Multiple Myeloma: An Overview

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Multiple myeloma (MM) is a plasma cell neoplasm accounting for 1% of all malignancies and 14% of malignant hematologic disorders (Jemal et al., 2004). It is characterized as a B cell malignancy with an increased production of one of the immunoglobulins and can present with skeletal, hematologic, renal, and neurologic complications. Compared to other hematologic malignancies, MM is less common, but recent developments of new therapies have heightened awareness and education. This article addresses etiology, pathophysiology, signs and symptoms, treatment options, and nursing implications.

Etiology, Incidence, and Risk Factors

About 15,270 new cases of MM are diagnosed each year, and MM causes approximately 11,070 deaths per year (Jemal et al., 2004). The annual incidence rate is about 4 per 100,000 people, with the incidence for African Americans almost twice that of Caucasians (Zaidi & Vesole, 2001). The median age at diagnosis is 65 years, and fewer than 3% of patients are younger than 40 years (Blade & Kyle, 1998).

The exact etiology of MM remains unknown. Although several risk factors are thought to be associated with the disease, no evidence exists to suggest a hereditary basis (George & Sadovsky, 1999). Exposure to ionizing radiation and pesticides (such as dioxin) has been identified as a risk factor for MM (Durie, 2001). MM is more common in farmers, wood and leather workers, and those exposed to petroleum products (Sheridan, 1996). Viruses such as human herpes 8 and simian virus 40 have been described in the pathogenesis of MM (Rettig et al., 1997). In addition, exposure to Agent Orange and HIV have been associated with MM (Zaidi & Vesole, 2001). Chromosomal translocations typically are seen in MM cell lines (Kaufmann, Urbauer, Ackermann, Huber, & Drach, 2001). Prevention measures may be forthcoming when etiologies of MM are more fully understood.

Pathophysiology

Knowledge of MM requires an understanding of normal hematopoiesis. All immune cells begin in the pluripotent stem cell, which has the ability to replicate or differentiate into either lymphoid or myeloid lineages. The myeloid lineage further differentiates into platelets, neutrophils, eosinophils, and basophils; the lymphoid stem cell divides into either T or B lymphocytes. B lymphocytes mature into immunoglobulin-producing plasma cells, which are responsible for humoral immunity. Each immunoglobulin is a protein consisting of four polypeptide chains, two light chains and two heavy chains. The light chains are kappa and lambda, and the heavy chains define the five classes of immunoglobulins: IgG, IgA, IgM, IgE, and IgD. Each immunoglobulin has a particular role and function in the immune response (see Table 1). In MM, an abnormal overproduction of one of these immunoglobulins occurs, with IgG being the most common (Harousseau, 2002) (see Table 1). This overproducing protein is referred to as the M protein, meaning the monoclonal protein or the myeloma protein.

The establishment of MM cells in bone marrow involves a complex interaction with the bone microenvironment. MM cells establish themselves by binding to bone marrow stromal cells, giving them a growth and survival advantage. This advantage comes from resistance to drug-induced apoptosis and an interaction leading to increased cytokine and interleukin-6 (IL-6) secretion. IL-6 has proven to be a significant MM growth and survival factor (Anderson, 2001, 2002). Current research efforts and novel therapies in MM are targeting this interaction between the bone microenvironment and MM cells. The advancement of novel therapies will rely on the pathophysiology and further understanding of the etiology of the disease.

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Diagnosis and Prognosis

The hallmark feature in the diagnosis of MM is described as a tall, narrow-based monoclonal-spike (M-spike) on electrophoresis of blood serum or urine. This M-spike in MM is indicative of an overproduction of an immunoglobulin (i.e., IgG, IgA, IgM, IgE, or IgD). Bence Jones proteinuria or light chains may be evident on urine dipsticks or 24-hour urine protein electrophoresis. Another hallmark feature for the diagnosis of myeloma is plasmacytosis (>10% plasma cells) on bone marrow biopsy. Anemia, leukopenia, thrombocytopenia, hypercalcemia, and elevated creatinine are common laboratory features seen in MM (see Table 2).

Appropriate diagnosis of MM is essential. Among the differential diagnoses of MM are monoclonal gammopathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM) (see Table 3). MGUS is a clinically benign condition of the plasma cell and does not require treatment, although an approximate 1% increased risk exists per year of progressing to myeloma (Harousseau, 2002). SMM usually does not require treatment initially but can be expected to progress to symptomatic MM, rendering the necessity of treatment. The median time to progression of SMM is two years, but it varies from months to years (Rajkumar, Kyle, & Gertz, 2002). MGUS and SMM can produce anxiety and psychosocial issues related to the uncertainty of disease course.

Survival with MM ranges from less than a year to more than 10 years. No known cure for MM exists, and the median survival is about 42 months (Harousseau, 2002). High-dose treatment followed by autologous stem cell transplantation increases survival but is not a cure (Attal et al., 1996). Figure 1 outlines favorable prognostic indicators, which can lead to longer disease-free intervals.

Symptoms and Clinical Features

MM is better understood when divided into common symptoms and their respective body systems. Symptoms and clinical features in MM can be categorized into three major body systems: skeletal, hematologic, and renal.

Skeletal System

The most common presenting symptom of MM is related to bone disease, which occurs in the majority of individuals, and pain is the most common symptom (Poulos, Gertz, Pankratz, & Post-White, 2001). Bone pain may be associated with compression fractures of the spine, pathologic fractures of the long bones, osteoporosis, or osteolytic lesions. About 30% of patients with MM present with a pathologic fracture (George & Sadovsky, 1999), and patients often have multiple osteolytic lesions, giving the bone a “punched out” effect on x-ray (see Figure 2). Skeletal survey, as opposed to bone scan, has proven to be the more effective means of evaluating lytic lesions in MM (Harousseau, 2002). The interaction between MM cells and the bone environment leads to increased bone resorption, not accompanied by a comparable increase in bone formation, resulting in bone disease (Kyle, 1999).

Hypercalcemia is frequent in MM and related to increased bone resorption and cytokine production. It can be associated with nausea, fatigue, confusion, polyuria, or constipation and contributes to renal insufficiency, which also is common in patients with MM. Spinal cord compression is another complication related to bone disease and occurs in 10%–15% of patients (Harousseau, 2002). It is characterized by pain, paresthesias, and sensory loss and requires immediate diagnosis and treatment.

Hematologic System

Recurrent infections are common in MM, and about 50%–70% of patients with MM will die as a result of bacterial infections (Sheridan, 1996). The most common sites of infection are the respiratory and urinary tracts. Recurrent infections in MM are related to decreased production of immunoglobulins and ineffectiveness of the overproduced immunoglobulin. Immunosuppression also can be related to neutropenia associated with plasma cell replacement in the bone marrow and defects in the neutrophil and complement system functioning.

Anemia is a clinical feature seen in two-thirds of patients at presentation and may be characterized by fatigue, weakness, and dyspnea on exertion (Harousseau, 2002). The cause of anemia is multifactorial and related to the replacement of erythrocyte progenitors in the bone marrow by plasma cells, decreased production of erythrocytes, low erythropoietin levels, and increased erythrocyte destruction (Sheridan, 1996).

### Table 1. Immunoglobulins and Their Roles

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Function</th>
<th>Incidence*</th>
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<tbody>
<tr>
<td>IgG</td>
<td>Coats microorganisms, allowing for uptake by other immune cells</td>
<td>55%</td>
</tr>
<tr>
<td>IgA</td>
<td>Protects entrances to the body; seen in tears, saliva, and respiratory and gastrointestinal secretions</td>
<td>26%</td>
</tr>
<tr>
<td>IgM</td>
<td>Found primarily in the blood stream, where it is effective at killing bacteria</td>
<td>Rare</td>
</tr>
<tr>
<td>IgE</td>
<td>Responsible for hypersensitivity and allergy response</td>
<td>Rare</td>
</tr>
<tr>
<td>IgD</td>
<td>Involved in B lymphocyte regulation and production</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Light chain (Bence Jones) multiple myeloma 14%; nonsecreting multiple myeloma 2%

**Note.** Based on information from Harousseau, 2002.

### Table 2. Baseline Diagnostic Tests for Multiple Myeloma

<table>
<thead>
<tr>
<th>Test</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Complete blood count with white blood cell differential count and peripheral smear</td>
<td>Monitor for anemia, neutropenia, and thrombocytopenia.</td>
</tr>
<tr>
<td>Creatinine level (baseline chemistry panel)</td>
<td>Check renal function; it may be elevated.</td>
</tr>
<tr>
<td>Calcium level</td>
<td>Monitor for hypercalcemia.</td>
</tr>
<tr>
<td>Serum protein electrophoresis with immunofixation</td>
<td>Assess monoclonal-spike (M-spike).</td>
</tr>
<tr>
<td>Quantitative immunoglobulins (IgG, IgA, IgM)</td>
<td>Identify gammopathy and abnormalities.</td>
</tr>
<tr>
<td>Urinalysis and 24-hour urine collection for electrophoresis (urinalysis plus urine protein electrophoresis)</td>
<td>Assess M-spike.</td>
</tr>
<tr>
<td>Skeletal bone survey</td>
<td>Check for lytic bone disease involvement.</td>
</tr>
<tr>
<td>Bone marrow biopsy and aspirate</td>
<td>Assess for bone marrow involvement.</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Kyle, 2002.
Bone marrow involvement in MM also can cause thrombocytopenia. The risk of bleeding can be complicated further by the negative effects of the M protein coating the platelets and interfering with platelet aggregation (Sheridan, 1996).

Hyperviscosity syndrome is a rare hematologic complication in MM, occurring in 4% of patients with IgG myeloma and 5%–10% of patients with IgA myeloma (Sheridan, 1996). It is caused by an increased concentration of proteins in the blood, leading to vascular sludging, and is characterized by oral bleeding, epistaxis, blurred vision, retinal changes, paresthesias, or congestive heart failure (Zaidi & Vesole, 2001). Hyperviscosity syndrome is treated by prompt initiation of plasmapheresis.

Renal System

Renal insufficiency is noted in half of patients with MM and detected by an elevated serum creatinine (Kyle, 1999). Renal insufficiency can be related to one or more of the following factors: myeloma kidney, hypercalcemia, amyloid deposits, and hyperviscosity syndrome (Sheridan, 1996). Myeloma kidney, the predominant cause of renal insufficiency, is the result of obstruction of the renal tubules in the kidney by Bence Jones protein. Bence Jones protein is the light-chain component of the abnormal immunoglobulin. Hypercalcemia is related to bone disease as previously discussed and can be nephrotoxic. Patients with MM can develop amyloid deposits; these deposits in the kidney can lead to hydronephrosis and renal insufficiency. Hyperviscosity can cause renal obstruction and subsequent damage.

Treatment

Treatment of MM involves conventional chemotherapy, autologous stem cell transplant, thalidomide, interferon, and bortezomib. Table 4 outlines some of the treatments, side effects, and nursing considerations of treatments for MM.

The cornerstone treatment has remained the conventional oral regimen of melphalan and prednisone. Another common regimen used is vincristine, doxorubicin, and dexamethasone (VAD). VAD therapy is the standard course for patients considering or planning autologous stem cell transplantation because melphalan can cause alkylator-mediated stem cell damage.

Because of improved response rates and survival rates, high-dose chemotherapy followed by autologous stem cell transplantation has evolved as the standard of care for eligible patients (Rajkumar et al., 2002). In general, eligibility is determined by age (< 70 years) and the absence of any comorbid factors. Transplantation usually involves three or four cycles of chemotherapy to minimize tumor burden (induction), then peripheral blood stem cell collection using apheresis (harvest), followed by high-dose myeloablative therapy (conditioning regimen), and finally reinfusion of stem cells. In initial studies, tandem (dual) stem cell transplants have improved survival and duration of response in patients with MM (Attal et al., 1996). Dual transplantation involves a second conditioning regimen of chemotherapy and stem cell reinfusion (collected in initial harvest) after recovery of the first transplant.

Thalomid® (thalidomide, Celgene Corporation, Warren, NJ) given with or without dexamethasone recently emerged as an optimistic treatment option for MM (Anderson, 2002). It also is being investigated as induction therapy to autologous stem cell transplant. The efficacy of thalidomide is thought to be related to its antiangiogenic and immunomodulation properties and may be related to its other effects on the bone microenvironment.

Interferon typically is used in the maintenance setting, although with the recent advances in newer therapies, it is not as common as in years past (Kyle, 1999; Rajkumar et al., 2002). Interferon can cause fatigue and depression and often is not tolerated well for a long period of time.

Recently, the U.S. Food and Drug Administration approved the proteasome inhibitor bortezomib (Velcade® [PS-341], Millennium Pharmaceuticals, Inc., Cambridge, MA) for the treatment of refractory MM. In early clinical trials, a 32% response rate occurred to bortezomib alone (Tariman, 2003). It seems to be tolerated well, considering that in clinical trials most of the patients had at least two prior regimens (Tariman).

In this x-ray of typical lytic lesions in multiple myeloma, notice the “punched-out” effect.

Figure 2. Typical Lytic Lesions

Note. From “Multiple Myeloma of the Skull,” by E.A. Brandser, Virtual Hospital. Copyright-protected material used with permission of the author and the University of Iowa’s Virtual Hospital, www.vh.org/adult/provider/radiology/icmrad/skeletal/Parts/Myeloma.html.

Table 3. Classification of Multiple Myeloma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal gammopathy of undetermined significance</td>
<td>Serum M protein &lt; 3 g/dl, &lt; 10% plasma cells in marrow</td>
<td>Watch and wait.</td>
</tr>
<tr>
<td>Smoldering multiple myeloma</td>
<td>Serum M protein &gt; 3 g/dl and/or &gt; 10% plasma cells in marrow</td>
<td>Watch and wait.</td>
</tr>
<tr>
<td>Indolent multiple myeloma</td>
<td>Serum M protein + serum/urine M protein, Marrow plasmacytosis, Mild anemia and/or few lytic lesions</td>
<td>Monitor at close intervals.</td>
</tr>
<tr>
<td>Symptomatic multiple myeloma</td>
<td>Serum M protein + serum/urine M protein, Marrow plasmacytosis</td>
<td>Start treatment.</td>
</tr>
</tbody>
</table>

- Beta 2 microglobulin < 2.5 mg/dl
- C-reactive protein < 4 mg/dl
- No chromosomal translocation (~13/13q)
- Plasma cell labeling index < 1%
- No plasmablastic morphology
- Lactic dehydrogenase normal

Figure 1. Favorable Prognostic Indicators

Note. Based on information from Munshi et al., 2001.

In this x-ray of typical lytic lesions in multiple myeloma, notice the “punched-out” effect.
Although none of these treatments results in a cure, many active areas of investigation currently are in clinical trials and development. One novel therapy showing antimyeloma effect in phase I/II trials is the thalidomide analog CC-5013 (Revimid™, Celgene Corporation, Warren, NJ) (Tariyan, 2003). It now is in phase III trials, and earlier trials have shown promising response rates in patients with refractory disease. CC-4047 (Actimid™, Celgene Corporation), another thalidomide analog, also is under investigation in phase I/II trials (Tariyan). Other areas of investigation include dendritic cell vaccination, 2 methoxyestradiol, farnesyl transferase inhibitors, flavopiridol, arsenic trioxide, and inhibitors of angiogenic cytokines (Rajkumar et al., 2002; Tariyan).

**Supportive Care**

Supportive care is an important component in the management of MM. Some of the clinical features requiring supportive care include skeletal complications, hypercalcemia, anemia, and infection.

- Skeletal complications such as osteoporosis, lytic lesions, spinal cord compression, compression fractures, and pathologic fractures are reduced by treatment with bisphosphonates (Kyle, 1999). The most commonly administered bisphosphonates are pamidronate and zoledronic acid. Both drugs have similar efficacy in preventing and reducing skeletal complications as well as reducing patient reports of pain and analgesic use (Jantunen, 2002). Painful lytic lesions and compression fractures also can be treated quite effectively with localized external beam radiation. Pain from bone disease may be helped with analgesics along with physical therapy and splinting or other orthopedic interventions such as vertebroplasty (Rajkumar et al., 2002). Treatment for spinal cord compression is radiation, steroids, and, in rare cases, surgical decompression. Patients often need to use opioid analgesics to control bone pain, and nonsteroidal anti-inflammatory agents may be used as well.

**Bisphosphonate therapy and nonsteroidal anti-inflammatory agents should be used cautiously in patients with MM because of the increased risk of renal toxicities. With the advent of bisphosphonate therapy, the incidence of hypercalcemia has been reduced. Hypercalcemia also can be treated with aggressive hydration and corticosteroid therapy.**

Anemia can cause a variety of symptoms such as shortness of breath, fatigue, and dizziness and impact quality of life for patients with MM. Treatment of the underlying disease often leads to improvement in hemoglobin concentration, although erythropoietin therapy may be needed as well.

Patients with MM also are prone to infection because of immunosuppression from the defects in immunoglobulins. The immune system can be compromised further by treatment with systemic chemotherapy. Patients with MM may be treated with prophylactic antibiotics in certain clinical situations, and patients with severe hypogammaglobulinemia and recurrent infections may be treated with monthly immunoglobulin infusions. Likewise, steroids are part of the treatment for MM and require close monitoring for fungal infections, which should be treated prophylactically if needed (Kyle, 1999).

**Nursing Considerations**

Nurses play a vital role in the care of patients with MM. Nurses require a clear understanding of each patient’s disease course and psychosocial dynamics so as to evaluate the impact of current therapies on the patient and family. Each patient requires monitoring for complications such as infections, renal insufficiency, bleeding, and pain. Because much of health care is delivered in the outpatient setting, nurses must educate patients and their families on essential daily care.

The psychosocial aspect of MM is difficult because no cure is available. Moreover, SMM and MGUS are difficult diagnoses for patients because many are informed of a watch-and-wait method that is difficult to understand in a society of “fix it.” A multidisciplinary approach can be helpful to assist with the psychosocial aspects of MM.

**Conclusion**

MM is the second most common hematologic disorder and is a complex disease. New treatment options are emerging in MM, and this requires nurses to keep abreast of current treatments and their related side effects. This article has provided a broad understanding of the pathophysiology and clinical features that impact patients with MM.

### Table 4. Common Treatment Regimens for Multiple Myeloma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Side Effects</th>
<th>Nursing Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan 8–10 mg/m² and prednisone 60 mg/m² by mouth days 1–4 every 28 days</td>
<td>Tolerated fairly well; renal toxicity, insomnia, restlessness, and dyspepsia</td>
<td>Monitor blood sugars, infections, medication instruction.</td>
</tr>
<tr>
<td>Vincristine 0.4 mg/d via IV on days 1–4 with doxorubicin 9 mg/m² via IV on days 1–4 and dexamethasone 40 mg by mouth on days 1–4, 9–12, and 17–20 every 28–35 days</td>
<td>Myelosuppression, nausea and vomiting, constipation, neuropathy, insomnia, restlessness, and dyspepsia</td>
<td>Check blood counts. Compliance with dexamethasone. Monitor steroid toxicity. Central line is required; monitor blood sugars.</td>
</tr>
<tr>
<td>Cyclophosphamide 150–250 mg/m² via IV and prednisone 100 mg every other day</td>
<td>Mild myelosuppression, hemorrhagic cystitis, insomnia, restlessness, and dyspepsia</td>
<td>Medication instruction</td>
</tr>
<tr>
<td>Dexamethasone 40 mg by mouth on days 1–4, 9–12, and 17–20 every 21 days (with or without thalidomide)</td>
<td>Steroid toxicity, hypercalcemia, insomnia, restlessness, and dyspepsia</td>
<td>Monitor blood sugars and compliance. Patient education. Sleep disruption</td>
</tr>
<tr>
<td>Thalidomide 200–800 mg by mouth daily (with or without dexamethasone)</td>
<td>Neuropathy, constipation, blood clots, drowsiness</td>
<td>Monitor compliance: System for Thalidomide Education and Prescribing Safety program birth control</td>
</tr>
<tr>
<td>Bortezomib 1.3 mg/m² twice weekly on days 1, 4, 8, and 11 every 21 days</td>
<td>Thrombocytopenia, hypotension, and neuropathy</td>
<td>Encourage patient to drink fluids and check blood counts.</td>
</tr>
<tr>
<td>Interferon 2 million international units subcutaneously three times a week</td>
<td>Fatigue and depression</td>
<td>Monitor for mood changes.</td>
</tr>
</tbody>
</table>
A better understanding of the etiology of the disease may lead to more novel therapies to improve outcomes for patients with MM and their quality of life.

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References


Rapid Recap

Multiple Myeloma: An Overview

- Multiple myeloma (MM) is a malignant blood disorder involving plasma cells.
- Skeletal complications such as pain and fractures are a common symptom in patients with MM.
- Patients should be monitored for hematologic, renal, and neurologic complications as well as infection.
- Treatment options for MM include chemotherapy regimens such as vincristine, doxorubicin, and dexamethasone; melphalan and prednisone; thalidomide; bortezomib; and stem cell transplantation.

For more information on this topic, visit the following Web sites.

Multiple Myeloma Research Foundation
www.multiplemyeloma.org

MedlinePlus: Multiple Myeloma

Multiple Myeloma Research Web Server
http://myeloma.med.cornell.edu

Links can be found at www.ons.org.