DePaul University

From the SelectedWorks of Joseph D Tariman PhD, RN, ANP-BC, FAAN

Fall November 1, 2005

The changing treatment paradigm in patients with newly diagnosed multiple myeloma: implications for nursing

Joseph D Tariman, PhD, *DePaul University*

The Changing Treatment Paradigm in Patients With Newly Diagnosed Multiple Myeloma: Implications for Nursing

Joseph D. Tariman, RN, APN, MN, APRN-BC, OCN®, and Stella Marie Estrella, BSN, RN

Purpose/Objectives: To review the changing treatment paradigm for newly diagnosed multiple myeloma and its implications for nursing.

Data Sources: Journal articles, textbooks, published research data.

Data Synthesis: The treatment approaches to newly diagnosed multiple myeloma are varied, and no consensus exists about the best choice of induction therapy prior to high-dose chemotherapy with autologous stem cell transplantation. Novel therapies that have shown strong clinical activity in patients with relapsed or refractory myeloma currently are being explored as first-line therapy with associated higher incidence of serious complications.

Conclusions: Novel approaches in the treatment of newly diagnosed multiple myeloma may lead to better overall patient survival. Research is ongoing to find ways to improve progression-free and overall survival in patients with multiple myeloma.

Implications for Nursing: Oncology nurses play vital roles in the assessment and monitoring of serious complications associated with various therapies for patients with newly diagnosed multiple myeloma. Key responsibilities include safe and effective administration of complex chemotherapeutic regimens, management of side effects, patient and family education, and coordination of a multidisciplinary approach.

Key Points . . .

➤ High-dose chemotherapy with autologous stem cell transplantation is the standard of therapy for patients newly diagnosed with multiple myeloma who are younger than age 70 or have no comorbidities.

➤ Novel therapies currently being explored are reported to have a higher incidence of potential serious complications.

➤ Oncology nurses play vital roles in the safe and effective administration of conventional and novel therapies for patients with newly diagnosed multiple myeloma.

Multiple myeloma is a clonal B-lymphocyte malignancy of the plasma cells. The hallmarks of multiple myeloma include the classic triad of the presence of a serum or urine monoclonal immunoglobulin (Ig) (commonly known as M protein or M spike), osteolytic lesions, and bone marrow plasmacytosis (> 30% plasma cell proliferation) (Lokhorst, 2002). Several novel agents recently have been introduced in the clinical setting and have shown promising results in improving patients' overall survival (Richardson et al., 2003; Tariman, 2003b). The role of angiogenesis in the pathogenesis of multiple myeloma continues to evolve, and with promising results of thalidomide (Thalomid®, Celgene Corporation, Warren, NJ) in newly diagnosed multiple myeloma (Rajkumar, Hayman, et al., 2002; Weber, Rankin, Gavino, Delasalle, & Alexanian, 2003), this novel agent is being used increasingly in the clinical setting (Rajkumar, Blood, Vesole, Shepard, & Greipp, 2004). Lenalidomide

(Revlimid™, Celgene Corporation), a thalidomide analog and an immunomodulatory derivative (IMiD), has shown promising results in phase II clinical trials and now is entering phase III (Richardson, Jagannath, et al., 2002). Another IMiD, CC-4047 (Actimid™, Celgene Corporation), also has shown promising results in phase I study (Schey et al., 2004). Lenalidomide and Actimid currently are being investigated as treatment for relapsed and refractory disease, but their use as front-line therapies is expected in the near future. New drugs

Joseph D. Tariman, RN, APN, MN, APRN-BC, OCN®, is a certified nurse practitioner in the Multiple Myeloma Program of the Department of Medicine in the Division of Hematology/Oncology at Northwestern University Medical Faculty Foundation and Stella Marie Estrella, BSN, RN, is a staff nurse in the Bone Marrow Transplant Unit of Northwestern Memorial Hospital, both in Chicago, IL. Tariman also is a consultant and a member of the speakers bureau for Millennium Pharmaceuticals, Inc., which manufactures Velcade®, a drug mentioned in this article. (Submitted October 2004. Accepted for publication February 28, 2005.) (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Forum *or the Oncology Nursing Society.)*

such as bortezomib (Velcade®, Millennium Pharmaceuticals, Inc., Cambridge, MA) and lenalidomide use a new treatment paradigm that targets not only multiple myeloma cells directly but also their microenvironment. Use of these novel biologically based therapeutic agents alone or in combination with conventional chemotherapy can overcome drug resistance and may result in better survival for patients with multiple myeloma (Anderson, 2003; Barlogie et al., 2004). A changing treatment paradigm in patients with multiple myeloma will have a significant effect on clinical practice. This article will explore new implications for nursing practice based on these latest treatment approaches.

Diagnosis and Staging

The Durie and Salmon myeloma diagnostic criteria (see Figure 1) are used widely in the United States and have been validated by large multicenter trials. The parameters are easily determined in the majority of rural or urban clinical practice settings (Harousseau & Moreau, 2002). The diagnostic criteria are divided into major and minor. In most cases, one major criterion together with one minor criterion is sufficient to diagnose multiple myeloma. Once the diagnostic criteria for multiple myeloma are met, Durie-Salmon clinical staging can be used to determine the stage of disease.

The Durie-Salmon clinical staging system incorporates the diagnositic system proposed in 1975 and the labeling index proposed by Durie and colleagues in 1980 (Durie & Salmon, 1975;

Durie, Salmon, & Moon, 1980). The diagnostic criteria are displayed in Table 1. This staging system is based on M protein levels, the number of bone lesions, and the severity of anemia or hypercalcemia (Durie & Salmon). Durie et al. identified a process to quantitate the total-body myeloma cell mass. This number is calculated by dividing the total-body M component synthetic rate per myeloma cell. In examining a large series of individuals with multiple myeloma, the authors identified three stages of the disease.

Stage I, or low cell mass, reflects counts of fewer than 0.6×10^{12} cells/m^2. Stage II, or intermediate cell mass, reflects more than $0.6–1.2 \times 10^{12}$ cells/m^2. Stage III, or high cell mass, reflects counts greater than 1.2×10^{12} cells/m^2. Further staging is done based on renal status at the time of diagnosis. Group A consists of individuals with a normal renal function (creatinine level less than 2.0 mg/dl), and group B consists of individuals with evidence of renal dysfunction (creatinine level greater than 2.0 mg/dl).

Pathophysiology

Understanding the nature of plasma cells and the Igs secreted by them is important to elucidate the pathobiologic changes in multiple myeloma. The production of monoclonal Igs is directly proportional to myeloma cell activity, except in nonsecretory cases.

Igs, or antibodies, are secretory products of plasma cells, and each Ig molecule has two heavy and two light chains (Kyle & Lust, 1996). Under normal circumstances, they constitute the humoral immune response to a foreign antigen. The five types of heavy chains are denoted by the Greek letters μ, δ, γ, α, and ε. The type of heavy chain present determines the class of the Ig: IgM, IgD, IgG, IgA, and IgE, respectively (Rajkumar & Greipp, 2002). The two types of light chains are denoted by the Greek letters kappa and lambda. Each heavy chain Ig molecule has either a kappa or a lambda subtype of light chain in association with one of the types of heavy chain (i.e., IgG kappa or IgG lambda) (see Figure 2). Because multiple myeloma is a neoplastic, clonal process, the malignant cells and the secreted Igs are either kappa- or lambda-restricted (restriction distinguishes normal plasma cells from malignant plasma cells). When plasma cells become aberrant, they continue to produce Igs, although about 3% of myeloma cases are nonsecretory (National Comprehensive Cancer Network [NCCN], 2004). Because the malignant proliferation of these plasma cells comes from one clone, they produce a homogenous Ig, leading to overproduction of a monoclonal Ig (could be heavy chain or light chain), known as M spike, either in the serum or urine. The M spike value, which commonly is expressed in g/dl (serum) or mg per 24 hours (urine), is the monoclonal protein fraction of the total Igs produced by myeloma cells that usually is obtained in serum and urine electrophoresis, respectively. M spike is a very important tumor marker in multiple myeloma because it is produced directly by myeloma cells. When the M spike value decreases while a patient is being actively treated, it directly correlates to the degree of response to therapy (Blade et al., 1998).

Heavy Chain Multiple Myeloma

The immunofixation test is the most sensitive and a more specific test that identifies the type of Ig produced by the myeloma cells. When monoclonal plasma cells produce heavy chain Ig, multiple myeloma then is subtyped into either IgG

Multiple Myeloma
Major criteria
1. Plasmacytoma on tissue biopsy
2. Bone marrow plasmacytosis with 30% plasma cells
3. Monoclonal globulin spike (M protein) on SPEP: IgG > 3.5 g/dl, IgA > 2.0 g/dl, light-chain excretion on UPEP $\geq$ 1 g per 24 hour in the absence of amyloidosis

Minor criteria
a. Bone marrow plasmacytosis with 10%–30% plasma cells
b. Monoclonal globulin spike present, but lower levels than defined in the major criteria
c. Lytic bone lesions
d. Normal IgM > 50 mg/dl, IgA > 100 mg/dl or IgG > 600 mg/dl

The diagnosis of myeloma requires a minimum of one major and one minor criterion (although 1 + a is not sufficient) or three minor criteria that must include a + b.

Indolent Myeloma
Criteria as for myeloma with the following limitations:
a. Absent or only limited bone lesions ($\leq$ 3 lytic lesions), no compression fractures
b. Stable paraprotein levels IgG level < 700 mg/dl, IgA < 500 mg/dl
c. No symptoms or associated disease features: Karnofsky performance status > 70%, hemoglobin > 10 g/dl, normal serum calcium, normal serum creatinine, no infections
d. Plasma cell labeling index $\leq$ 0.5%

Ig—immunoglobulin; SPEP—serum protein electrophoresis; UPEP—urine protein electrophoresis

Figure 1. Diagnostic Criteria by Durie and Salmon
Note. From "Clinical Features and Diagnostic Criteria" (p. 155), by H. Lokhorst in J. Mehta & S. Singhal (Eds.), *Myeloma,* 2002, London: Martin Dunitz. Copyright 2002 by Martin Dunitz. Reprinted with permission.

Table 1. Multiple Myeloma Staging System

Criteria	Estimated Myeloma Mass (Cells x $10^{12}/m^2$)
Stage I	< 0.6
All of the following	(low burden)
Hemoglobin value > 10 g/dl	
Normal serum calcium	
Normal bone structure	
Low M protein production	
IgG value < 5 g/dl	
IgA value < 3 g/dl	
Urine kappa or lambda < 4 g/24 hr	
Stage II	0.6–1.2
Overall data fits in neither stage I nor stage III	(intermediate burden)
Stage III	> 1.2
One or more of the following	(high burden)
Hemoglobin value < 8.5 g/dl	
Serum calcium value > 12 mg/dl	
More than 3 lytic bone lesions	
High M protein production	
IgG value > 7 g/dl	
IgA value > 5g/dl	
Urine kappa or lambda	
M component > 12 g/24 hr	
Subclassification	
A = creatinine value < 2.0 mg/dl	
B = creatinine value $\geq$ 2.0 mg/dl	

hr—hour; Ig—immunoglobulin

Note. From "A Clinical Staging System for Multiple Myeloma," by B.G. Durie and S.E. Salmon, 1975, *Cancer, 36,* p. 852. Copyright 1975 by the American Cancer Society. Reprinted with permission from John Wiley and Sons, Inc.

kappa or lambda or IgA kappa or lambda. IgD and IgE types of myeloma are rare and have an incidence of less than 1%. IgM gammopathy (i.e., the presence of monoclonal IgM in the serum) usually is associated with Waldenstrom macroglobulinemia rather than myeloma.

Light Chain Multiple Myeloma

When myeloma cells produce only light chain Igs (originally described by Bence Jones, MD; hence, the name Bence Jones protein is synonymous with light chain proteinuria), they are subtyped into kappa light chain or lambda light chain multiple myeloma. Most patients with myeloma have serum proteins with or without associated urinary proteins, but 20% of patients have urinary proteins only (Kyle et al., 2003). For patients with light chain myeloma, a 24-hour urine protein electrophoresis must be performed regularly as part of surveillance for disease progression because urine M protein, not serum M protein, is the tumor marker.

Treatment

The 2004 NCCN guidelines outline several conventional therapies for newly diagnosed multiple myeloma. These therapies are offered routinely outside the context of clinical trials because their safety and efficacy have been validated (see Figure 3).

Patients with monoclonal gammopathy of undetermined significance (MGUS), indolent, or smoldering multiple myeloma (see Figure 4) are observed initially for months and may do well without treatment for many years (NCCN, 2004). A comprehensive review of randomized controlled trials with a parallel design that compared early with deferred treatment for patients with early-stage multiple myeloma concluded that early treatment inhibited disease progression and may have reduced vertebral compression but no significant effects on response rate and overall survival existed (He et al., 2003).

When disease progression is evident, demonstrated by a sustained 25% increase or greater in M protein in serum or urine or development of new sites of skeletal lytic lesion or hypercalcemia, treatment should be started immediately (NCCN, 2004). Systemic therapy with oral or IV chemotherapy is the preferred initial approach to symptomatic multiple myeloma. Alkylating agents (mustards such as melphalan and cyclophosphamide) and nitrosoureas (carmustine or lomustine) typically are used. Radiation therapy use in multiple myeloma should be limited and reserved for symptomatic or painful discrete lesions, such as in cases of epidural extension with impending cord compression. In addition, radiation could further deplete the bone marrow reserve for patients who may be eligible for stem cell transplantation (SCT).

Age older than 65 years and comorbid conditions such as renal compromise used to be negative factors in the selection of transplant candidates. Recently, studies have shown that neither of these two factors is an important adverse parameter affecting the outcome of high-dose therapy and autotransplantation (Badros, Barlogie, Stiegel, Roberts, et al., 2001; Magagnoli et al., 2003; Siegel et al., 1999; Sirohi et al., 2001; Terpos, Apperley, et al., 2003). These reports have led to an increase in the number of patients who are eligible for autologous SCT for treatment for multiple myeloma (Zomas & Dimopoulos, 2002). Therefore, high-dose chemotherapy with autologous SCT is recommended for patients 70 years of age or younger who do not have severe comorbidities (Barosi et al., 2004; Kyle, 2002; NCCN, 2004; Singhal, 2002). Ideally, hematopoietic stem cells are collected before patients are exposed to alkylating agents. The NCCN myeloma panel recommended high-dose chemotherapy followed by autologous SCT as a primary treatment in patients with symptomatic multiple myeloma with uniform consensus based on high-level evidence (category 1 consensus from the NCCN panel, the highest level of consensus among myeloma experts). Common induction therapies administered prior to high-dose chemotherapy include pulse dexamethasone; vincristine, doxorubicin, and dexamethasone (VAD); and, most recently, thalidomide plus dexamethasone.

Serum heavy chain immunoglobulins (77% of cases)
- Immunoglobulin G kappa or lambda multiple myeloma
- Immunoglobulin A kappa or lambda multiple myeloma

Urinary light chain immunoglobulins or Bence Jones proteins (20% of cases)
- Kappa light chain multiple myeloma
- Lambda light chain multiple myeloma

No serum or urine M proteins (3% of cases)
- Nonsecretory multiple myeloma

Figure 2. Subtypes of Multiple Myeloma Based on Specific Monoclonal Immunoglobulins or M Proteins Produced by Myeloma Cells

Note. Based on information from Kyle et al., 2003.

Patients not eligible for autologous stem cell transplant
• Melphalan and prednisone

Patients eligible for autologous stem cell transplant
• Vincristine, doxorubicin, and dexamethasone
• High-dose pulsed dexamethasone
• Thalidomide and dexamethasone (insufficient data to recommend treatment duration)
• Liposomal doxorubicin, vincristine, and dexamethasone

Figure 3. Conventional Therapies in Patients With Newly Diagnosed Multiple Myeloma

Note. Based on information from the National Comprehensive Cancer Network, 2004.

Induction Chemotherapy

High-dose pulsed dexamethasone: High-dose pulsed dexamethasone is a primary treatment regimen in patients with multiple myeloma, with response and survival rates that are similar to those achieved with other standard regimens such as VAD (Alexanian, Dimopoulos, Delasalle, & Barlogie, 1992; Kumar et al., 2004). It has the convenience of oral administration. Dexamethasone 40 mg usually is given on days 1–4, 9–12, and 17–20 with a one-week break (28-day cycle) or two-week break (35-day cycle). Because dexamethasone is not associated with myelosuppression, this agent is indicated when radiotherapy is needed for the treatment of painful bone lesions or in patients with impending cord compression and may be the primary treatment of choice in patients who present with pancytopenia (Zomas & Dimopoulos, 2002).

The major drawbacks of dexamethasone therapy among older adults are steroid-related toxicities (Gautier & Cohen, 1994). Prophylactic antacid or proton pump inhibitors and anti-infectives usually are administered concomitantly to prevent common steroidal side effects, such as gastrointestinal (GI) ulcers and infection. Monitoring of signs and symptoms of ulcers, severe dyspepsia, fluid and sodium retention, corticosteroid myopathy, acute pancreatitis, insulin-dependent hyperglycemia, steroid psychosis, and infections is important. Patient and family education should include instructions to report signs and symptoms of gastritis, including nausea and vomiting with or without hematemesis, to clinicians to prevent serious complications such as GI bleeding.

Monoclonal gammopathy of undetermined significance
• Less than 10% plasmacytosis
• Absence of myeloma-associated signs and symptoms[a]
Smoldering multiple myeloma
• Plasmacytosis greater than 10% but not greater than 30%
• Absence of myeloma-associated signs and symptoms[a]
Indolent multiple myeloma
• Plasmacytosis greater than 10% but not greater than 30%
• May have mild anemia, few lytic lesions (less than three)
• No other myeloma-associated signs and symptoms

[a] Myeloma-associated signs and symptoms include anemia, bone pain, bone lytic lesions, renal insufficiency, and hypercalcemia.

Figure 4. Characteristics of Monoclonal Gammopathy of Undetermined Significance and Early-Stage Multiple Myeloma

Note. Based on information from Kyle et al., 2003; Kyle & Greipp, 1980.

Older adult patients require close monitoring, particularly those with concurrent diseases such as congestive heart failure, because steroid-associated sodium and water retention can exacerbate symptoms (Gautier & Cohen, 1994). Monitoring patients for weight gain and peripheral edema on a daily basis will help in detecting pulmonary edema and cardiopulmonary compromise. Inform patients and their family members to report to their clinicians any weight gain greater than five pounds in one day. Individuals with preexisting diabetes require close monitoring for signs and symptoms of steroid-induced hyperglycemia. Teaching patients and their families how to monitor blood sugar and when to report side effects to clinicians is an important aspect of treatment. Assess these patients for the presence of polydipsia, polyuria, and polyphagia at each visit. Homecare visits by an RN two to three times per week during the first cycle of high-dose dexamethasone may be needed to monitor blood pressure, blood sugar levels, and other steroid-related side effects. These visits may be continued through the second and third cycles of therapy as clinically indicated. Dose reductions or change of treatment regimen may be required if steroid-related psychosis or diabetic ketoacidosis occurs or if side effects are more pronounced and the risks outweigh the benefits of treatment.

Vincristine, doxorubicin, and dexamethasone: Using VAD as a treatment for myeloma was developed by the University of Texas M.D. Anderson Cancer Center in Houston in the early 1980s (Alexanian, Barlogie, & Tucker, 1990). The response rate in chemotherapy-naive patients is reported to be 60%–80%, with 10%–15% complete remission (Alexanian et al., 1990; Samson et al., 1989). The VAD regimen may be preferable for patients in whom rapid tumor control is desired, such as those with hypercalcemia, renal failure, or widespread painful bone lesions. It is especially indicated in patients with plasma cell leukemia (myeloma associated with circulating plasma cells greater than 20%) because standard alkylating agents are ineffective (Dimopoulos, Palumbo, Delasalle, & Alexanian, 1994). VAD also is useful in patients with renal failure because none of its components is nephrotoxic or excreted renally. No more than three courses of VAD usually are needed to confirm partial response (defined as a 50% reduction of M protein) or resistance (continued rise in M protein) to this regimen (Alexanian et al., 1990). Monitoring the total dose of doxorubicin and treating patients to a maximum tolerated dose of 450 mg/m^2 can prevent potential cardiotoxicity.

Major drawbacks of the VAD regimen are the need for central line access (doxorubicin is a vesicant) and steroid-related toxicities mentioned previously. The use of pegylated liposomal doxorubicin (nonvesicant formulation) has been reported, and the treatment regimen appears to be as effective as treatment with standard doxorubicin (Hussein, 2003).

The dose of dexamethasone in the VAD regimen is the same as in the pulsed dexamethasone regimen; therefore, similar steroid-related toxicities must be anticipated as well as the added concerns of central line infection (where patients are at risk for infection because the central line serves as a portal of entry of pathogenic organisms). Deep vein thrombosis is a risk if VAD is combined with thalidomide. Vincristine and doxorubicin are given on days 1–4 of each cycle of VAD, whereas dexamethasone is continued on days 9–12 and 17–20 on each cycle. Patients and family members must receive clear instructions from the healthcare team that dexamethasone is the most important component of the VAD regimen. Strict

compliance to this somewhat complex schedule is crucial to the success of induction therapy to reduce myeloma tumor burden quickly.

Thalidomide and dexamethasone: Thalidomide was reintroduced into the oncology clinical setting in 1998 and since then has demonstrated significant activity against relapsed and refractory multiple myeloma (Singhal et al., 1999). Thalidomide has immunomodulatory properties, such as stimulation of the secretion of interleukin-2 (IL-2) and interferon-γ (IFN-γ) by CD8+ T cells, thereby increasing antitumor immunity (Raje & Anderson, 2002).Thalidomide has antitumor properties against relapsed or refractory multiple myeloma with response rates averaging 30%–35% (response rate is > 50% reduction of M protein) (Barlogie, Tricot, & Anaissie, 2001; Kyle & Rajkumar, 2001; Yakoub-Agha et al., 2002). The median duration of response to thalidomide is approximately eight to nine months (ranges from 2 to more than 30 months) (Durie & Stepan, 2001).

The most commonly reported side effects of thalidomide are constipation, somnolence, and fatigue. Fairly common to least common side effects include peripheral neuropathy, skin rash, and deep vein thrombosis (Tariman, 2003a). Thalidomide is highly teratogenic. Clinicians and patients must adhere strictly to the System for Thalidomide Education and Prescribing Safety program (Zeldis, Williams, Thomas, & Elsayed, 1999). Therapeutic anticoagulation also may be essential during thalidomide therapy in newly diagnosed patients (Rajkumar, Hayman, et al., 2002; Weber et al., 2003) and when combined with cytotoxic chemotherapy because deep vein thrombosis incidence was reported to be as high as 25% (Zangari et al., 2003).

A reasonable approach for use of thalidomide in multiple myeloma is to initiate therapy at 50–100 mg nightly and escalate every two weeks in 50–100 mg increments as tolerated. Efforts should be made to titrate the dose up to 600 mg per day for patients with poor prognostic features such as in relapsed or refractory myeloma (Barlogie, Desikan, et al., 2001; Thompson & Hansen, 2003).

Autologous Stem Cell Transplantation

Collection of peripheral blood stem cells: In general, collection and cryopreservation of blood stem cells should be initiated as soon as the best achievable response is confirmed (i.e., 50% reduction of M protein from baseline) (Zomas & Dimopoulos, 2002). Chemomobilization, the use of chemotherapeutic agent(s) prior to stem cell collection and cryopreservation, commonly is used. Use of growth factor alone (i.e., granulocyte colony-stimulating factor or granulocyte macrophage–colony-stimulating factor) without chemotherapy prior to stem collection to mobilize stem cells (growth factor mobilization) may be effective in a select group of patients. Sequential administration of VAD followed by high-dose cyclophosphamide and consolidated by the combination of etoposide, dexamethasone, cytarabine, and cisplatin has improved complete response rates and allowed the collection of an adequate number of stem cells to support two autologous transplants (Barlogie et al., 1997). Other chemomobilization regimens prior to stem cell collection include high-dose cyclophosphamide and cyclophosphamide, dexamethasone, etoposide, and cisplatin.

Purging (removal of lingering malignant plasma cells) with monoclonal antibodies or 4-hydroperoxycyclophosphamide and positive selection of CD34+ progenitor cells (myeloma cells do not express the CD34 antigen) has been done to obtain tumor-free stem cells and improve response rates and overall survival. A long-term follow-up of a randomized study (Vescio et al., 1999) showed no survival benefit from CD34+ selection; therefore, purging and positive selection of stem cells remain questionable (Singhal, 2002).

Conditioning regimen: High-dose melphalan is considered the standard regimen for ablating the bone marrow of patients with multiple myeloma (Anagnostopoulos et al., 2004). Other combination regimens containing busulfan or etoposide are complex and have shown no obvious additional benefit (Anagnostopoulos et al.; Singhal, 2002). The most commonly used regimens in clinical practice are high-dose melphalan at 200 mg/m^2 given in one dose or at 100 mg/m^2 on two consecutive days followed by reinfusion of stem cells 24 hours after the completion of melphalan administration.

The half-life of melphalan is believed to be 50–170 minutes (Singhal, 2002). The dose of melphalan sometimes is reduced depending on the age of the patient (i.e., > 70 years) or if comorbid conditions are present. A reduced dose of melphalan at 140 mg/m^2 for patients older than 70 years of age usually is employed (Badros, Barlogie, Siegel, Morris, et al., 2001).

Tandem Autologous Stem Cell Transplantation

Tandem autologous transplantation, a sequential administration of two high doses of melphalan at least three months apart, each followed by SCT, has been used in an attempt to improve response rates and survival in patients with multiple myeloma. Evidence to support this treatment approach is insufficient because the only study showing benefit for tandem transplants used a conditioning regimen known to be associated with inferior outcome. However, tandem autologous SCT is recommended for patients who have responded to the first autologous SCT but are not in complete remission or are near a complete response (Attal et al., 2003). Studies on tandem autologous transplantation still are ongoing, and no other single study has shown to date that it offers overall survival advantage compared to one transplant (see Table 2).

Allogeneic Stem Cell Transplantation

Allogeneic SCT has been used to treat some patients with multiple myeloma, but to date patient outcomes have been dismal (Mehta, 2002). Several factors may account for this poor outcome, such as the underlying disease, the patient's condition, and the treatment regimen, including supportive therapy. Among them are advanced Durie-Salmon stage, extensive prior therapy, high β$_2$M, high lactate dehydrogenase serum values, a long diagnosis to transplant interval, low serum albumin, prior autograft, refractory disease, and renal dysfunction. Poor patient selection (e.g., those with poor performance status and terminal disease) has been responsible for these dismal results (Mehta). The role of nonmyeloablative allogeneic transplantation (i.e., mini-allogeneic transplantation) currently is being investigated because of a lower mortality rate and possible therapeutic benefit.

Treatment Options for Patients Not Eligible for High-Dose Chemotherapy With Autologous Stem Cell Transplantation

Melphalan and prednisone: For patients with symptomatic multiple myeloma who are older than 70 years or in younger

Table 2. Types of Responses for Single Versus Tandem Autologous Stem Cell Transplant

Single	Tandem	p
42% complete response or very good partial response	50% complete response or very good partial response	0.1
10% seven-year event-free survival	20% seven-year event-free survival	0.03
21% seven-year overall survival	42% seven-year overall survival	0.01

Note. Based on information from Attal et al., 2003.

patients for whom transplant is not feasible, intermittent systemic oral melphalan and prednisone (MP) has been the first line of therapy since the 1970s (Anderson, Hamblin, & Traynor, 1999; Kyle, 2002; Rajkumar, Gertz, Kyle, & Greipp, 2002). The relative importance of two active agents in the MP regimen has been debated because of conflicting results in either MP combination or intermittent melphalan alone. An analysis clearly has shown the usefulness of steroids by correlating survival with prednisone dose intensity and not with the total melphalan dose (Palmer, Belch, Hanson, & Brox, 1988). In general, corticosteroids as part of primary treatment for multiple myeloma demonstrate high activity in plasma cells with concomitant sparing of normal hematopoietic elements. Corticosteroids may increase the speed of response without added myelosuppression while improving patients' sense of well-being (Zomas & Dimopoulos, 2002).

Before high-dose chemotherapy and stem cell rescue, the MP oral regimen was the most frequent treatment for newly diagnosed multiple myeloma (Sonneveld & Segeren, 2003). With this regimen, the response rate is 50%–60% and the mean survival rate is about 24–36 months (Bataille & Harousseau, 1997). The survival rates at 5 and 10 years are 25% and 8%, respectively (Munshi, Desikan, & Barlogie, 2000). Standard MP chemotherapy consists of melphalan 8 mg per day for seven days and prednisone 20 mg three times a day for the same seven days every six weeks (Kyle, 2002). Melphalan also can be given at 8 mg/m^2 daily for four consecutive days and prednisone at 60 mg/m^2 daily by mouth, also for four consecutive days.

White blood cells and platelets are checked every three weeks after beginning each cycle of therapy. The dosage of melphalan must be adjusted until modest midcycle cytopenia occurs (Kyle, 2002). If the serum creatinine level is more than 2 mg/dl, the dose of melphalan should be reduced by 25% to prevent severe myelosuppression. If cytopenia does not occur, the dose of melphalan should be increased in a stepwise escalation by 2–3 mg/m^2 (Kyle; Zomas & Dimopoulos, 2002).

A minimum of three courses of MP should be given before therapy is discontinued because delayed responses are common. An objective response may not be seen for 6–12 months or even longer in some patients. If pain is alleviated and no evidence of progressive disease is present (i.e., no increase in serum or urine M protein, no new bone lesions, no hypercalcemia), the regimen should be continued.

Oral melphalan must be taken on an empty stomach at least two hours before meals or three hours after eating because food reduces its absorption by at least 50% (Alberts, Chang, Chen, Evans, & Moon, 1979), unlike prednisone, which

needs to be taken with meals. Patients may take H$_2$-histamine receptor antagonists to prevent gastric distress associated with steroids. Older individuals who are at risk for infectious or GI complications must be monitored closely.

Novel Therapies

Bortezomib: Bortezomib is a novel, first-in-class proteasome inhibitor agent that inhibits the 26S proteasome (Adams, 2003b). The mechanism of action of bortezomib in multiple myeloma has been described and the potential effects of bortezomib in myeloma and other types of cancer are outlined in Figure 5 (Adams, 2003a).

In May 2003, the U.S. Food and Drug Administration approved bortezomib as a treatment for relapsed and refractory myeloma. In a landmark phase II trial (protocol M34101-025, also known as the Summit Protocol), 193 of 202 patients were evaluable for response to bortezomib alone and the combined complete and partial response rate was 28% regardless of the number or type of previous therapies or baseline patient characteristics, including performance status, myeloma type, β_2M, or chromosome 13 deletion status. Predictors of a poor response included greater than 50% plasma cells in the bone marrow and abnormal bone marrow cytogenetics other than chromosome 13 deletion status. Median time to response was 38 days (two cycles). Median major response duration was 12 months, and the overall response was as high as 35% when minimal responses were included. Grade 3 adverse events included thrombocytopenia (28%), fatigue (12%), and neutropenia (11%). Grade 4 adverse events, which included thrombocytopenia, diarrhea, vomiting, and peripheral neuropathy, occurred in 14% of patients (Richardson et al., 2003).

Although bortezomib has been approved for patients with multiple myeloma who have failed at least two different types of treatment (Colson, Doss, Swift, Tariman, & Thomas, 2004), it also has been used with patients with newly diagnosed multiple myeloma. In a phase II trial, patients received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 with a 10-day break (21-day cycle) for a maximum of six cycles. Dexamethasone 40 mg the day of and the day after bortezomib administration was given after two cycles to patients whose M spike value was less than half from baseline and after four cycles to patients who did not achieve complete disappearance of M spike. Nineteen patients were accrued in this study, and 12 patients completed six cycles and were evaluable for response. Four patients (33%) achieved near complete remission (defined as negative M spike value but still immunofixation positive), and five patients (42%) had a partial response after six cycles (Jagannath et al., 2004). The most common adverse events (grade 1–3) were fatigue (67%); GI-related symptoms such as diarrhea (58%), constipation (42%), nausea (42%), and vom-

- Increases apoptosis by inhibiting antiapoptotic factors
- Decreases production of cellular adhesion molecules which confer resistance to standard chemotherapies
- Inhibits interleukin-6 cytokine, a major proliferative factor of myeloma cells
- Decreases production of cyclins and cell cycle regulators

Figure 5. Potential Effects of Bortezomib in Multiple Myeloma

Note. Based on information from Chauhan et al., 1996; Mitsiades et al., 2002; Richardson et al., 2003.

iting (33%); and peripheral neuropathy (33%). Of particular note, subsequent to receiving bortezomib, one patient had undergone high-dose chemotherapy with SCT and attained complete hematologic recovery (Jagannath et al.).

Another study also reported using bortezomib in combination with doxorubicin and dexamethasone for untreated multiple myeloma (Cavenagh et al., 2004). Fifteen patients with previously untreated multiple myeloma were enrolled. All patients received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 and oral dexamethasone 40 mg on days 1–4, 8–11, and 15–18 cycle 1 (day 1–4 only during cycles 2–4). For doxorubicin dosing, patients were divided into three cohorts. The first cohort (n = 3) received no doxorubicin, the second (n = 4) received doxorubicin 4.5 mg/m^2 on days 1–4, and the third (n = 8) received 9 mg/m^2 on days 1–4 of the cycle. All patients achieved at least a partial response (50% reduction of M protein); two patients achieved a complete response (100% reduction of M protein).

Patients receiving bortezomib therapy need to be monitored closely for any adverse effects. Failure to assess or institute appropriate early interventions may jeopardize patients' health. Peripheral neuropathy needs close monitoring, and appropriate dose or schedule modification based on patients' degree of neuropathy is recommended (Tariman & Lemoine, 2003). Complete blood counts before each dose and weekly chemistries are necessary to monitor any electrolyte imbalance or creatinine abnormality (Tariman & Lemoine). Transfusion support and use of growth factors may be clinically indicated. Grade 4 hematologic toxicities will require dose modification. The dose usually is held until symptoms return to a grade 3 level with or without transfusion or use of growth factors. Antidiarrheals and antiemetics may be used as clinically indicated. Oncology nurses play a vital role in the assessment and monitoring of these adverse effects and in the initiatation of immediate interventions before serious health conditions or irreversible damage occur (Colson et al., 2004).

Immunomodulatory drugs: As the use of thalidomide in the treatment of patients with newly diagnosed, relapsed, or refractory myeloma has increased, so has interest in immunomodulatory drugs that are potent thalidomide derivatives or analogs that markedly stimulate T-cell proliferation, as well as IL-2 and IFN-α production (Corral et al., 1999). Lenalidomide, an IMiD that is 50–2,000 times more potent than thalidomide in stimulating T-cell proliferation triggered via the T-cell receptor and 50–100 times more potent than thalidomide in augmenting IL-2 and IFN-α, thereby stimulating peripheral blood mononuclear cells and augmenting natural killer cells function (Richardson, Schlossman, et al., 2002). In addition, lenalidomide triggers dose-dependent decreased secretion of tumor necrosis factor-α (TNF-α), IL-1, and IL-6, which promote myeloma cell proliferation and trigger increased secretion of IL-10. Lenalidomide decreases multiple myeloma cell proliferation by reducing binding of multiple myeloma cells to bone marrow stromal cells, inhibiting the production in the bone marrow milieu of cytokines (IL-6, vascular endothelial growth factor, TNF-α) that mediate the growth and survival of multiple myeloma cells, blocking angiogenesis, and stimulating host antimultiple myeloma natural killer cell immunity (Davies et al., 2001; Gupta et al., 2001; Hideshima et al., 2000; Richardson, Schlossman, et al., 2002).

Another thalidomide analogue, Actimid, is the second IMiD to enter clinical trials. In in vitro models, it demonstrated ap-

proximately 15,000-fold greater inhibition of TNF-α activity than thalidomide. It also inhibits IL-1 levels and multiple myeloma cell proliferation. Actimid and lenalidomide have different tumor activity profiles and currently are being tested in different malignancies. These two novel thalidomide analogs display antiangiogenic activity independent of their immunomodulatory effect (Dredge et al., 2002). To date, most studies on lenalidomide and Actimid have been done with patients with relapsed or refractory myeloma.

A phase I study of lenalidomide showed that it overcomes conventional drug resistance and is well tolerated in patients with relapsed multiple myeloma. More importantly, no significant somnolence, constipation, or neuropathy (common toxicities of thalidomide) was reported among four cohorts of patients who received the drug at doses of 5, 10, 25, and 50 mg per day (Richardson et al., 2001). Best responses in M spike, with a reduction of greater than 25%, were seen in 12 of 19 evaluable patients (63%) and less than 25% in an additional 3 patients; 4 patients had no response. This study demonstrated that lenalidomide has antitumor activity and acceptable toxicity and provides the framework for further studies. Dose-limiting toxicities, including grade 3 and 4 leukopenia, neutropenia, and thrombocytopenia, were found in all except the 5 mg per day cohort.

A similar phase I study with 15 patients (all patients had chemorefractory disease, having relapsed after at least one high chemotherapy dose, with a median of 10 prior cycles of chemotherapy) enrolled concluded that three patients (20%) showed a greater than 50% M spike reduction with a concomitant reduction of plasma cell involvement in bone marrow biopsy (Zangari et al., 2003). However, responses were observed only at the 25 and 50 mg doses. This study also found the same significant myelosuppression reported by Richardson et al. (2001), even in patients with adequate platelet counts and marrow cellularity. Furthermore, this particular study suggested that lenalidomide had the potential to cause cardiovascular problems such as thromboembolism (two patients) and syncope (one patient).

A follow-up phase II study supported phase I findings and demonstrated that lenalidomide has an acceptable toxicity profile and the convenience of daily oral dosing (Richardson, Jagannath, et al., 2002). After successful phase I and II trials, a phase III multicenter, international trial at 50 sites was conducted. It currently is closed for enrollment after successful accrual of 302 patients with relapsed or refractory multiple myeloma. The primary objective of this study is to compare the efficacy of oral lenalidomide in combination with oral pulse high-dose dexamethasone to that of placebo and oral high-dose pulse dexamethasone (Weber, 2003). Most recently, a Southwest Oncology Group phase III multicenter study was initiated to study lenalidomide in newly diagnosed, untreated patients with multiple myeloma. This study expects to accrue 500 patients.

The primary side effects of lenalidomide are myelosuppression and thromboembolic events. Appropriate and timely use of growth factors and blood product transfusions are crucial to prevent serious complications such as sepsis and bleeding from severe neutropenia and thrombocytopenia, respectively. A thorough assessment for signs and symptoms of thromboembolic events is also unequivocally important to prevent serious complications such as pulmonary embolism.

Other agents: Several other biologically based therapeutic agents currently are under preclinical and clinical investigation

for multiple myeloma. These include NF-kB inhibitor (PS-1145), 2-methoxyestradiol, tyrosine kinase inhibitor (PTK787), histone deacetylase inhibitor (NVP-LAQ824), farnesyl transferase inhibitor (R115777), and osteoprotegerin (Alsina et al., 2004; Catley et al., 2003; Chauhan et al., 2002; Hayashi, Hideshima, & Anderson, 2003; Lin et al., 2002; Mitsiades et al., 2004; Mooberry, 2003; Ochiai et al., 2003; Santucci, Mackley, Sebti, & Alsina, 2003; Vanderkerken et al., 2003). These novel agents are mostly in phase I and phase II clinical trials and have shown promising activity against multiple myeloma. They are potential additions to the treatment armamentarium for myeloma. Application of cytogenetics and molecular genetics, especially gene expression profiling, may soon aid in a molecular classification of multiple myeloma potentially leading to new treatment strategy (Bumm et al., 2002; Claudio, Masih-Khan, & Stewart, 2004; Zhan et al., 2002).

Adjunctive Treatment

Bisphosphonates: Bisphosphonates directly inhibit the osteolytic activity of osteoclasts and reduce their survival. They have been shown to provide a meaningful supportive benefit to patients with multiple myeloma and lytic bone disease (Berenson et al., 2002). Pamidronate, a second-generation aminobisphosphonate, has been evaluated in a randomized, double-blind trial in patients with advanced multiple myeloma (Berenson et al., 1996). Bone pain and analgesic requirements were significantly reduced in the pamidronate group. The total number of occurrences of pathologic fracture and episodes of hypercalcemia was reduced by half. Pamidronate currently is used at a dose of 90 mg once a month given in a two-hour infusion. Long-term indefinite use of this agent has been shown to be safe and efficacious (Ali et al., 2001). Pamidronate in comparison with ibandronate (a first-generation bisphosphonate) was found to be superior in reducing osteoclast activity, bone resorption, IL-6, and, possibly, tumor burden in multiple myeloma (Terpos, Viniou, et al., 2003).

A more potent third-generation bisphosphonate, zoledronic acid (Zometa®, Novartis Pharmaceuticals, East Hanover, NJ), has proven superior to pamidronate in the treatment of hypercalcemia and skeletal metastasis (Major et al., 2001). Similar to pamidronate, prolonged use of zoledronic acid seems to be well tolerated and safe (Ali et al., 2001; Rosen et al., 2003). Zoledronic acid currently is used at a dose of 4 mg once a month in a 15- to 30-minute IV infusion, indefinitely. Concerns about the nephrotoxicity of zoledronic acid have been reported (Berenson et al., 2002), but one study reported that in patients with mildly to moderately reduced renal function, dosage adjustment of zoledronic acid likely is not necessary (Skerjanec et al., 2003). Zoledronic acid and pamidronate can reduce the risk of vertebral, wrist, and hip fractures by 30%–50% (Body, 2003). Zolendronate is the first and only bisphosphonate to be proven effective in patients with all types of bone lesions, from osteolytic (commonly found in patients with multiple myeloma) to osteoblastic (bone damage from metastases of solid tumor to the bones) and therefore represents an important therapeutic advancement of bone metastases (Rosen, Harland, & Oosterlinck, 2002).

The American Society of Clinical Oncology has published its clinical practice guidelines for the use of bisphosphonates in the prevention and treatment of lytic bone disease in patients with multiple myeloma (Berenson et al., 2002). The committee has recommended IV pamidronate or zoledronic acid only for the prevention of skeletal events. The superiority of one agent over the other cannot be definitively established; therefore, the choice of pamidronate or zoledronic acid will depend on choosing between the higher drug cost of zoledronic acid, with its shorter, more convenient infusion time of 15 minutes, versus the less expensive drug, pamidronate, with its longer infusion time of two hours (Berenson et al., 2002).

Common side effects from IV bisphosphonates include bone pain, nausea, fatigue, fever, vomiting, diarrhea, and myalgias (Rosen et al., 2003). Supportive care measures include assessing dehydration and electrolyte levels and administering antiemetics, antipyretics, antidiarrheals, and analgesics as clinically indicated (Maxwell, Swift, Goode, Doane, & Rogers, 2003). Blood chemistry results usually are reviewed before IV bisphosphonate administration, and serum creatinine is monitored on a regular basis. An increase in creatinine of 0.5 mg/dl in patients with normal baseline and 1.0 mg/dl in patients with abnormal baseline creatinine would require the dose to be held until the creatinine returns to within 10% of the baseline value. Patients who are receiving any bisphosphonate therapy for malignant bone disease are instructed to take daily calcium (500 mg) and vitamin D (400 IU) supplements (Maxwell et al.).

Implications for Nursing

Many advances have occurred in the care of patients with newly diagnosed multiple myeloma. Improvement in supportive care, high-dose chemotherapy with autologous SCT, and novel therapeutic agents are among the most recent developments. The changing treatment paradigm for newly diagnosed patients with multiple myeloma eventually may lead to better quality of life and improved overall survival. However, as discussed previously, new side effects and serious complications (deep vein thrombosis, pulmonary embolism, severe myelosuppression, and infection or sepsis and peripheral neuropathy) also may come along with these advancements.

Nursing interventions are directed toward addressing the clinical issues that, in some cases, could be fatal. Nurses play an important role in maintaining patients' strict adherence to complex chemotherapy regimens, supportive therapies (growth factor support and bisphosphonates), and prophylactic therapy for deep vein thromboses and infection prophylaxis. When planning nursing care, the entire treatment team must understand a patient's therapeutic plan and potential complications associated with treatment. Careful monitoring of potential life-threatening complications is a pivotal role of oncology nurses. It also is critical to include patients and family members when discussing therapeutic goals, treatment options, and adverse effects to watch. An ongoing, adequate pain assessment and effective management of the chemotherapy side effects such as the use of antiemetics, antidiarrheals, and hydration are critical in maintaining patients' sense of well-being. Specific nursing interventions for pain include assessment and documentation of an individual's severity of pain (0–10 scale), proper positioning of affected limbs, use of supports and braces (cervical collar, back brace, sling) to prevent additional stress on bones, and consultation with physical or occupational therapists. Effective pain control is possible in patients with multiple myeloma using a three-step treatment plan, the World Health Organization pain treatment ladder

("Cancer Pain Relief and Palliative Care," 1990), which has been used widely for the treatment of tumor pain. Pain management also should incorporate nonpharmacologic therapies such as aromatherapy, massage, heat, cold, relaxation, and immobilization (Fellowes, Barnes, & Wilkinson, 2004).

The respiratory system is the most frequent site of infection in patients with multiple myeloma. Nurses can teach patients and their families how to decrease pooling of pulmonary secretions and increase gas exchange (e.g., coughing and deep-breathing exercises, use of incentive spirometers, avoiding contact with individuals with signs and symptoms of upper respiratory tract infections). Patient and family instructions such as immediate notification of the healthcare team when patients manifest fever, cough, sore throat, and sputum production are important (Tariman, 2005). Because of its defective humoral immunity, vaccination with live organisms is contraindicated in patients with multiple myeloma and exposure to others who may have received live organism vaccines (e.g., children immunized with oral polio) should be avoided (Wong, 1995). All patients with multiple myeloma, and in particular those older than age 65, should be immunized with a single dose of the 23-valent pneumococcal vaccine ("Prevention of Pneumococcal Disease," 1997) and a yearly influenza vaccine.

Oncology nurses play a vital role in ensuring that patients receive the optimal psychological support necessary to promote well-being and overall quality of life. Information on support groups and multiple myeloma organizations is beneficial for patients and families. Organizations such as the International Myeloma Foundation (www.myeloma.org) and Multiple Myeloma Research Foundation (www.multiplemyeloma.org) provide individual and group support. These organizations also have written patient educational materials regarding multiple myeloma and current treatment for the disease. Many of these organizations can be accessed via the Internet.

Finally, oncology nurses play a key role in educating patients and their families regarding novel agents and help them make informed decisions when determining whether patients should participate in clinical trials.

Conclusions

Therapeutic options have increased, patient outcomes have improved, and further insights have been gained into the biology and genetics of multiple myeloma (Barlogie et al., 2004). Healthcare providers are witnessing increasing utilization of new technologies and biologically based novel therapeutics (Hayashi et al., 2003). The use of tumor- and host-directed therapies may be an important adjunct in effecting a traditional cure or return to a chronic benign state such as MGUS or smoldering myeloma (Barlogie et al., 2004).

The nursing management of patients with multiple myeloma and their families offers nurses an opportunity to care for patients experiencing both acute and chronic sequelae of the disease. Nursing care can have a direct effect on early recognition of complications and management of treatment-related toxicity. Patient and family education regarding the disease, conventional and novel treatments, and early recognition of signs and symptoms of complications can contribute to an overall improvement in quality of life. Nurses play an important role not only as direct caregivers but also as patient advocates and educators. Oncology nurses must continue to keep abreast of recent changes and advances in the care of patients with multiple myeloma (Tariman, 2005).

Author Contact: Joseph D. Tariman, RN, APN, MN, APRN-BC, OCN®, can be reached at jtariman@nmff.org, with copy to editor at ONFEditor@ons.org.

References

Adams, J. (2003a). Potential for proteasome inhibition in the treatment of cancer. *Drug Discovery Today, 8,* 307–315.

Adams, J. (2003b). The proteasome: Structure, function, and role in the cell. *Cancer Treatment Reviews, 29*(Suppl. 1), 3–9.

Alberts, D.S., Chang, S.Y., Chen, H.S., Evans, T.L., & Moon, T.E. (1979). Oral melphalan kinetics. *Clinical Pharmacology and Therapeutics, 26,* 737–745.

Alexanian, R., Barlogie, B., & Tucker, S. (1990). VAD-based regimens as primary treatment for multiple myeloma. *American Journal of Hematology, 33*(2), 86–89.

Alexanian, R., Dimopoulos, M.A., Delasalle, K., & Barlogie, B. (1992). Primary dexamethasone treatment of multiple myeloma. *Blood, 80,* 887–890.

Ali, S.M., Esteva, F.J., Hortobagyi, G., Harvey, H., Seaman, J., Knight, R., et al. (2001). Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. *Journal of Clinical Oncology, 19,* 3434–3437.

Alsina, M., Fonseca, R., Wilson, E.F., Belle, A.N., Gerbino, E., Price-Toska, T., et al. (2004). Farnesyltransferase inhibitor tipifarnib is well tolerated, induces stabilization of disease and inhibits farnesylation and oncogenic/tumor survival pathways in patients with advanced multiple myeloma. *Blood, 103,* 3271–3277.

Anagnostopoulos, A., Aleman, A., Ayers, G., Donato, M., Champlin, R., Weber, D., et al. (2004). Comparison of high-dose melphalan with a more intensive regimen of thiotepa, busulfan, and cyclophosphamide for patients with multiple myeloma. *Cancer, 100,* 2607–2612.

Anderson, K.C. (2003). Moving disease biology from lab to the clinic. *Cancer, 97*(3, Suppl.), 796–801.

Anderson, K.C., Hamblin, T.J., & Traynor, A. (1999). Management of multiple myeloma today. *Seminars in Hematology, 36*(1, Suppl. 3), 3–8.

Attal, M., Harousseau, J.L., Facon, T., Guilhot, F., Doyen, C., Fuzibet, J.G., et al. (2003). Single versus double autologous stem-cell transplantation for multiple myeloma. *New England Journal of Medicine, 349,* 2495–2502.

Badros, A., Barlogie, B., Siegel, E., Morris, C., Desikan, R., Zangari, M., et al. (2001). Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. *British Journal of Haematology, 114,* 600–607.

Badros, A., Barlogie, B., Siegel, E., Roberts, J., Langmaid, C., Zangari, M., et al. (2001). Results of autologous stem cell transplant in multiple myeloma patients with renal failure. *British Journal of Haematology, 114,* 822–829.

Barlogie, B., Desikan, R., Eddlemon, P., Spencer, T., Zeldis, J., Munshi, N., et al. (2001). Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: Identification of prognostic factors in a phase 2 study of 169 patients. *Blood, 98,* 492–494.

Barlogie, B., Jagannath, S., Vesole, D.H., Naucke, S., Cheson, B., Mattox, S., et al. (1997). Superiority of tandem transplantation over standard therapy for previously untreated multiple myeloma. *Blood, 89,* 789–793.

Barlogie, B., Shaughnessy, J., Tricot, G., Jacobson, J., Zangari, M., Anaissie, E., et al. (2004). Treatment of multiple myeloma. *Blood, 103,* 20–32.

Barlogie, B., Tricot, G., & Anaissie, E. (2001). Thalidomide in the management of multiple myeloma. *Seminars in Oncology, 28,* 577–582.

Barosi, G., Boccadoro, M., Cavo, M., Corradini, P., Marchetti, M., Massaia, M., et al. (2004). Management of multiple myeloma and related-disorders: Guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO). *Haematologica, 89,* 717–741.

Bataille, R., & Harousseau, J.L. (1997). Multiple myeloma. *New England Journal of Medicine, 336,* 1657–1664.

Berenson, J.B., Lichtenstein, A., Porter, L., Dimopoulos, M.A., Bordoni, R., George, S., et al. (1996). Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *New England Journal of Medicine, 334,* 488–493.

Berenson, J.R., Hillner, B.E., Kyle, R.A., Anderson, K., Lipton, A., Yee, G.C., et al. (2002). American Society of Clinical Oncology clinical practice guidelines: The role of bisphosphonates in multiple myeloma. *Journal of Clinical Oncology, 20,* 3719–3736.

Blade, J., Sampson, D., Reece, D., Apperley, J., Bjorkstrand, B., Gahrton, G., et al. (1998). Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplant. *British Journal of Haematology, 102,* 1115–1123.

Body, J.J. (2003). Zoledronic acid: An advance in tumour bone disease therapy and a new hope for osteoporosis. *Expert Opinion on Pharmacotherapy, 4,* 567–580.

Bumm, K., Zheng, M., Bailey, C., Zhan, F., Chiriva-Internati, M., Eddlemon, P., et al. (2002). CGO: Utilizing and integrating gene expression microarray data in clinical research and data management. *Bioinformatics, 18,* 327–328.

Cancer pain relief and palliative care: Report of a WHO expert committee. (1990). *World Health Organization Technical Reports and Service, 804,* 1–75.

Catley, L., Weisberg, E., Tai, Y.T., Atadja, P., Remiszewski, S., Hideshima, T., et al. (2003). NVP-LAQ824 is a potent novel histone deacetylase inhibitor with significant activity against multiple myeloma. *Blood, 102,* 2615–2622.

Cavenagh, J.D., Curry, N., Stec, J., Drake, M., Morris, T.C.M., Agrawal, S., et al. (2004). PAD therapy (bortezomib, doxorubicin and dexamethasone) for untreated multiple myeloma (multiple myeloma) [Abstract 6550]. *Proceedings of the American Society of Clinical Oncology, 22,* 570s.

Chauhan, D., Catley, L., Hideshima, T., Li, G., Leblanc, R., Gupta, D., et al. (2002). 2-Methoxyestradiol overcomes drug resistance in multiple myeloma cells. *Blood, 100,* 2187–2194.

Chauhan, D., Uchiyama, H., Akbarali, Y., Urashima, M., Yamamoto, K., Libermann, T.A., et al. (1996). Multiple myeloma cell adhesion-induced interleukin-6 expression in bone marrow stromal cells involves activation of NF-kappa B. *Blood, 87,* 1104–1112.

Claudio, J.O., Masih-Khan, E., & Stewart, A.K. (2004). Insights from the gene expression profiling of multiple myeloma. *Current Hematology Reports, 3,* 67–73.

Colson, K., Doss, D.S., Swift, R., Tariman, J., & Thomas, T.E. (2004). Bortezomib, a newly approved proteasome inhibitor for the treatment of multiple myeloma: Nursing implications. *Clinical Journal of Oncology Nursing, 8,* 473–480.

Corral, L.G., Haslett, P.A., Muller, G.W., Chen, R., Wong, L.M., Ocampo, C.J., et al. (1999). Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *Journal of Immunology, 163,* 380–386.

Davies, F.E., Raje, N., Hideshima, T., Lentzsch, S., Young, G., Tai, Y.T., et al. (2001). Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood, 98,* 210–216.

Dimopoulos, M.A., Palumbo, A., Delasalle, K.B., & Alexanian, R. (1994). Primary plasma cell leukemia. *British Journal of Haematology, 88,* 754–759.

Dredge, K., Marriott, J.B., Macdonald, C.D., Man, H.W., Chen, R., Muller, G., et al. (2002). Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects. *British Journal of Cancer, 87,* 1166–1172.

Durie, B., & Stepan, D. (2001). Low dose thalidomide alone and in combination: Long term follow-up [Abstract 688]. *Blood, 98,* 163a.

Durie, B.G., & Salmon, S.E. (1975). A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. *Cancer, 36,* 842–854.

Durie, B.G., Salmon, S.E., & Moon, T.E. (1980). Pretreatment tumor mass cell kinetics and prognosis in multiple myeloma. *Blood, 55,* 364–372.

Fellowes, D., Barnes, K., & Wilkinson, S. (2004). Aromatherapy and massage for symptom relief in patients with cancer. *Cochrane Database of Systematic Reviews, 2,* CD002287.

Gautier, M., & Cohen, H.J. (1994). Multiple myeloma in the elderly. *Journal of American Geriatrics Society, 42,* 653–664.

Gupta, D., Treon, S.P., Shima, Y., Hideshima, T., Podar, K., Tai, Y.T., et al. (2001). Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: Therapeutic applications. *Leukemia, 15,* 1950–1961.

Harousseau, J.L., & Moreau, P. (2002). Prognostic factors in myeloma. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 169–183). London: Martin Dunitz.

Hayashi, T., Hideshima, T., & Anderson, K.C. (2003). Novel therapies for multiple myeloma. *British Journal of Haematology, 120,* 10–17.

He, Y., Wheatley, K., Clark, O., Glasmacher, A., Ross, H., & Djulbegovic, B. (2003). Early versus deferred treatment for early stage multiple myeloma. *Cochrane Database of Systematic Reviews, 1,* CD004023.

Hideshima, T., Chauhan, D., Shima, Y., Raje, N., Davies, F.E., Tai, Y.T., et al. (2000). Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. *Blood, 96,* 2943–2950.

Hussein, M. (2003). Pegylated liposomal doxorubicin, vincristine, and reduced-dose dexamethasone as first-line therapy for multiple myeloma. *Clinical Lymphoma, 4*(Suppl. 1), S18–S22.

Jagannath, S., Durie, B., Wolf, J., Camacho, E., Irwin, D., Lutzky, J., et al. (2004). First-line therapy with bortezomib (formerly PS-341) in patients with multiple myeloma (multiple myeloma) [Abstract 6551]. *Proceedings of the American Society of Clinical Oncology, 22,* 570s.

Kumar, S., Lacy, M.Q., Dispenzieri, A., Rajkumar, S.V., Fonseca, R., Geyer, S., et al. (2004). Single agent dexamethasone for pre-stem cell transplant induction therapy for multiple myeloma. *Bone Marrow Transplantation, 34,* 485–490.

Kyle, R.A. (2002). Diagnosis and treatment of multiple myeloma in the elderly. *Clinical Geriatrics, 10*(11), 47–56.

Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A., et al. (2003). Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings, 78,* 21–33.

Kyle, R.A., & Greipp, P.R. (1980). Smoldering multiple myeloma. *New England Journal of Medicine, 302,* 1347–1349.

Kyle, R.A., & Lust, J.A. (1996). Immunoglobulins and laboratory recognition of monoclonal proteins. In R.A. Kyle (Ed.), *Neoplastic diseases of the blood* (pp. 453–475). New York: Churchill Livingstone.

Kyle, R.A., & Rajkumar, S.V. (2001). Therapeutic application of thalidomide in multiple myeloma. *Seminars in Oncology, 28,* 583–587.

Lin, B., Podar, K., Gupta, D., Tai, Y.T., Li, S., Weller, E., et al. (2002). The vascular endothelial growth factor receptor tyrosine kinase inhibitor PTK787/ZK222584 inhibits growth and migration of multiple myeloma cells in the bone marrow microenvironment. *Cancer Research, 62,* 5019–5026.

Lokhorst, H. (2002). Clinical features and diagnostic criteria. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 151–168). London: Martin Dunitz.

Magagnoli, M., Castagna, L., Balzarotti, M., Sarina, B., Timofeeva, I., Bertuzzi, A., et al. (2003). Feasibility and toxicity of high-dose therapy (HDT) supported by peripheral blood stem cells in elderly patients with multiple myeloma and non-Hodgkin's lymphoma: Survey from a single institution. *American Journal of Hematology, 73,* 267–272.

Major, P., Lortholary, A., Hon, J., Abdi, E., Mills, G., Menssen, H.D., et al. (2001). Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. *Journal of Clinical Oncology, 19,* 558–567.

Maxwell, C., Swift, R., Goode, M., Doane, L., & Rogers, M. (2003). Advances in supportive care of patients with cancer and bone metastasis:

Nursing implications of zoledronic acid. *Clinical Journal of Oncology Nursing, 7,* 403–408.

Mehta, J. (2002). Allogeneic hematopoietic stem cell transplantation in myeloma. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 349–365). London: Martin Dunitz.

Mitsiades, C.S., Mitsiades, N.S., McMullan, C.J., Poulaki, V., Shringarpure, R., Hideshima, T., et al. (2004). Transcriptional signature of histone deacetylase inhibition in multiple myeloma: Biological and clinical applications. *Proceedings of National Academy of Sciences of the United States of America, 101,* 540–545.

Mitsiades, N., Mitsiades, C.S., Poulaki, V., Chauhan, D., Fanourakis, G., Gu, X., et al. (2002). Molecular sequelae of proteasome inhibition in human multiple myeloma cells. *Proceedings of National Academy of Sciences of the United States of America, 99,* 14374–14379.

Mooberry, S.L. (2003). New insights into 2-methoxyestradiol, a promising antiangiogenic and antitumor agent. *Current Opinion in Oncology, 15,* 425–430.

Munshi, N., Desikan, K., & Barlogie, B. (2000). Clinical experience with thalidomide in multiple myeloma: Phase II trials in refractory disease and ongoing studies. *Seminars in Hematology, 37*(Suppl. 3), 15–21.

National Comprehensive Cancer Network. (2004). *NCCN 2004 clinical practice guidelines in oncology: Multiple myeloma* [CD-ROM]. Jenkintown, PA: Author.

Ochiai, N., Uchida, R., Fuchida, S., Okano, A., Okamoto, M., Ashihara, E., et al. (2003). Effect of farnesyl transferase inhibitor R115777 on the growth of fresh and cloned myeloma cells in vitro. *Blood, 102,* 3349–3353.

Palmer, M., Belch, A., Hanson, J., & Brox, L. (1988). Dose intensity analysis of melphalan and prednisone in multiple myeloma. *Journal of the National Cancer Institute, 80,* 414–418.

Prevention of Pneumococcal disease: Recommendations of the advisory committee immunization practices (ACIP). (1997). *Morbidity and Mortality Weekly Report, 4*(46), 1–24.

Raje, N., & Anderson, K.C. (2002). Thalidomide and immunomodulatory drugs as cancer therapy. *Current Opinion in Oncology, 14,* 635–640.

Rajkumar, S.V., Blood, E., Vesole, D.H., Shepard, R., & Greipp, P.R. (2004). A randomized phase II trial of thalidomide plus dexamethasone versus dexamethasone in newly diagnosed multiple myeloma (E1A00): A trial coordinated by the Eastern Cooperative Group [Abstract 6508]. *Proceedings of the American Society of Clinical Oncology, 22,* 560s.

Rajkumar, S.V., Gertz, M.A., Kyle, R.A., & Greipp, P.R. (2002). Current therapy for multiple myeloma. *Mayo Clinic Proceedings, 77,* 813–822.

Rajkumar, S.V., & Greipp, P.R. (2002). Plasma cells and immunoglobulins. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 3–23). London: Martin Dunitz.

Rajkumar, S.V., Hayman, S., Gertz, M.A., Dispenzieri, A., Lacy, M.Q., Greipp, P.R., et al. (2002). Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *Journal of Clinical Oncology, 20,* 4319–4323.

Richardson, P., Jagannath, S., Schlossman, R.L., Weller, E., Zeldenrust, S., Rajkumar, V., et al. (2002). A multi-center, randomized, phase II study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma [Abstract 386]. *Blood, 100,* 104a.

Richardson, P., Schlossman, R.L., Hideshima, T., Davies, F.E., Leblanc, R., Catley, L., et al. (2001). A phase 1 study of oral CC5013, an immunomodulatory thalidomide (thal) derivative, in patients with relapsed and refractory multiple myeloma [Abstract 3225]. *Blood, 98,* 775a.

Richardson, P.G., Barlogie, B., Berenson, J., Singhal, S., Jagannath, S., Irwin, D., et al. (2003). A phase 2 study of bortezomib in relapsed, refractory myeloma. *New England Journal of Medicine, 348,* 2609–2617.

Richardson, P.G., Schlossman, R.L., Weller, E., Hideshima, T., Mitsiades, C., Davies, F., et al. (2002). Immunomodulatory drug CC5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood, 100,* 3063–3067.

Rosen, L., Harland, S.J., & Oosterlinck, W. (2002). Broad clinical activity of zoledronic acid in osteolytic to osteoblastic bone lesions in patients with a broad range of solid tumors. *American Journal of Clinical Oncology, 25*(6, Suppl. 1), S19–S24.

Rosen, L.S., Gordon, D., Kaminsky, M., Howell, A., Belch, A., Mackey, J., et al. (2003). Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: A randomized, double blind, multicenter, comparative trial. *Cancer, 98,* 1735–1744.

Samson, D., Gaminara, E., Newland, A., Van de Pette, J., Kearney, J., McCarthy, D., et al. (1989). Infusion of vincristine and doxorubicin with oral dexamethasone as first-line therapy for multiple myeloma. *Lancet, 2,* 882–885.

Santucci, R., Mackley, P.A., Sebti, S., & Alsina, M. (2003). Farnesyltransferase inhibitors and their role in the treatment of multiple myeloma. *Cancer Control, 10,* 384–387.

Schey, S.A., Fields, P., Bartlett, J.B., Clark, I.A., Ashan, G., Knight, R.D., et al. (2004). Phase I study of an immunomodulatory thalidomide analogue, CC-4047, in relapsed or refractory multiple myeloma. *Journal of Clinical Oncology, 22,* 3269–3276.

Siegel, D.S., Desikan, K.R., Mehta, J., Singhal, S., Fassas, A., Munshi, N., et al. (1999). Age is not a prognostic variable with autotransplants for multiple myeloma. *Blood, 93,* 51–54.

Singhal, S. (2002). High-dose therapy and autologous transplantation. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 327–347). London: Martin Dunitz.

Singhal, S., Mehta, J., Desikan, R., Ayers, D., Roberson, P., Eddlemon, P., et al. (1999). Antitumor activity of thalidomide in refractory multiple myeloma. *New England Journal of Medicine, 341,* 1565–1571.

Sirohi, B., Powles, R., Mehta, J., Treleaven, J., Raje, N., Kulkarni, S., et al. (2001). The implication of compromised renal function at presentation in myeloma: Similar outcome in patients who receive high-dose therapy: A single-center study of 251 previously untreated patients. *Medical Oncology, 18,* 39–50.

Skerjanec, A., Berenson, J., Hsu, C., Major, P., Miller, W.H., Jr., Ravera, C., et al. (2003). The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degree of renal function. *Journal of Clinical Pharmacology, 43,* 154–162.

Sonneveld, P., & Segeren, C.M. (2003). Changing concepts in multiple myeloma: From conventional chemotherapy to high-dose treatment. *European Journal of Cancer, 39,* 9–18.

Tariman, J.D. (2003a). Thalidomide: Current therapeutic uses and management of its toxicities. *Clinical Journal of Oncology Nursing, 7,* 143–147.

Tariman, J.D. (2003b). Understanding novel therapeutic agents for multiple myeloma. *Clinical Journal of Oncology Nursing, 7,* 521–528.

Tariman, J.D. (2005). Multiple myeloma. In C.H. Yarbro, M.H. Frogge, & M. Goodman (Eds.), *Cancer nursing principles and practice* (6th ed., pp. 1460–1489). Sudbury, MA: Jones and Bartlett

Tariman, J.D., & Lemoine, C. (2003). Bortezomib. *Clinical Journal of Oncology Nursing, 7,* 687–689.

Terpos, E., Apperley, J.F., Samson, D., Giles, C., Crawley, C., Kanfer, E., et al. (2003). Autologous stem cell transplantation in multiple myeloma: Improved survival in nonsecretory multiple myeloma but lack of influence of age, status at transplant, previous treatment and conditioning regimen. A single-centre experience in 127 patients. *Bone Marrow Transplantation, 31,* 163–170.

Terpos, E., Viniou, N., de la Fuente, J., Meletis, J., Voskaridou, E., Karkantaris, C., et al. (2003). Pamidronate is superior to ibandronate in decreasing bone resorption, interleukin-6 and beta 2-microglobulin in multiple myeloma. *European Journal of Haematology, 70,* 34–42.

Thompson, J.L., & Hansen, L.A. (2003). Thalidomide dosing in patients with relapsed or refractory multiple myeloma. *Annals of Pharmacotherapy, 37,* 571–576.

Vanderkerken, K., De Leenheer, E., Shipman, C., Asosingh, K., Willems, A., Van Camp, B., et al. (2003). Recombinant osteoprotegerin decreases tumor burden and increases survival in a murine model of multiple myeloma. *Cancer Research, 63,* 287–289.

Vescio, R., Schiller, G., Stewart, A.K., Ballester, O., Noga, S., Rugo, H., et al. (1999). Multicenter phase III trial to evaluate CD34(+) selected versus unselected autologous peripheral blood progenitor cell transplantation in multiple myeloma. *Blood, 93,* 1858–1868.

Weber, D., Rankin, K., Gavino, M., Delasalle, K., & Alexanian, R. (2003). Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *Journal of Clinical Oncology, 21,* 16–19.

Weber, D.M. (2003). A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of CC-5013 plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma: Protocol CC-5013-multiple myeloma-009. Retrieved December 20, 2004, from http://www.cro.lurie.northwestern.edu/Trials/MultipleMyeloma/MM_studies.htm

Wong, D.L. (1995). Health promotion of the infant and family. In D. Wilson (Ed.), *Nursing care of infants and children* (pp. 514–573). St. Louis, MO: Mosby.

Yakoub-Agha, I., Attal, M., Dumontet, C., Delannoy, V., Moreau, P., Berthou, C., et al. (2002). Thalidomide in patients with advanced multiple myeloma: A study of 83 patients—Report of the intergroupe francophone du myelome (IFM). *Hematology Journal, 3,* 185–192.

Zangari, M., Barlogie, B., Thertulien, R., Jacobson, J., Eddleman, P., Fink, L., et al. (2003). Thalidomide and deep vein thrombosis in multiple myeloma: Risk factors and effect on survival. *Clinical Lymphoma, 4,* 32–35.

Zeldis, J.B., Williams, B.A., Thomas, S.D., & Elsayed, M.E. (1999). S.T.E.P.S.: A comprehensive program for controlling and monitoring access to thalidomide. *Clinical Therapeutics, 21,* 319–330.

Zhan, F., Hardin, J., Kordsmeier, B., Bumm, K., Zheng, M., Tian, E., et al. (2002). Global gene expression profiling of multiple myeloma, monoclonal gammopathy of undetermined significance, and normal bone marrow plasma cells. *Blood, 99,* 1745–1757.

Zomas, A., & Dimopoulos, M.A. (2002). Conventional treatment of myeloma. In J. Mehta & S. Singhal (Eds.), *Myeloma* (pp. 313–326). London: Martin Dunitz.