Multiple myeloma is a clonal B-cell tumor of slowly proliferating plasma cells in the bone marrow, accounting for approximately 1% of all new cancers (Vescio & Berenson, 2000). In the United States, 19,900 new patients are expected to be diagnosed with multiple myeloma in 2007, with more than 10,000 deaths resulting from the disease annually (American Cancer Society, 2007). The age of people with multiple myeloma ranges from 20–100 years and beyond, but peak occurrence of the disease is among people in their 50s–70s (Jemal et al., 2006). The strongest potential risk factors include age, radiation, and agricultural exposures (Hussein, 1994). Although multiple myeloma is an incurable disease, better understanding of its biology has led to more treatment options, improved survival, and the development of new drugs, which currently are under investigation.

Hematologists and opinion leaders from around the world discussed some of the many innovative strategies currently under investigation for multiple myeloma, including pairing newer immunomodulatory and novel agents with older, standard drug therapies, at the 48th annual meeting of the American Society of Hematology (ASH) in December 2006, with updates in June 2007 at the 43rd annual meeting of the American Society of Clinical Oncology (ASCO) and the 11th International Myeloma Workshop (IMW). Clinical research was presented that may alter the current therapies administered to patients with newly diagnosed multiple myeloma, as well as those with relapsed or refractory disease. Such changes will have a significant effect on nursing and patient care. The aim of this article is to provide an overview of multiple myeloma, its current diagnosis and staging, and updated information about treatment research.

Multiple Myeloma: An Overview

Multiple myeloma is a cancer of the plasma cells in which abnormal plasma cells proliferate in the bone marrow, often resulting in bone lesions, hypercalcemia, anemia, and renal impairment. New therapeutic agents target the bone marrow microenvironment, which plays an important role in the development of malignant cells; the new treatment regimens may provide better outcomes than the current standard of care.

As new treatment regimens become available, oncology nurses will be at the front line, helping patients understand the benefits of treatment, how to manage side effects, and the importance of treatment adherence.

At a Glance

- Multiple myeloma is a cancer of the plasma cells in which abnormal plasma cells proliferate in the bone marrow, often resulting in bone lesions, hypercalcemia, anemia, and renal impairment.
- New therapeutic agents target the bone marrow microenvironment, which plays an important role in the development of malignant cells; the new treatment regimens may provide better outcomes than the current standard of care.
- As new treatment regimens become available, oncology nurses will be at the front line, helping patients understand the benefits of treatment, how to manage side effects, and the importance of treatment adherence.
Etiology

Little is known about the etiology of plasma cell dyscrasias, yet skeletal evidence of multiple myeloma has been obtained from Egyptian mummies (Hussein, 1994). One of the first case reports of multiple myeloma was described by Solly in 1844. He identified a 39-year-old housewife named Sarah Newbury who developed fatigue and back pain in 1842. Spontaneous fractures of her femurs and right humerus developed as her husband carried her into bed one evening. Despite an attempt to manage the disease with an infusion of orange peel, rhubarb pills, and opiates, she died suddenly. Autopsy revealed destruction of the femurs by myelomatous tumor.

Individuals entering Hiroshima, Japan, within three days of the 1945 nuclear blast had a 60% increased chance of dying from multiple myeloma, which suggests that radiation is a risk factor for developing the disease (Hussein, 1994). Chronic, low-level exposure to radiation may lead to increased risk as well. Occupational exposures to herbicides in the agriculture and farming communities also have been implicated as risk factors (Hussein; Sheridan & Serrano, 2000). A study by Brown et al. (1999) suggested that first-degree relatives of patients with multiple myeloma may have an increased incidence of developing the disease themselves, maybe as high as fourfold. Furthermore, more than 75 families have been described in the literature as having multiple myeloma (Vescio & Berenson, 2000), and the number is growing. Cytogenetic abnormalities may be an independent risk factor, but they also indicate prognosis, including chromosome 13 deletion and t(4;14) translocation (Tricot et al., 1997). Research into potential risk factors is ongoing, which will lead to a better understanding of the biology and complexity of multiple myeloma.

Plasma Cell Dyscrasias: Differential Diagnosis

Multiple myeloma often is suspected because of one or more clinical presentations of the disease noted asymptomatically during routine evaluation. Clinical presentations include anemia (which may be caused by vitamin deficiency or an altered bone marrow environment), hypercalcemia, increased serum total protein concentration, and elevated levels of serum creatinine. Other than fatigue, back pain or bone pain at other sites is the number-one presenting symptom that prompts people to seek medical care, leading to further investigational studies.

Serum or urine protein electrophoresis then may be performed; if a monoclonal protein is found, complete serum, urine, and radiologic testing follow. Based on the results, patients may fall into a category of monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, indolent multiple myeloma, plasma cytoma, plasma cell leukemia, or amyloidosis. Many factors should be taken into consideration at diagnosis and throughout the treatment continuum to correctly manage patients. Laboratory studies, such as serum or urine protein electrophoresis with monoclonal protein analysis, are critical in identifying the presence or absence of a monoclonal protein. Common tests, such as a complete blood count, may illustrate the presence of macrocytic anemia, leukopenia, or thrombocytopenia, which may suggest changes to the bone marrow environment or vitamin deficiencies. Obtaining a metabolic profile may show hypercalcemia, hyperuricemia, or renal impairment.

Bone marrow aspirate and biopsy are valuable tools at diagnosis to determine the extent of monoclonal plasmacytosis for known or strongly suspected multiple myeloma, assess iron stores and hematopoiesis, identify potential chromosomal abnormalities, or eliminate other diseases. Radiologic testing, such as complete bone survey to rule out lytic lesions, may identify bone loss as a result of cytokine release and osteoclast-stimulating factors from plasma cell activity. Beta-2-microglobulin levels generally are found to be elevated in patients with active multiple myeloma and, in conjunction with serum albumin measurements, represent a new staging system (described later). Cytogenetics and fluorescent in situ hybridization (FISH) testing (described later) are performed at baseline and at the end of therapy to evaluate disease status.

Staging

The staging of multiple myeloma, as with any hematologic or oncologic malignancy, provides a guide to prognosis and treatment. The Durie-Salmon staging system (see Table 1), in use since 1975, attempts to correlate measured multiple myeloma cell mass with presenting clinical features in response to treatment and survival (Durie & Salmon, 1975). More recently, another staging system has been developed and has become widely accepted. The International Myeloma Working Group reviewed criteria for the classification of multiple myeloma and related disorders from more than 10,000 patients on three continents and developed the International Staging System (see Table 2). The system uses only two measurements, serum beta-2-microglobulin and serum albumin, to predict median survival of several groups, staged I-III (Greipp et al., 2005).

The Bone Marrow Microenvironment

Researchers do not know at what point plasma cells turn malignant in multiple myeloma, but the bone marrow microenvironment plays an important role in cell development, as the multiple myeloma cells adhere to the bone marrow stroma. Newer therapeutic agents target those cells, and some genetic and molecular defects may contribute to the disease through its evolution. FISH analysis may find chromosomal changes and abnormalities in 80%–90% of patients with multiple myeloma. FISH is a molecular cytogenetic technique used to analyze genes, chromosomes, and their aberrations; it is highly specific. The technique can identify specific chromosomal areas by attachment of a probe to a targeted region of DNA. Recurrent translocations that could lead to the upregulation of oncogenes may be accountable for changing the biology of the disease. Pilarski, Mant, and Ruether (1985) reported the presence of myeloid and megakaryocytic antigens on the plasma cell clone, which suggests that multiple myeloma development may be programmed into cells prior to B-cell transformation. Chromosome 13 deletion and t(4;14) translocation, seen on FISH testing, have been noted to be negative prognosticators. Lenalidomide, thalidomide, and bortezomib have been reported to overcome the
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poor prognosis associated with these cytogenetic abnormalities (Malpas, Bergsagel, Kyle, & Anderson, 2004).

Cytokines, such as interleukin-6 (IL-6), have been implicated in multiple myeloma cell growth. IL-6 has been identified in vitro and in vivo as a major autocrine and paracrine growth factor in the development of multiple myeloma. The bone marrow stromal cells provide the ideal microenvironment for the malignant plasma cells to secrete large quantities of IL-6; the production is enhanced by the adhesion of multiple myeloma cells to stromal cell cultures. Some researchers have suggested that IL-6 appears to protect plasma cells from chemotherapy-induced apoptosis or cell death (Pelliniemi et al., 1995; Sheridan & Serrano, 2000; Vescio & Berenson, 2000). Tumor necrosis factor alpha has been found to protect multiple myeloma cells deprived of IL-6 from apoptosis and can induce the growth of some multiple myeloma cell lines. Immunomodulatory drugs, such as thalidomide and lenalidomide, may inhibit the cytokine, as well as signal T-cell proliferation associated with interferon gamma and interleukin-2 production (Davies et al., 2001; Vescio & Berenson). In addition, lenalidomide may overcome multidrug resistance in previously treated patients and is well tolerated in patients with multiple myeloma.

### Table 1. Durie-Salmon Staging System for Multiple Myeloma

<table>
<thead>
<tr>
<th>STAGE</th>
<th>CRITERIA</th>
<th>MEASURED MYELOMA CELL MASS (CELLS X 10^12/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All of the following:</td>
<td>&lt; 0.6 (low)</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin value &gt; 10 g/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Serum calcium value normal (≤ 12 mg/100 ml)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• On x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low M-component production rates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG value &lt; 5 g/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA value &lt; 3 g/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Urine light chain M-component on electrophoresis &lt; 4 g per 24 hours</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Fitting neither stage I nor stage III</td>
<td>0.6–1.20 (intermediate)</td>
</tr>
<tr>
<td>III</td>
<td>One or more of the following:</td>
<td>&gt; 1.20 (high)</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin value &lt; 8.5 g/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Serum calcium value &gt; 12 mg/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Advanced lytic bone lesions (scale 3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High M-component production rates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG value &gt; 7 g/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA value &gt; 5 g/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Urine light chain M-component on electrophoresis &gt; 12 g per 24 hours</td>
<td></td>
</tr>
</tbody>
</table>


### Treatment Options for Newly Diagnosed Multiple Myeloma

Increased knowledge of the complexity of the bone marrow microenvironment and how multiple myeloma cells evolve has provided several therapeutic options in terms of combining older, standard-of-care therapies with newer therapies. The options may include standard agents, such as oral melphalan and prednisone, combined with newer drugs, such as lenalidomide, thalidomide, liposomal doxorubicin, and bortezomib.

Clinical research presented at the 2006 meeting of ASH, the 2007 meeting of ASCO, and the 11th IMW showed newer therapeutic combinations to be well tolerated and effective in patients with multiple myeloma. An overview of the presented data is shown in Table 3 and will be described in more detail later in this article.

The Eastern Cooperative Oncology Group (ECOG) also presented noteworthy data on a phase II study using bortezomib (Dispenzieri, Zhang, Fonseca, Vesole, & Greipp, 2006). In high-risk patients, bortezomib as a first-line, single-agent therapy appeared to result in comparable response rates to those reported for unselected cohorts of patients with newly diagnosed multiple myeloma, with an overall response rate (ORR) of 49%. The most common adverse events of grade 3 or higher included neutropenia (33%), diarrhea (31%), hyponatremia (21%), anemia (19%), thrombocytopenia (16%), and fatigue (14%), but they were manageable.

Jagannath et al. (2006) reported long-term follow-up results of a multicenter study using bortezomib alone or in combination with dexamethasone in patients with newly diagnosed multiple myeloma. The trial had response rates of 90%, of which 19% of patients achieved a complete response (CR) or a near CR (nCR). At one year, the study found an 80% overall survival (OS) rate. The most common grade 2 adverse events for bortezomib and dexamethasone were sensory neuropathy and neuropathic pain (37%), fatigue (20%), constipation (16%), nausea (12%), and neutropenia (12%). Two patients developed grade 4 events (one neutropenia and one thrombocytopenia), but the regimen generally was well tolerated and effective for patients with newly diagnosed myeloma.

### Table 2. International Staging System for Multiple Myeloma

<table>
<thead>
<tr>
<th>STAGE</th>
<th>CRITERIA</th>
<th>MEDIAN SURVIVAL (MONTHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum beta-2-microglobulin &lt; 3.5 mg/l Serum albumin ≥ 3.5 g/dl</td>
<td>62</td>
</tr>
<tr>
<td>II</td>
<td>Not stage I or III</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>Serum beta-2-microglobulin ≥ 5.5 mg/l</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 3. Summary of Presented Data Regarding Patients Newly Diagnosed With Multiple Myeloma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Plan</th>
<th>Overall Response Rate</th>
<th>Major Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (Dispensieri et al., 2006)</td>
<td>Bortezomib 1.3 mg/m² on days 1, 4, 8, and 11, every 21 days for eight cycles as induction. Maintenance therapy consisted of bortezomib 1.3 mg/m² every other week indefinitely.</td>
<td>49%</td>
<td>Grade ≥ 3 adverse events: neutropenia (33%), diarrhea (31%), hyponatremia (21%), anemia (19%), thrombocytopenia (16%), and fatigue (14%)</td>
</tr>
<tr>
<td>Bortezomib with or without dexamethasone (Jagannath et al., 2006)</td>
<td>Bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 of a three-week cycle for as many as six cycles. Dexamethasone 40 mg by mouth was added on the day of and day after bortezomib for patients with less than partial response after four cycles.</td>
<td>90%</td>
<td>Grade ≥ 2 adverse events: sensory neuropathy and neuropathic pain (37%), fatigue (20%), constipation (16%), nausea (12%), and neutropenia (12%)</td>
</tr>
<tr>
<td>Bortezomib and pegylated liposomal doxorubicin (Orlowski, Peterson, et al., 2006)</td>
<td>Bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 of every 21-day cycle, along with doxorubicin 30 mg/m² on day 4, for a maximum of eight cycles</td>
<td>58%</td>
<td>Grade 3 and 4 adverse events, respectively: neutropenia (16% and 2%), fatigue (16% and none), sensory neuropathy (11% and 2%), thrombocytopenia (9% and 5%), hand-foot syndrome (9% and none), and anemia (7% and 2%)</td>
</tr>
<tr>
<td>Thalidomide plus dexamethasone (Rajkumar et al., 2006)</td>
<td>Thalidomide 50 mg by mouth daily, escalated to 100 mg on day 15 and to 200 mg from day 1 of cycle 2 plus dexamethasone 40 mg by mouth on days 1–4, 9–12, and 17–20</td>
<td>59%</td>
<td>Grade ≥ 3 adverse events: venous thromboembolism (18%), myocardi al ischemia (4%), cerebral ischemia (3%), and neuropathy (3%)</td>
</tr>
<tr>
<td>Lenalidomide plus dexamethasone (Lacy et al., 2006)</td>
<td>Lenalidomide 25 mg by mouth daily on days 1–21 of a 28-day cycle. Dexamethasone 40 mg by mouth daily on days 1–4, 9–12, and 17–20 of each cycle</td>
<td>91%</td>
<td>Grade ≥ 3 adverse events: fatigue (21%), neutropenia (21%), anxiety (6%), pneumonitis (6%), muscle weakness (6%), and rash (6%)</td>
</tr>
<tr>
<td>Lenalidomide plus low-dose dexamethasone (Rajkumar et al., 2007)</td>
<td>Lenalidomide 25 mg by mouth daily on days 1–21 of a 28-day cycle. Dexamethasone 40 mg by mouth daily on days 1–4, 9–12, and 17–20 (high dose), or 40 mg daily on days 1, 8, 15, and 22 (low dose)</td>
<td>Not reported; overall survival was 86% (high dose) versus 97% (low dose)</td>
<td>Grade ≥ 3 adverse events with high dose versus low dose, respectively: venous thromboembolism (22% and 6%), infection and pneumonia (16% and 8%), and hyperglycemia (10% and 7%)</td>
</tr>
<tr>
<td>Lenalidomide plus melphalan and prednisone (Palumbo, Falco, et al., 2006)</td>
<td>Melphalan 0.18 mg/kg plus lenalidomide 10 mg per day</td>
<td>85%</td>
<td>Most common adverse events: neutropenia (66%), thrombocytopenia (34%), and anemia (17%). The major grade 3–4 nonhematologic toxicity was rash (10%).</td>
</tr>
<tr>
<td>Clarithromycin plus lenalidomide and dexamethasone (Niesvizky et al., 2007)</td>
<td>Dexamethasone 40 mg by mouth on days 1, 2, 3, 8, 15, and 22 during cycle 1 and weekly on days 1, 8, 15, and 22 of each subsequent cycle. Clarithromycin 500 mg by mouth twice a day beginning on day 2 of cycle 1. Lenalidomide 25 mg by mouth daily on days 3–21 of cycle 1 and on days 1–21 of subsequent cycles</td>
<td>88%</td>
<td>Manageable toxicities; no further details reported</td>
</tr>
</tbody>
</table>

Orlowski, Peterson, et al. (2006) presented data on a steroid-free regimen using bortezomib and liposomal doxorubicin in 63 patients with newly diagnosed multiple myeloma. The preliminary ORR was 58% (compared with 40% with bortezomib alone), with a 16% CR or nCR rate. Hematologic adverse events included neutropenia (grade 3 in 16% and grade 4 in 2% of patients), thrombocytopenia (9% and 5%, respectively), and anemia (7% and 2%, respectively); only one episode of febrile neutropenia occurred. Noteworthy nonhematologic toxicities included fatigue (grade 3 in 16%, grade 4 in none), sensory neuropathy (11% and 2%, respectively), and hand-foot syndrome (9% and none, respectively). Overall, the steroid-free regimen appeared to be effective and generally well tolerated in newly diagnosed patients.

Rajkumar et al. (2006) presented data from the MM-003 trial, in which 235 patients were randomized to thalidomide plus dexamethasone (arm A) and 235 patients to placebo plus dexamethasone (arm B). Patients in arm A received 50 mg of oral thalidomide daily, which was escalated to 100 mg on day 15 of a 28-day cycle and to 200 mg from day 1 of cycle 2. Oral dexamethasone 40 mg was given on days 1–4, 9–12, and 17–20. Patients in arm B received placebo instead of thalidomide, and...
oral dexamethasone 40 mg on days 1–4, 9–12, and 17–20, as in arm A. The combination of thalidomide and dexamethasone provided better ORR than dexamethasone alone (59% versus 42%, respectively) and a longer median time to progression (TTP) (not yet reached versus 8.1 months, respectively). Grade 3 or higher venous thromboembolism (VTE) complications also were higher with the combination of thalidomide and dexamethasone.

Lacy et al. (2006) presented data from the Lenalidomide Plus Dexamethasone (Rev/Dex) in Newly Diagnosed Multiple Myeloma Trial, which showed a response rate of 91%; of those, 56% had a complete remission or very good partial response (VGPR). For patients not proceeding to stem cell transplantation, complete remission or VGPR was 67%. At two years, the progression rate remained low. Fifty-five percent of patients experienced grade 3 or higher nonhematologic toxicity at some point during therapy, most commonly fatigue (21%) and neutropenia (21%). One of the 34 patients developed a pulmonary embolism (grade 4 toxicity) but recovered with therapy; no other patient developed VTE.

Interestingly, Rajkumar et al. (2007) presented data from another ECOG trial, which compared treatment with lenalidomide plus high-dose dexamethasone (40 mg orally on days 1–4, 9–12, and 17–20) to lenalidomide plus low-dose pulsed dexamethasone (40 mg orally on days 1, 8, 15, and 22). Major grade 3 or higher toxicities after lenalidomide plus high-dose or low-dose dexamethasone included infection and pneumonia (16% versus 8%, respectively) and hyperglycemia (10% versus 7%). Overall, grade 3 or higher nonhematologic toxicities occurred in 66% versus 55% of patients, respectively. The study design did not require VTE prophylaxis, but because of the 22% incidence of grade 3 or higher VTE with high-dose pulsed dexamethasone, the use of aspirin, warfarin, or low-molecular-weight heparin was suggested. The incidence of grade 3 or higher VTE with low-dose dexamethasone was 6%. Besides having a more favorable safety profile, the combination of lenalidomide plus low-dose dexamethasone also showed a significantly superior OS rate (97% versus 86% with high-dose dexamethasone). The survival benefit was seen in patients younger and older than 65 years.

Palumbo, Falco, et al. (2006) from the Italian Multiple Myeloma Group presented results from a phase I/II trial using lenalidomide plus melphalan and prednisone (R-MP) in 53 newly diagnosed patients who were not candidates for stem cell transplantation. Early interim analysis suggested that, compared with previous data from thalidomide plus melphalan and prednisone (T-MP) or melphalan plus prednisone alone (MP) (Palumbo, Bringhen, et al., 2006), the R-MP regimen yielded earlier response rates and longer overall event-free survival (83% at 20 months), with significantly increased CR (24% with R-MP in patients receiving the maximum tolerated dose [0.18 mg/kg melphalan and 10 mg lenalidomide; N = 21], 16% with T-MP, and 2% with MP). The most common adverse events were hematologic toxicities: neutropenia (66%), thrombocytopenia (34%), and anemia (17%); the major grade 3–4 nonhematologic toxicity was rash (10%). The responses with lenalidomide were independent of several traditional predictors of poor prognosis, such as chromosome 13 deletion or t(4;14) translocation.

Niesvizky et al. (2007) presented results of a trial using a combination of clarithromycin, lenalidomide, and dexamethasone. The treatment resulted in a CR of 31%, an nCR of 10%, and a VGPR of 22%, with manageable toxicities in the 72 patients enrolled. The researchers concluded that the results suggest that lenalidomide-based therapy can be used long term in selected patient populations, when high-dose chemotherapy is declined.

Treatment Options for Relapsed or Refractory Multiple Myeloma

Patients with multiple myeloma present a unique challenge, especially those who have received stem cell transplantsations, have received multiple prior therapies, or have poorer performance status. For such patients, more therapeutic options now are available; Table 4 provides an overview of presented data.

Recent pooled final data from two phase III studies investigating the efficacy and safety of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma have been presented. The results showed that patients treated with the combination had significantly improved TTP (median = 48 versus 20 weeks), ORR (61% versus 22%), and OS (median = 35 versus 31 months) compared with those treated with dexamethasone alone (Anagnostopoulos et al., 2007). The clinical benefit of lenalidomide was present even in patients who relapsed or were refractory to prior thalidomide (Wang et al., 2007). Also, older and young patients were shown to benefit equally from lenalidomide treatment (Chanani-Khan, Weber, et al., 2006; Lonial et al., 2007). Patients with renal impairment had a higher rate of grade 3–4 thrombocytopenia compared to patients with a normal creatinine level, but the incidence of grade 3–4 neutropenia was similar. Overall, however, lenalidomide with or without corticosteroids appeared to be safe in patients with an elevated serum creatinine level, and the response rate, progression-free survival, and their OS seemed to be similar to that of patients with normal serum creatinine levels (Reece et al., 2006). These and other data on the efficacy and safety of lenalidomide in relapsed or refractory multiple myeloma were summarized and presented by Weber (2007).

Knop et al. (2007) presented preliminary study results from a trial using lenalidomide plus adriamycin and dexamethasone intensively in patients with pretreated myeloma. The treatment resulted in a promising ORR of 78%, including CR or nCR in 76% of patients. The incidence of grade 3 or higher toxicity was very acceptable, and no treatment-related mortality, somnolence, constipation, or neuropathy was observed.

Richardson et al. (2006) presented promising phase I study results using lenalidomide plus bortezomib in a heavily pretreated group. The combination therapy showed a 58% response rate, including a CR or nCR rate of 6%, and was relatively well tolerated. In the small trial, no significant (grade 3 or higher) fatigue or peripheral neuropathy was noted, and no antiagulant prophylaxis was required.

Richardson et al. (2007) presented preliminary data from a phase II trial of lenalidomide plus bortezomib and dexamethasone. In 10 evaluable patients, the ORR currently is 50%. No significant (grade 3 or higher) fatigue, VTE, or peripheral neuropathy has been reported. The dexamethasone dose had
to be reduced in most patients, but the combination has been otherwise well tolerated.

Orlowski, Zhuang, et al. (2006) and Harousseau et al. (2007) discussed the results of an international phase III trial (DOXIL-MY-3001) of bortezomib plus liposomal doxorubicin, compared with bortezomib alone, in 646 patients with relapsed or refractory multiple myeloma. Although the combination therapy showed an increase in toxicity compared with single-agent bortezomib therapy, it also showed significantly better duration of response (10.2 versus 7.0 months) and TTP (9.3 versus 6.5 months). The benefit of the combination also was demonstrated to be independent of age (San Miguel et al., 2007), prior stem cell transplantation (Nagler et al., 2007), prior thalidomide (Sonneveld, Hajek, et al., 2007a), prior stem cell transplantation (Nagler et al., 2007; San Miguel et al., 2007), and beta-2-microglobulin level (Spencer et al., 2007).

Chanan-Khan, Padmanabhan, et al. (2006) presented data from a phase II study of bortezomib, liposomal doxorubicin, and thalidomide in patients with relapsed or refractory disease who previously were treated with a median of five therapies, given as a steroid-free regimen. The heavily pretreated group had an ORR of 65%, with 23% complete remissions, as illustrated by negative paraprotein by immunofixation; overall, the treatment was very well tolerated.

### Table 4. Summary of Presented Data Regarding Patients With Relapsed or Refractory Multiple Myeloma

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>TREATMENT PLAN</th>
<th>OVERALL RESPONSE RATE</th>
<th>MAJOR TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide plus dexamethasone (Anagnostopoulos et al., 2007; Weber, 2007) (subgroups in Chanan-Khan, Weber, et al., 2006; Lonial et al., 2007; Reece et al., 2006; Wang et al., 2007)</td>
<td>Lenalidomide 25 mg by mouth daily for 21 days and dexamethasone 40 mg by mouth on days 1–4, 9–12, and 17–20</td>
<td>61%</td>
<td>Grade 3 or higher adverse events; no absolute values specifically reported, but included neutropenia, thrombocytopenia, anemia, pneumonia, and venous thromboembolism</td>
</tr>
<tr>
<td>Lenalidomide plus doxorubicin and dexamethasone (Knop et al., 2007)</td>
<td>Lenalidomide 25 mg on days 1–21 in combination with doxorubicin 9 mg/m² on days 1–4 (continuous infusion) and dexamethasone 40 mg on days 1–4 and 17–20</td>
<td>83%</td>
<td>Grade 3 or higher adverse events; no treatment-related mortality, somnolence, constipation, or neuropathy was observed</td>
</tr>
<tr>
<td>Lenalidomide plus bortezomib (Richardson et al., 2006)</td>
<td>Lenalidomide 15 mg on days 1–14 and bortezomib 1.0 mg/m² on days 1, 4, 8, and 11</td>
<td>58%</td>
<td>Grade 3 or higher adverse events; no significant fatigue or peripheral neuropathy</td>
</tr>
<tr>
<td>Lenalidomide plus bortezomib and dexamethasone (Richardson et al., 2007)</td>
<td>As many as eight 21-day cycles of bortezomib 1.0 mg/m² on days 1, 4, 8, and 11; lenalidomide 15 mg on days 1–14; and dexamethasone 40 mg (cycles 1–4), followed by 20 mg (cycles 5–8) on days of or after bortezomib dosing</td>
<td>50%</td>
<td>Grade 3 or higher adverse events; no fatigue, venous thromboembolism, or peripheral neuropathy. Two episodes of grade 3 atrial fibrillation, which was reversible with cardiac medication</td>
</tr>
<tr>
<td>Bortezomib plus pegylated liposomal doxorubicin (Harousseau et al., 2007; Orlowski, Zhuang, et al., 2006) (subgroups in Nagler et al., 2007; San Miguel et al., 2007; Sonneveld, Hajek, et al., 2007; Spencer et al., 2007)</td>
<td>Bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 of every 21-day cycle and doxorubicin 30 mg/m² on day 4</td>
<td>48%</td>
<td>Grade 3 or higher adverse events: myelosuppression and gastrointestinal toxicities; no further details were reported.</td>
</tr>
<tr>
<td>Bortezomib plus liposomal doxorubicin and thalidomide (Chanan-Khan, Padmanabhan, et al., 2006)</td>
<td>Bortezomib 1.3 mg/m² on days 1, 4, 15, and 18. Doxorubicin 20 mg/m² on days 1 and 15 every four weeks. Thalidomide 200 mg for 4–6 cycles</td>
<td>65%</td>
<td>Two patients developed grade 2 palmar-plantar erythrodysthesia, and one patient had grade 3 cellulitis. No venous thromboembolism was noted, and no significant nonhematologic grade 3 toxicity was seen.</td>
</tr>
</tbody>
</table>

### Better Understanding of Novel Therapies

Phase III randomized, controlled trials are essential to identify which newer agents are superior to current standard-of-care regimens. Ongoing clinical research has identified certain agents that may be effective by themselves or in combination with other therapies, that may provide better outcomes than what currently is considered the standard of care for treatment of multiple myeloma. For example, the National Comprehensive Cancer Network (2007) recommended the use of the combination of vincristine, adriamycin, and dexamethasone or melphalan plus prednisone in patients with newly diagnosed multiple myeloma (see Figure 1). However, with the new immunomodulatory agents, such as lenalidomide and thalidomide, and the proteasome inhibitor bortezomib, clinical research will continue to provide valuable information that may replace older therapies with regimens such as T-MP or R-MP in patients who are not candidates for stem cell transplantation. In patients who are candidates for stem cell transplantation, thalidomide plus dexamethasone, bortezomib plus dexamethasone, or lenalidomide plus dexamethasone may provide better response rates and less toxicity than current standard regimens. Although the
efficacy and tolerability of several regimens have been described in this article, future clinical trial results will yield data to support an evidence-based approach to managing patients with myeloma in years to come.

Managing Adverse Events

The nursing care of patients with myeloma has evolved significantly with the advent of novel agents, which may produce different side-effect profiles than traditional chemotherapeutic agents. Although patients may benefit from increased OS, they may experience different side effects related to the disease or treatment. Side effects of traditional chemotherapy, such as nausea and vomiting, also are seen with newer agents and respond to treatment with prophylactic antiemetics, as well as those used for acute and delayed nausea and vomiting. Fatigue, an adverse effect that may be related to disease or treatment, often is debilitating to patients. Peripheral neuropathy that is seen with bortezomib and thalidomide often is irreversible, and dose adjustments may be made to protect nerve function. Nurses may refer to the Oncology Nursing Society Putting Evidence Into Practice® resources for strategic recommendations in treating fatigue (Mitchell, Beck, Hood, Moore, & Tanner, 2005), nausea and vomiting (Tipton et al., 2005), and peripheral neuropathy (Visovsky, Collins, Hart, Abbott, & Aschenbrenner, 2005) that may be seen with novel therapies.

Osteonecrosis of the Jaw

Bisphosphonates remain the treatment of choice for hypercalcemia of malignancy and have become an integral part of the current treatment of skeletal lesions, reducing the incidence of skeletal-related complications and delaying their onset (Berenson et al., 1998). In addition, bisphosphonates may reduce tumor burden by making the bone microenvironment a less favorable site for the growth of tumor cells. Because this class of drugs, when used as prophylaxis, may reduce bone pain, delay the onset of fractures, and reduce fracture incidence in patients who already have osteolytic disease, it is recommended by the National Comprehensive Cancer Network (2007) supportive care guidelines for managing patients with multiple myeloma.

Many retrospective studies have focused on the use of long-term bisphosphonates and the risk of osteonecrosis of the jaw; although the mechanism of multiple myeloma–related lytic bony disease is believed to be secondary to increased osteoclastic activity and impaired osteoblastic activity, little is understood about how the condition develops (Mehrotra & Ruggiero, 2006). The long-term use of bisphosphonates, such as pamidronate and zoledronic acid, has been linked to this condition at a rate of 2% for less than a year of therapy and 12% with continuing therapy. Patients receiving or considering bisphosphonate therapy should be made aware of the risk of osteonecrosis of the jaw, advised to avoid invasive dental procedures and maintain good oral health, and monitored regularly for osteonecrosis of the jaw by dental and oncology healthcare professionals.

Venous Thromboembolism

Patients with multiple myeloma have an increased risk of VTE because of many factors, including the biology of the disease and inactivity caused by pain or fatigue. In addition, newer agents, such as the immunomodulators and their combinations, also increase the risk of VTE in patients with multiple myeloma. The baseline risk of VTE in patients with multiple myeloma is hard to quantify but is believed to be 5%–10%. Several prophylactic strategies have been effective in lowering the risk of developing VTE, including daily aspirin (81–325 mg per day), full-intensity warfarin (to target international normalized ratio 2–3), and prophylactic enoxaparin (40 mg per day subcutaneously). Low, fixed-dose warfarin also may reduce the risk of VTE, but the data are inconclusive.

Side Effects of Novel Therapies

Lenalidomide

Lenalidomide, a structural analog of thalidomide belonging to a class of drugs called immunomodulatory agents, carries a different side-effect profile than many existing chemotherapy agents. Approved by the U.S. Food and Drug Administration (FDA) for patients with relapsed or refractory multiple myeloma, lenalidomide is administered orally, at a dose of 25 mg daily, for 1–21 days of a 28-day cycle. Common nonhematologic toxicities include fatigue and constipation; hematologic toxicities include anemia, leukopenia, and thrombocytopenia (Doss, 2006). Because of a potential for cumulative myelosuppression, once a patient starts lenalidomide, blood counts should be monitored at least every two weeks (Sonneveld, Dimopoulos, et al., 2007).

Growth factors, such as granulocyte-colony-stimulating factor, may be administered if neutropenia develops, and erythropoietic stimulating agents may be given to patients to maintain their hemoglobin at 12 g/dl (Sonneveld, Dimopoulos, et al.).

Primary Conventional Chemotherapy

- Melphalan plus prednisone
- Vincristine plus adriamycin plus dexamethasone (VAD)
- Dexamethasone
- Thalidomide plus dexamethasone
- Liposomal doxorubicin plus vincristine plus dexamethasone

Maintenance Therapy

- Steroids (50 mg prednisone every other day)
- Interferon

Salvage Therapy

- Repeat primary conventional therapy (if relapse at > 6 months)
- Lenalidomide plus high-dose steroids
- Cyclophosphamide and VAD
- High-dose cyclophosphamide
- Thalidomide with or without dexamethasone (consider prophylactic anticoagulation)
- Bortezomib
- DT-PACE (dexamethasone, daily thalidomide, and four days of continuous-infusion cisplatin, doxorubicin, cyclophosphamide, and etoposide) (consider prophylactic anticoagulation)
- Arsenic trioxide plus vitamin C
- High-dose steroids
Also important to note is the high incidence of VTE in patients receiving lenalidomide in combination with high-dose dexamethasone and other therapies, such as pegylated doxorubicin. Nurses should assess each patient’s risk factors for VTE, which may include advanced age, sedentary lifestyle, prior blood clot, smoking, or genetic mutations such as factor V Leiden. Anticoagulation should be considered for all patients with risk factors who are receiving lenalidomide (Palumbo et al., 2007; Zonder, 2006). In addition, regardless of patients’ coagulation status, nurses should educate them regarding the possibility of VTE and primary prevention strategies, such as being active, maintaining oral hydration, and monitoring the signs of blood clot, such as calf tenderness and unilateral swelling (Doss, 2006).

Bortezomib

A proteasome inhibitor, bortezomib is in a class of its own. Proteasomes are enzymes found inside the nucleus of all cells, responsible for the regulation and degradation of proteins. Cancerous cells depend on proteins regulated by the proteasome for proliferation, metastasis, and survival. When the proteasome is inhibited, protein degradation and signaling within cancer cells are blocked. Normal cells can recover, but cancerous cells are unsuccessful and do not survive (Colson, Doss, Swift, Tari- man, & Thomas, 2004). The FDA approved its use for relapsed multiple myeloma in patients who have failed more than one prior therapy. The drug also can be given safely to patients with renal insufficiency or renal impairment. The most common side effects of bortezomib include thrombocytopenia and peripheral neuropathy, but diarrhea also is common. Thrombocytopenia will be the lowest on day 11 of bortezomib administration. Oftentimes, in the presence of a normal bone marrow environment, blood platelet counts will recover to near-normal levels by the next cycle. Peripheral neuropathy usually is reversible and improves with lower dosage adjustments (Millennium Pharmaceuticals, Inc., 2007). Patients should be encouraged to report adverse effects, such as painful neuropathy, easy bruising, or bleeding related to low platelet counts, so that appropriate modifications can be made before the effects interfere with quality of life (Colson et al.).

Thalidomide

Thalidomide has emerged as a very effective oral agent in the treatment of myeloma, either alone, for maintenance after stem cell transplantation, or in combination with other therapies. Common adverse effects of thalidomide include fatigue, somnolence, constipation, and rash; they often are dose dependent (Doss, 2006). To help combat fatigue and somnolence, patients can use evening dosing and avoid alcohol and other medications that can cause sedation. Constipation is less common with lower doses of thalidomide and may be prevented with a high-fiber diet and a bowel regimen containing bulk-forming laxatives as well as stool softeners.

Peripheral neuropathy may occur with long-term use and often is irreversible. This is more of a concern now with other emerging therapies that may cause neuropathy, such as bortezomib. Assessing for signs and symptoms of neuropathy, including numbness in fingers and toes, and performing a baseline sensory assessment are important nursing interventions. In addition, nurses should instruct patients to protect their extremities from extreme temperature changes and that dose reductions may be considered to decrease the severity of symptoms. Patients may be at decreased risk of developing peripheral neuropathy when using thalidomide in lower doses. Patients should be advised to report symptoms of neuropathy as soon as they are noted. Hematologic adverse reactions are rare, but thalidomide should not be administered if the absolute neutrophil count is below 750 mm$^3$ (Celgene Corporation, 2007). As with lenalidomide, treatment with thalidomide is associated with a higher risk for VTE. Anticoagulation should be considered for all patients with VTE risk factors receiving thalidomide, especially those on regimens with other contributing factors for VTE, such as erythropoietin (Zonder, 2006).

Implications for Oncology Nursing

The side-effect profiles of novel agents can be compounded once combination therapy is initiated, but they often are predictable and remain manageable. Regimens combining newer agents may yield an increase in cumulative toxicity; however, nurses must be aware of the risks and benefits of all regimens and educate patients about newer side-effect profiles and potentially life-threatening complications to therapy of which they may not be aware, such as deep vein thrombosis and hematologic toxicity. Prophylaxis of deep vein thrombosis is critical in high-risk populations, such as those on high doses of steroids, those receiving anthracycline chemotherapy, and those with a history of thrombus or other blood-clotting defects. Hematologic toxicity also is common with other chemotherapeutic regimens and will respond to appropriate dose adjustments and hematopoietic growth factors, as indicated. If the toxicities are severe, dosage adjustments may be required.

Gastrointestinal effects of novel agents, such as nausea, vomiting, diarrhea, and constipation, may be relieved with similar interventions as those with chemotherapy. Prophylactic antiemetics with bortezomib and a strict bowel regimen for patients on thalidomide are important to maintaining patients’ sense of well-being.

Other toxicities that should be discussed with patients may not focus on novel therapies but may relate to existing supportive care, such as osteonecrosis of the jaw related to bisphosphonate use. Baseline and routine dental examinations, good oral hygiene, and prompt reporting of symptoms may help to decrease severity.

Each patient with multiple myeloma is unique and provides oncology nurses with an opportunity to help improve the group’s OS by reviewing the therapeutic plan of care, establishing goals of therapy, and providing interventions that may help them adhere to prescribed therapies. Hopefully, research will be able to identify a regimen with low toxicity that will achieve maximum benefit. Until then, specialized nurses must attempt to have a better understanding of the biology of the disease and the side effects of therapy and to educate patients regarding the side effects of different regimens in an attempt to improve patient outcomes and adherence to treatment plans.

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