treatment-related toxicities to ensure that any survival advantage enjoyed by patients is enhanced by a good quality of life. ●

TABLE 3 Management of Thalidomide Toxicities		
TOXICITY	INCIDENCE (%)	INTERVENTION
Peripheral neuropathy (tingling/numbness, burning sensation, coldness in feet)	Mild: 85 Severe: 3–5	<ul style="list-style-type: none"> <li>• Early detection and appropriate dose/schedule modification may result in resolution of improvement of neuropathy</li> <li>• Instruct patients to contact physician if new or worsening symptoms of peripheral neuropathy occur</li> <li>• Use neuropathy questionnaire</li> <li>• Symptom control with medication</li> </ul>
Sedation	Mild: 75 Severe: 5–10	<ul style="list-style-type: none"> <li>• Dose at night</li> <li>• Gradually increase dose over 2 weeks</li> <li>• Patients usually acclimate within 2–4 weeks</li> <li>• Divided doses for elderly</li> </ul>
Constipation	Mild: 80–90 Severe: 5	<ul style="list-style-type: none"> <li>• Bowel regimen (call physician if no bowel movement in 3 days)                             <ul style="list-style-type: none"> <li>– Increase fluid and fiber intake; prunes or prune juice</li> <li>– Use stool softener (morning and night)</li> <li>– Use bowel stimulant if needed</li> <li>– Use laxative as last resort</li> </ul> </li> </ul>
Rash	Mild: 45	<ul style="list-style-type: none"> <li>• Antihistamine; low-dose prednisone; discontinue thalidomide if any systemic symptoms</li> </ul>
Peripheral edema	Mild: 15 Anasarca: 3	<ul style="list-style-type: none"> <li>• Limb elevation, elastic stockings, gentle diuretics</li> </ul>
Thromboembolic events (DVT, PE)	Thal alone: 1–3 Thal + dex: 10–12	<ul style="list-style-type: none"> <li>• Anticoagulation recommended</li> <li>• Monitor coagulation assays</li> </ul>
Weakness	Mild: 60 Severe: 3–5	<ul style="list-style-type: none"> <li>• Hold dose until toxicity resolves; restart at 50% lower dose</li> </ul>

(Thalomid® prescribing information, 2005; Ghobrial & Rajkumar, 2003)  
 Peripheral neuropathy, sedation, and constipation may occur in patients receiving thalidomide.  
 DVT = deep vein thrombosis; PE = pulmonary embolism.

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# CASE STUDY

## CASE PRESENTATION: OLDER ADULT WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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Mr. S is a 78-year-old man who presents for routine follow-up in the nephrology clinic for chronic renal insufficiency (stage III). He complains of diffuse aches and a generalized “slowing down” that interferes with his activities of daily living.

His past medical history includes 40-pack-per-year smoking, which he quit 20 years ago. He has hypertension, hyperuricemia, atrial fibrillation, a possible cerebrovascular accident 20 years ago, and neuropathy. Mr. S is retired and lives at home with his wife.

Diagnostic workup reveals the following hallmarks of multiple myeloma (MM): renal insufficiency (creatinine, 1.4 mg/dL) and anemia (hemoglobin, 7.8 mg/dL; Table 1). In addition, bone marrow biopsy reveals 40% cellularity with 10% plasma cells, and skeletal survey shows osseous involvement.

### TRANSPLANT ELIGIBILITY

Age is the most significant risk factor for MM. The incidence of MM is higher in older patients, with a median age at diagnosis of 70 years. Approximately 64% of patients are 65 years of age or older at the time of diagnosis, and approximately 4% of all cases occur in those younger than 45 years (National Cancer Institute, 2005). Due to his advanced age, Mr. S is not considered for an autologous stem cell transplant (Harousseau et al, 2008). However, there are conflicting data regarding whether advanced age is a poor prognostic indicator for transplant and whether physiological age as opposed to chronological age should determine transplant eligibility. Some centers may consider transplant in patients who are in their early 70s with a good performance status and no comorbidities (Görner & Späth-Schwalbe, 2008; San Miguel et al, 2008).

### INDIVIDUALIZING TREATMENT

A thorough assessment to determine comorbidities and functional status is

essential in establishing individualized treatment goals for older patients with MM. Common disease-related symptoms include bone pain, anemia, severe fatigue, neurologic symptoms, hypercalcemia, hyperviscosity, renal dysfunction, and infections (Görner & Späth-Schwalbe, 2008; Extermann et al, 2007). The choice of treatment should take into account patient age, performance status, stage of disease, comorbid conditions, and prognostic indicators. For those not eligible for transplant, National Comprehensive Cancer Network (NCCN) guidelines recommend melphalan/prednisone (MP) plus thalidomide or MP plus bortezomib (2009). Other potential options include thalidomide plus low-dose dexamethasone, lenalidomide plus low-dose dexamethasone, and MP alone (Görner & Späth-Schwalbe, 2008; San Miguel et al, 2008; Facon et al, 2007; Rajkumar et al, 2007).

Lifestyle should also be considered

when deciding upon treatment, as severe toxicities may negatively affect functional status and quality of life (Table 2). Patients receiving MP should be monitored for anemia, neutropenia, thrombocytopenia, and infection. Increased risk of venous thromboembolism (VTE; eg, deep vein thrombosis [DVT] and pulmonary embolus) is associated with thalidomide/lenalidomide and dexamethasone (Thalomid® prescribing information, 2007; Revlimid® prescribing information, 2009). Assessment for signs of thromboembolic events is critical and involves the use of Doppler ultrasound in case of suspected DVT. Patients should be advised to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling, or difficulty moving. Mr. S' risk factors for DVT include sedentary lifestyle, presence of cancer, and atrial fibrillation. Guidelines for VTE prophylaxis have been established by the American

**TABLE 1** Diagnostic Workup

Laboratory Results	
Hemoglobin	7.8 g/dL
Total protein	9.8 g/dL
Albumin	3 g/dL
Immunoglobulin G	5,502 mg/dL (IgA/IgM depressed)
Free lambda light chain	423 mg/L
SPEP	4.5 g/dL
SIFE	IgG lambda
UPEP	Not available
UIFE	Lambda free light chains
Creatinine	1.4 mg/dL
Bone marrow biopsy	40% cellularity with 10% plasma cells
Cytogenetics	Unremarkable
Radiographic imaging	Skeletal survey revealed osseous involvement

Mr. S' diagnostic work-up reveals renal insufficiency and anemia, which are hallmarks of multiple myeloma.

SPEP = serum protein electrophoresis; SIFE = serum immunofixation electrophoresis; UPEP = urine protein electrophoresis; UIFE = urine immunofixation electrophoresis.

Society of Clinical Oncology and include anticoagulation therapy with low-molecular-weight heparin and adjusted-dose warfarin (Lyman et al, 2007). Thromboprophylaxis strategies are recommended based on individual patient risk and type of treatment (Palumbo et al, 2007; Rome et al, 2008). Aspirin is recommended for patients with one or no risk factor. Patients with at least two risk factors should receive low-molecular-weight heparin or full-dose warfarin as thromboprophylaxis. Patients with therapy-related risks (eg, high-dose dexamethasone, doxorubicin, multiagent chemotherapy) should receive low-molecular-weight heparin or full-dose warfarin (Rome et al, 2008; Palumbo et al, 2007). Other strategies include mechanical prophylaxis (eg, sequential compression devices, antiembolism stockings, exercise), myeloma regimen-related prophylaxis (eg, reducing thalidomide from 100 mg to 50 mg daily), and antithrombotic pharmaceutical prophylaxis (ie, low- and standard-dose aspirin). Studies are ongoing to determine an optimal prophylactic strategy.

Mr. S receives melphalan 0.25 mg/kg/day plus prednisone 60 mg/day on Days 1 to 4 and achieves stable disease after two cycles. However, his melphalan dose is decreased by 20% due to cytopenias. During Cycle 3, he develops severe diverticulitis and treatment is discontinued (Alkeran® prescribing information, 2007; NCCN, 2009; San Miguel et al, 2008). He is then started on thalidomide 100 mg every night at bedtime plus dexamethasone 40 mg weekly with DVT prophylaxis (Thalomid® prescribing information, 2007). He achieves a partial response but therapy is complicated by bilateral lower extremity edema that is not amendable to diuretic therapy (Robin et al, 2008). Lower extremity Doppler is negative for DVT.

Although he experiences progressive leukopenia and thrombocytopenia, Mr. S has a good response to therapy. As a result, he is able to discontinue therapy with monthly monitoring of his IgG and serum protein electrophoresis levels.

**DISEASE RELAPSE**

Approximately 5 months after therapy was discontinued, Mr. S returns to

the clinic for his monthly assessment and complains of fatigue and worsening neuropathy in both feet, these symptoms are consistent with a relapse of MM. For patients with relapsed disease, prior therapy and response to prior therapy should be factors in choosing a new treatment. NCCN guidelines recommend the option of retreatment if the duration of response was longer than 6 months (Table 3).

Mr. S is started on a regimen of lenalidomide (25 mg/day) plus dexamethasone (40 mg/day), both agents administered orally. Lenalidomide is administered on Days 1 to 21 of repeated 28-day cycles, whereas dexamethasone is administered on Days 1, 8, 15, and 22 every 28 days. Patients receiving lenalidomide/dexamethasone should have their blood counts monitored biweekly during the first three

cycles of treatment and then monthly thereafter. Close monitoring of blood counts is an essential part of neutropenic fever and sepsis prevention (Revlimid® prescribing information, 2009). In the case of myelosuppression, withholding lenalidomide and reducing the dosage is recommended (Table 4).

**SUPPORTIVE CARE ISSUES SPECIFIC TO OLDER ADULTS**

To ensure optimal outcomes for older patients with MM, it is important to integrate psychological, social, spiritual, and medical care to ease the process of living with the disease and its treatment. Pain management, psychiatric care, emotional counseling, and support groups may provide significant benefit. Fall assessment should

**TABLE 2 Regimens Used in the Treatment of Older Patients With Multiple Myeloma**

Regimens	Overall Survival	Adverse Events (≥ Grade 3)
MPT	80% at 3 years	VTE, leukopenia, thrombocytopenia, anemia, N&V, diarrhea, PN
MPV	90% at 1.3 years	PN, thrombocytopenia/neutropenia, TLS, asthenia, diarrhea, anemia
Thalidomide + dexamethasone	~ 70% at 3 years	Fatigue, VTE, hyperglycemia, PN
Lenalidomide + dexamethasone	90% at 2 years	Neutropenia, anemia, gastrointestinal toxicities, fatigue, VTE, PE
Melphalan + prednisone	64% at 2 years	Leukopenia, thrombocytopenia, anemia, N&V, diarrhea

(Palumbo et al, 2005; Palumbo et al, 2008; Görner & Späth-Schwalbe, 2008; Revlimid® prescribing information, 2009; Velcade® prescribing information, 2007)

Lifestyle should be considered when choosing treatment for multiple myeloma, as severe toxicities may negatively affect functional status and quality of life.

MPT = melphalan/prednisone/thalidomide; MPV = melphalan/prednisone/bortezomib; VTE = venous thromboembolism; TLS = tumor lysis syndrome; PN = peripheral neuropathy; N&V = nausea and vomiting.

**TABLE 3 Treatment Options for Relapsed/Refractory Multiple Myeloma**

<ul style="list-style-type: none"> <li>• Bendamustine</li> <li>• Bortezomib</li> <li>• Bortezomib/dexamethasone</li> <li>• Bortezomib/lenalidomide/dexamethasone</li> <li>• Bortezomib/liposomal doxorubicin</li> <li>• Cyclophosphamide-VAD</li> <li>• Dexamethasone</li> <li>• Dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP)</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE)</li> <li>• High-dose cyclophosphamide</li> <li>• Lenalidomide/dexamethasone</li> <li>• Lenalidomide</li> <li>• Repeat primary induction therapy (if relapse at &gt; 6 months)</li> <li>• Thalidomide</li> <li>• Thalidomide/dexamethasone</li> </ul>
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(NCCN, 2009)

For patients with relapsed disease, prior therapy and response to prior therapy should be factors in choosing a new treatment.

VAD = vincristine, doxorubicin, dexamethasone.

be conducted to help prevent fractures. When employed in an appropriate and timely manner, supportive care measures can improve adherence to treatment, increase patient functionality, and preserve quality of life (Extermann & Hurria, 2007; Schubert et al, 2008).

### CONCLUSION

The incidence of MM is higher in older adults, with a median age at diagnosis of 70 years. Pre-existing comorbidities may make aggressive treatment with stem cell transplant nonviable in this population. Regimens that combine MP or dexamethasone with novel agents such as bortezomib, thalidomide, and lenalidomide offer treatment options with increased tolerability and improved survival rates. Oncology nurses should maintain a working knowledge of novel agents to effectively manage side effects and maximize therapeutic benefit. ●

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**TABLE 4** Managing Myelosuppression in Patients Receiving Lenalidomide

<b>Neutropenia</b> If the ANC falls to < 1.0 x 10 <sup>9</sup> /L	Interrupt lenalidomide, consider granulocyte colony-stimulating factor, and monitor CBC weekly. If neutropenia is the only toxicity, and ANC returns to 1.0 x 10 <sup>9</sup> /L, lenalidomide may be resumed at 25 mg daily, or at previous dose, if lower. If other toxicities are present and ANC returns to > 1.0 x 10 <sup>9</sup> /L, resume at 15 mg daily.
For each subsequent drop of ANC to > 1.0 x 10 <sup>9</sup> /L	Interrupt lenalidomide. When ANC returns to ≥ 1.0 x 10 <sup>9</sup> /L, resume lenalidomide at 5 mg less than previous dose.
<b>Thrombocytopenia</b> If platelet count falls to < 30 x 10 <sup>9</sup> /L	Interrupt lenalidomide treatment and monitor CBC weekly. Once platelets return to 30 x 10 <sup>9</sup> /L, restart lenalidomide at 15 mg daily.
For each subsequent drop of platelets to < 30 x 10 <sup>9</sup> /L	Interrupt lenalidomide treatment. When platelets return to 30 x 10 <sup>9</sup> /L restart at a dose 5 mg less than previous dose.

(Miceli et al, 2008)

ANC = absolute neutrophil count; CBC = complete blood count.

In the case of myelosuppression, withholding lenalidomide and reducing the dosage is recommended.

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### Glossary

- alkylating agents:** a substance that causes replacement of hydrogen by an alkyl group especially in a biologically important molecule; specifically, one with mutagenic activity that inhibits cell division and growth
- autologous transplant:** a procedure in which tissue from the person's body is removed from a person, stored, and then given back to the person after intensive treatment
- erythropoiesis:** the formation or production of red blood cells

- fluorescent in situ hybridization (FISH):** an important molecular cytogenetic method for identifying chromosomes and parts of chromosomes, deciphering chromosome rearrangements, and locating genes on chromosomes
- hyperdiploid:** having a chromosome number greater than the diploid number
- immunomodulatory:** a chemical agent that modifies the immune response or the functioning of the immune system
- induction:** the first step towards evaluating response to drugs and other agents
- myelosuppression:** inhibition of cell production
- neutropenia:** abnormally low level of neutrophils in the blood
- partial response:** a decrease in the size of a tumor or in the extent of cancer in the body in response to treatment
- phase III clinical trial:** trial in which the experimental study drug or treatment is given to a large groups of people (1,000-3,000) to confirm its effectiveness, monitor its side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely
- platelets:** fragments of a megakaryocyte located in the bone marrow that adhere to areas of blood vessel damage and release chemical signals that direct the formation of a blood clot
- targeted therapy:** a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with rapidly dividing cells
- thrombocytopenia:** an abnormal drop in the number of blood cells involved in the formation of blood clots



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### Pharmaceutical Glossary

Generic Name	Trade Name
bendamustine	Treanda™
bortezomib	Velcade®
cisplatin	Platinol®
cyclophosphamide	Cytoxan® Neosar®
dexamethasone	Decadron® Dexameth Dexone® Hexadrol®
doxorubicin	Adriamycin® Rubex®
duloxetine	Cymbalta®
etoposide	Toposar® Vepesid®
gabapentin	Neurontin®
lenalidomide	Revlimid®
loperamide hydrochloride	Imodium®
LMWH/heparin/ enoxaparin	Lovenox® Clexane®
melphalan	Alkeran®
pamidronate disodium	Aredia®
pegylated liposomal doxorubicin	Doxil®
prednisone	Sterapred®
pregabalin	Lyrica®
thalidomide	Thalomid®
vincristine	Oncovin® Vincasar PFS Vincrex
warfarin	Coumadin®
zoledronic acid	Zometa® Reclast®

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**Posttest for Multiple Myeloma: Nursing Roundtable Discussions**  
(please record the correct answer for each question in the answer key.)

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1. Which of the following regimens is recommended treatment as primary induction therapy for patients with multiple myeloma (MM) who are transplant candidates?
  - a. Bortezomib/dexamethasone
  - b. Melphalan/prednisone
  - c. Bendamustine
  - d. None of the above
2. In the new International Staging System for MM, stage I is categorized as a serum beta-2-microglobulin level of < 3.5 mg/L and is characterized by a median survival of 62 months.
  - a. True
  - b. False
3. Stem cell transplant has been shown to improve the outcomes for patients with:
  - a. t(4:14) deletions
  - b. (Del) 17p
  - c. Very good responses
  - d. Stable disease or primary resistant disease
  - e. None of the above
4. Bortezomib treatment should be held if a patient's platelet count is < 25,000/mL at the onset of therapy and can be reinitiated at 25% reduced dose with acceptable platelet recovery.
  - a. True
  - b. False
5. A patient with relapsed/refractory MM is given lenalidomide 25 mg once daily for 21 days and pulsed with dexamethasone 40 mg and develops neutropenia. What should be done with this patient to manage the neutropenia?
  - a. Hold lenalidomide and give growth colony-stimulating factors, resume at 25 mg dose when his absolute neutrophil count increases
  - b. Discontinue lenalidomide
  - c. Continue lenalidomide and recheck complete blood count in 1 week
  - d. None of the above
6. What is the optimal treatment for an older patient (> 65 years) with newly diagnosed MM that is not a candidate for stem cell transplant?
  - a. Melphalan, prednisone, thalidomide
  - b. Melphalan, prednisone, bortezomib
  - c. Cyclophosphamide
  - d. None of the above
  - e. A and B only
7. Patients using thalidomide/lenalidomide plus dexamethasone therapy for MM are at a higher risk for developing:
  - a. Venous thromboembolic disease
  - b. Neuropathy
  - c. Infections
  - d. All of the above
  - e. A and C only

**Evaluation Form – Multiple Myeloma: Nursing Roundtable Discussions**

IMER respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgement of participation for this activity.

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor
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**Extent to Which Program Activities Met the Identified Purpose**

- To educate nurses on the latest treatment and nursing management strategies for patients with MM.      5   4   3   2   1

**Extent to Which Program Activities Met the Identified Objectives**

Upon completion of this activity, participants should be able to:

- Describe changes in the standard of care for patients with newly diagnosed MM      5   4   3   2   1
- Identify new combination therapies for patients who are not candidates for transplant      5   4   3   2   1
- Describe new options for treating patients with relapsed or refractory MM      5   4   3   2   1
- Describe toxicities of novel agents and novel combinations used to treat MM      5   4   3   2   1
- Outline treatment considerations for older adults with newly diagnosed and relapsed MM      5   4   3   2   1
- Identify the supportive care needs of older adults with MM      5   4   3   2   1
- Describe the role of clinical trials in the treatment schema of patients      5   4   3   2   1

**Overall Effectiveness of the Activity**

- Was timely and will influence how I practice      5   4   3   2   1
- Will assist me in improving patient care      5   4   3   2   1
- Fulfilled my educational needs      5   4   3   2   1
- Avoided commercial bias or influence      5   4   3   2   1

Approximately what percentage of the program content was new to you?

- 0–20%    21–40%    41–60%    61–80%    81–100%

**Impact of the Activity**

Do you feel that the activity:

- Reinforced your current practice/treatment habits       Yes    No
- Will improve your practice/patient outcomes       Yes    No
- Enhanced your current knowledge base       Yes    No
- Will cause you to make changes in your practice?       Yes    No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity: \_\_\_\_\_

How committed are you to making these changes?

(very committed) 5   4   3   2   1 (not committed)

Additional comments about this activity: \_\_\_\_\_

**Future Activities**

Do you feel future activities on this subject matter are necessary and/or important to your practice?       Yes    No

Please list any other topics that would be of interest to you for future educational activities: \_\_\_\_\_

Was there anything not covered that would have better helped meet the learning objectives? \_\_\_\_\_

What prompted you to participate in this educational activity? \_\_\_\_\_

What are your perceived barriers to implementing the information presented in this activity? \_\_\_\_\_

Is there a gap between the information provided in this activity and your practice habits?       Yes    No

If yes, please describe: \_\_\_\_\_

Would you recommend this activity to a colleague?       Yes    No

If you wish to receive acknowledgement of participation for this activity, please fill out your contact information.

Mail or fax this test and evaluation form to receive your certification of completion.

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This newsletter can be viewed on our Web site, [www.IMERonline.com](http://www.IMERonline.com). On the homepage, click on the CE/CME tab, select On-Demand Education, and select **Multiple Myeloma: Nursing Roundtable Discussions**.

**Posttest Answer Key**

1	2	3	4	5	6	7	8

Please send me FREE IMER CE programs and invitations to IMER's FREE CE symposia.

**I'm also interested in these other types of cancers:**

- lung     breast     lymphoma     leukemia
- colorectal     prostate     ovarian     head & neck
- other

(please describe) \_\_\_\_\_

While we strive not to send duplicates, we hope that you will share yours with a friend if you receive more than one copy.

**The following items do not need to be completed to receive acknowledgement of participation for this activity.**

**Follow-up**

Years in practice:

- < 2 years
- 2-5 years
- 6-10 years
- >10 years

Educational background (highest degree):

- Associate/Diploma
- BSN
- MSN
- PhD
- Other \_\_\_\_\_

Primary functional area:

- Patient care
- Education
- Administration
- Research
- Other \_\_\_\_\_

Primary specialty:

- Chemotherapy/biotherapy
- GI oncology
- Pediatric oncology
- Thoracic oncology
- Prevention/detection
- Other \_\_\_\_\_
- Breast oncology
- Hematology/BMT
- Radiation oncology
- Patient education
- Palliative care

Primary position:

- Academic educator
- Clinical trials nurse
- Clinical nurse specialist
- Director/asst. director/VP
- Nurse manager/coordinator
- Nurse practitioner

Do you prefer educational CE seminars or mail CE programs?

- Seminars
- Mail

I most prefer CE programs that are:

- On a Web site that I can visit
- Audio CDs
- Print materials
- Teleconferences
- CD-ROMs (audio plus slideshow)

I least prefer CE programs that are:

- On a Web site that I can visit
- Audio CDs
- Print materials
- Teleconferences
- CD-ROMs (audio plus slideshow)

As part of our ongoing quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

- Yes, I would be interested in participating in a follow-up survey
- No, I'm not interested in participating in a follow-up survey

**Privacy Policy**

When you participate in an educational activity provided by the Institute for Medical Education & Research ("IMER" or "we"), we ask you for your name, degree, affiliation, street address, telephone number, fax number, and e-mail address (the "Information"). We use that Information in the following ways:  
 We use the Information to grade your posttest and to send you a certificate of completion of the educational activity. If we use a third-party company to grade your posttest and issue certificates of completion, we will give the Information to that company for that purpose only.  
 For each educational activity that you take, you must complete an evaluation questionnaire. That questionnaire asks if you are willing to participate in a follow-up survey. If you answer yes, we will use your name and contact information to send you the survey.  
 We may use the Information to invite you to participate in other educational activities that IMER or its affiliates may offer.  
 On occasion, the commercial supporter of an educational activity will ask us for a list of the people who participated in that activity, so that it may document the first level of outcomes-based evaluation in the educational activity (i.e., who attended, which medical specialties/practices were represented, how this compares to the target audience, and whether the activity needs to be repeated because significant numbers of the target audience did not attend). In that event, we will provide the supporter with your name, title and affiliation, but we will request in writing that the supporter not contact you directly for any purpose.  
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 Any changes to our privacy policy will be posted here immediately.