Maintaining Bone Health in Patients With Multiple Myeloma: Survivorship Care Plan of the International Myeloma Foundation Nurse Leadership Board

Teresa S. Miceli, RN, BSN, OCN®, Kathleen Colson, RN, BSN, BS, Beth M. Faiman, MSN, APRN-BC, AOCN®, Kena Miller, RN, MSN, FNP, Joseph D. Tariman, PhD, APRN, BC, and the International Myeloma Foundation Nurse Leadership Board

About 90% of individuals with multiple myeloma will develop osteolytic bone lesions from increased osteoclastic and decreased osteoblastic activity. Severe morbidities from pathologic fractures and other skeletal events can lead to poor circulation, blood clots, muscle wasting, compromised performance status, and overall poor survival. Supportive care targeting bone disease is an essential adjunct to antimyeloma therapy. In addition, the maintenance of bone health in patients with multiple myeloma can significantly improve quality of life. Oncology nurses and other healthcare providers play a central role in the management of bone disease and maintenance throughout the course of treatment. Safe administration of bisphosphonates, promotion of exercise, maintenance of adequate nutrition, vitamin and mineral supplementation, scheduled radiographic examinations, and monitoring of bone complications are among the important functions that oncology nurses and healthcare providers perform in clinical practice.

A main feature of multiple myeloma (MM) is bone destruction, and many patients will initially present with pain related to osteolytic lesions or vertebral compression fractures (Sezer, 2009). Destructive bone lesions and diffuse osteopenia are secondary to the stimulation of osteoclast-activating growth factors, cytokine release, and the lack of osteoblastic response (Esteve & Roodman, 2007). The clinical consequences of osteolytic bone lesions—fractures, severe bone pain, spinal cord compression, hypercalcemia, and renal insufficiency—can be devastating for patients, negatively affecting immediate and ongoing quality of life and worsening survival prospects (Kyle, Gertz, et al., 2003).

At a Glance

- Most patients with multiple myeloma will develop osteolytic bone lesions. Pathologic fractures and other skeletal events can result in poor circulation, blood clots, muscle wasting, and decreased survival.
- Supportive care targeting bone disease is an essential part of myeloma therapy.
- Oncology nurses play a key role in the management of bone disease and maintenance of adequate bone health throughout the course of myeloma.

Teresa S. Miceli, RN, BSN, OCN®, is the bone marrow transplant RN coordinator at the Mayo Clinic in Rochester, MN; Kathleen Colson, RN, BSN, BS, is a clinical research nurse in the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute in Boston, MA; Beth M. Faiman, MSN, APRN-BC, AOCN®, is a nurse practitioner in the Hematology and Medical Oncology Department at the Cleveland Clinic in Ohio; Kena Miller, RN, MSN, FNP, is a nurse practitioner in the Department of Medicine, Lymphoma/Myeloma Division, at Roswell Park Cancer Institute in Buffalo, NY; and Joseph D. Tariman, PhD, APRN, BC, is an advanced practice nurse in the myeloma program at Northwestern University in Chicago, IL. The authors take full responsibility for the content of this article. Publication of this supplement was made possible through an unrestricted educational grant to the International Myeloma Foundation from Celgene Corp. and Millennium: The Takeda Oncology Company. Colson is a consultant with Merck & Co., Inc., and Millennium: The Takeda Oncology Company; Faiman is a consultant and on the speakers bureau at Celgene Corp. and Millennium: The Takeda Oncology Company; Miller is an advanced practice nurse in the myeloma program at Northwestern University. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by independent peer reviewers or editorial staff. (First submission February 2011. Revision submitted March 30, 2011. Accepted for publication April 5, 2011.)

Digital Object Identifier: 10.1188/11.S1.CJON.9-23
Pathophysiology of Myeloma Bone Disease

Bone disease is the major cause of morbidity and mortality in patients with MM (Coleman, 2006). Osteolytic lesions found with MM are caused by rapid bone turnover, which occurs as a result of increased osteoclastic resorption that is not accompanied by a comparable increase in bone formation (Berenson, Rajdev, & Border, 2006; Epstein & Walker, 2006). Normal bone formation is initiated by osteoblasts, and bone resorption is initiated by osteoclasts. Osteoprotegerin is a cytokine that inhibits production of osteoclasts. Osteoprotegerin maintains the balance between bone resorption and formation. Bone destruction in MM is believed to be multifactorial, resulting from an interaction of bone marrow stromal cells and myeloma tumor cells within the microenvironment of the bone marrow (Coleman, 2001). Bone destruction is characterized by overproduction of osteoclasts and reduced stimulation of osteoblasts resulting in unbalanced bone turnover.

Bone pain and the incidence of pathologic fracture are high among patients living with MM as a result of osteolytic bone lesions and bone turnover related to excess cytokine levels. Fractures typically occur near the time of diagnosis or relapse and are pathologic in nature. The most common locations of fracture are within the vertebral bodies (55%–70%), particularly in the lumbar vertebral bodies, flat and long bones (including the ribs), the extremities, and pelvis (Melton, Kyle, Achenbach, Oberg, & Rajkumar, 2005).

Long-Term Effects of Bone Disease

As noted, the majority of patients with MM will experience a pathologic fracture over the natural duration of their illness. As a result, 80% of patients will experience pain and altered quality of life (Roodman, 2008). The severity of bone disease and number of lesions present at the time of the diagnosis help to classify patients who are considered high risk. The Durie/Salmon PLUS staging system provides the following advantages. Based on information from Durie, 2006; Roodman, 2008.

The Durie/Salmon PLUS staging system (Durie, 2006) assimilates imaging methods into a new generation of anatomic and functional myeloma staging. Table 1 outlines the diagnostic imaging commonly used for patients with MM. With the use of MRI, whole body fluorodeoxyglucose (FDG) PET scanning and whole body computed tomography (CT), combined with PET directly or by fusion, the Durie-Salmon staging system has now been enhanced to include anatomic and functional staging. The new system may provide better classification of early disease. The Durie/Salmon PLUS staging system provides the following advantages.

- Assessment of cell mass
- More accurate staging for patients who lack traditional biomarkers because of hyposecretory or nonsecretory disease
- Identifies patients at poor risk who have more than 20 focal lesions and/or extramedullary disease
- Confirms stage I active disease for patients with negative x-rays
- Provides a more detailed discernment between those diagnosed with stage II and III disease

The degree of bone involvement affects quality of life as well as prognosis. Compromised skeletal structure because of lytic lesions and vertebral compression fracture can result in altered mobility and function; therefore, early detection can offer potential benefits to patients. The life-altering mobility and functional aspects of myeloma are further described in Rome, Jenkins, Lilleby, and the International Myeloma Foundation Nurse Leadership Board (2011).

Assessment of Myeloma Bone Disease

Laboratory Testing

Laboratory tests to assess bone include calcium, vitamin D, fractionated alkaline phosphatase, and creatinine. Hypercalcemia, defined as a corrected serum calcium greater than 11.5 mg/dl, is seen in 10%–15% of patients at presentation and is considered

<table>
<thead>
<tr>
<th>Table 1. Diagnostic Imaging in Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIAGNOSTIC IMAGING</strong></td>
</tr>
<tr>
<td>Bone density test</td>
</tr>
<tr>
<td>Bone scan</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Positron-emission tomography/computed tomography</td>
</tr>
<tr>
<td>Skeletal survey</td>
</tr>
</tbody>
</table>

Note: Based on information from Durie, 2006; Roodman, 2008.
Bone imaging is an important tool for diagnosis and monitoring bone disease in patients with myeloma. Patients often are initially diagnosed because of the onset of acute bone pain or pathologic fracture. Any bone may be affected in MM; the bones with the highest chance of being affected are the spine with more than a 49% risk, the skull with more than a 35% risk, the pelvis at 34% risk, the humeri with 22% risk, the femora at 13% risk, and the mandible at 10% (Roodman, 2008) (see Figure 1). Of note, bone disease in myeloma is caused by an imbalance of osteoblast and osteoclast activity causing bone destruction and absence of bone formation. Therefore, bone scans are not the imaging technique of choice because the degree of bone disease may be underestimated (Roodman, 2008). A complete skeletal survey, the standard method of imaging in patients with MM, detects fractures, tumors, or degenerative changes in the bone. Metastatic bone surveys show that skeletal abnormalities are present in 79% of newly diagnosed patients. Osteosclerotic lesions are rarely seen (Kyle, Gertz, et al., 2003).

Metastatic bone survey, the gold standard for assessing bone disease in myeloma, is able to only identify the lytic disease where a minimum of 30% of the trabecular bone has been destroyed, which basically renders the method somewhat insensitive. In addition, this technique does not demonstrate response to therapy (Roodman, 2008). These limitations of the skeletal survey have led to the use of three additional imaging techniques: CT, PET, and MRI. These three are not considered standard of care in the diagnosis of myeloma bone disease, but can be helpful in discerning suspicious lesions or areas of focal bone destruction. The more sensitive CT may reveal bone lesions not seen on a metastatic bone survey, particularly for patients who are experiencing pain. An MRI may reveal the presence of bone marrow involvement or spinal cord compression. For patients with nonsecretory or oligosecretory myeloma, MRI may reveal the presence and progression of disease and provide prognostic information as discussed in the Durie/Salmon PLUS staging system. For patients with renal insufficiency, which occurs in 20%–60% of patients throughout their disease, care should be taken to avoid the use of gadolinium (Angtuaco, Fassas, Walker, Sethi, & Barlogie, 2004; Kyle, Schreiman, McLeod, & Beabout, 1985; Mariette et al., 1999; Tariman & Faiman, 2011; Tryciecky, Gottschalk, & Ludema, 1997).

Although MRI has a higher sensitivity compared to a typical radiograph in providing anatomic information about the bone marrow, it lacks specificity because of the small signal strength on T1- and T2-weighted images. MRI is the diagnostic tool of choice for spinal cord compression. CT has a higher sensitivity for smaller lesions and is useful in detecting extrasosseous extensions of the disease and to determine bone destruction. PET scans are useful in detecting bone disease, bone marrow infiltration, and extramedullary disease. Whole-body PET scans are much more sensitive than x-rays and other diagnostic imaging tools. The PET scan uses a radio-labeled sugar-based radiotracer.
PET/CT may miss small lytic lesions and diffuse spinal uptake the tracer at greater rates. This provides a mechanism for imaging areas of infection or malignancy (Tryciecek et al., 1997). The use of whole-body \(^{18}\)F-FDG PET, combined with either CT alone or PET/CT, has been found to be useful in the detection of residual disease for myeloma that has been treated and is the imaging of choice for evaluation of extramedullary disease (Bartel et al., 2009). However, critics warn that the PET/CT tool requires additional study before it becomes part of the standard of care in patients with MM for the following reasons (Dimopoulos, Moulopoulos, & Terpos, 2009).

- PET/CT may miss small lytic lesions and diffuse spinal involvement readily detected through use of an MRI.
- PET/CT have been known to provide “false-positive” results, particularly in areas of inflammation and infection, postsurgical sites, and vertebroplasty or other metastatic disease.
- Reimbursement remains an issue.

**Treatment of Myeloma Bone Disease**

The management of MM-related bone disease involves treatment of the disease itself, which controls the myeloma and the underlying manifestations of the disease. The most common forms of treatment are chemotherapy and autologous stem cell transplantation (for eligible patients). For patients with bone involvement who do not experience bone-related pain, systemic therapy often is the primary treatment choice. Adjuvant therapies include localized radiation, orthopedic surgical interventions including kyphoplasty or vertebroplasty for vertebral fractures, and the use of agents that can inhibit bone resorption, such as bisphosphonates.

**Novel Antimyeloma Agents**

Novel agents used today in the treatment of MM may positively affect bone metabolism. Management of active MM with effective antimyeloma therapies will help to decrease the risk of worsening bone structure and risk of fracture. However, these therapies are far from perfect, and it now is clear that skeletal disease may progress despite the achievement of stable disease (Kanis & McCloskey, 2000).

The proteasome inhibitor bortezomib appears to have an effect on myeloma bone disease. It inhibits nuclear factor kappa-B (NF-kB) activity, a critical factor for osteoclast formation and survival. It appears to act during the initial and ending stages of osteoclast differentiation. Several clinical trials conducted with bortezomib have demonstrated that it may increase osteoblast activity, leading to new bone formation, as researchers have reported an increase in bone formation markers in some patients (Pennisi, Li, Ling, Khan, Zangari, & Yaccoby, 2009).

The novel agent thalidomide may halt receptor activator of NF-kB ligand (RANKL)-induced osteoclast formation in vitro (Terpos et al., 2008). Lenalidomide, an immunomodulatory drug (I MiD) and an analog of thalidomide that is more active with an improved side-effect profile, decreases osteoclast formation and activity (Bolzoni et al., 2010; Breitkreutz et al., 2008; Terpos et al., 2009). In vitro studies demonstrate that thalidomide and the currently investigational immunomodulatory drug pomalidomide can inhibit the osteoclast activation process (Bolzoni et al., 2010). The effect of thalidomide combined with dexamethasone reduces bone resorption (Roodman, 2008). The combination of bortezomib, thalidomide, and dexamethasone reduces bone resorption and the RANKL/osteoprotegerin ratio; however, no impact on the formation of bones was observed (Terpos et al., 2009). Whether combining lenalidomide with bortezomib would enhance the osseous effects of each agent alone is unknown; potentially this is a topic for future study. As the understanding of myeloma bone biology develops, more targeted therapies have the potential to emerge (Yeh & Berenson, 2006).

**Bisphosphonates**

Bisphosphonates are strong inhibitors of bone resorption and are effective in the management of hypercalcemia of malignancy, decrease risk of fractures, and may decrease pain in some patients. Bisphosphonates bind to mineralized bone throughout resorption as well as inhibit osteoclast maturation. They cause osteoclast apoptosis as well as prevent attachment to the bone. The bisphosphonates that generally are administered to patients with MM in the United States include pamidronate and zoledronic acid. Both are given via IV, but the time of infusion differs for each. Skeletal-related events can be reduced with bisphosphonates, which decrease bone complications and improve quality of life (Fitch & Maxwell, 2008). It also has been suggested that pamidronate has an antimyeloma effect (Terpos & Dimopoulos, 2005); an antimyeloma effect has recently been shown for zoledronic acid (Morgan et al., 2010).

**Radiation**

Myeloma cells have a high level of sensitivity to radiation, and radiation to affected areas of bone is a useful management modality for some patients with MM, providing local pain and tumor control as well as preventing or treating skeletal fractures. Radiation may be curative in patients with solitary bone plasmacytomas (Yeh & Berenson, 2006). Unfortunately, solitary bone plasmacytoma will evolve to MM in the majority of patients within two to three years. Fortunately, about 15%–45% of patients will remain disease free at 10 years following diagnosis with an overall median survival of 7–12 years (Weber, 2005). Total body irradiation was used in the past to treat MM but, because of its severe toxicities and modest benefit, this treatment modality is rarely used today (Hu & Yahalom, 2000). The use of radiation should be limited as it may cause permanent bone marrow damage in the treatment areas and compromise organ function within the treatment fields (National Comprehensive Cancer Network, 2010; Roodman, 2008; Yeh & Berenson, 2006).

**Surgical Procedures**

A large lytic lesion that is present but has not yet progressed to a pathologic fracture may require stabilization to prevent a fracture. A surgical procedure may become a necessity to decrease the size of the tumor, control pain, and prevent or treat...
Risk Factors Adversely Affecting Bone Health

In addition to the diagnosis of MM, patients can have comorbid conditions that may place them at risk for poor bone health, such as osteoporosis, metastatic malignancies, immobility, side effects from long-term steroid and other drug use, and hormone changes. Factors contributing to osteoporosis include renal disease, natural or therapy-induced gonadal failure, depression, diabetes, and vitamin deficiencies (Mauck & Clarke, 2006; Mezuk, Eaton, & Golden, 2008).

Osteoporosis and Risk of Fracture

Risk factors for osteoporosis are numerous and can be classified as primary or secondary (Mauck & Clarke, 2006) (see Table 2). Primary causes are those that cannot be modified (Cashman, 2007), and include female gender, increased age, family history of osteoporosis or fracture, small or thin frame, and low levels of sex hormones (Mauck & Clarke, 2006). Secondary causes are potentially modifiable through medical intervention and behavioral changes; they include nutritional deficits, chronic medical conditions, inactivity, smoking, alcohol abuse, and certain medications (Cashman, 2007; Mauck & Clarke, 2006). Thirty to 60% of men experience osteoporosis related to decreased gonadal function, use of glucocorticosteroids, and alcoholism; 50% of women will experience osteoporosis related to primary and secondary risk factors such as decreased estrogen, glucocorticosteroid use, and hyperthyroidism (Mauck & Clarke, 2006).

Table 2. Risk Factors Contributing to Bone Loss, Osteoporosis, and Risk of Fracture

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary risk factors</td>
<td>Older than age 50 for men and women, female gender, postmenopausal at any age, men with lower testosterone and estrogen levels, personal and first-degree relative with a history of fracture as an adult, dementia, and ethnicity (Caucasians and Asian Americans have a higher incidence than Hispanics and African Americans).</td>
</tr>
<tr>
<td>Secondary risk factors</td>
<td>Low body weight (less than 127 lbs.), smoking, certain medications, hypogonadism (hormone deficiency and being younger than age 45), comorbid conditions, poor health and frailty, recent falls, inactivity and immobility (i.e., prolonged bed rest or wheelchair bound), and diet (more than two alcoholic drinks per day, low calcium intake, vitamin D deficiency of any cause, and excess consumption of vitamin A, caffeine, sodium, and protein)</td>
</tr>
</tbody>
</table>

*Difference in ethnic prevalence may be related to underreporting in some ethnic groups.

Note. Based on information from Adami, 2009; Cashman, 2007; Everitt, et al., 2006; Guise, 2006; Mezuk, Eaton, & Golden, 2008; Mezuk, Eaton, Golden, Wand, et al., 2008; Mauck & Clarke, 2006; National Osteoporosis Foundation, 2010; Szulc et al., 2008; Wick, 2009.
Gonadal failure can be a natural risk for the development of osteoporosis. An estimated 10 million individuals are affected by the disease, with more than 34 million at risk as evidenced by low bone mass. Osteoporosis is a chronic and progressive disease characterized by decreased bone mass, leading to structural changes within the bone, placing an individual at a higher risk for developing a fracture, particularly of the spine, wrist, or hip. Osteoporosis affects four times as many women as it does men, with significant risk seen among all ethnic backgrounds (Mauck & Clarke, 2006).

The National Osteoporosis Foundation ([NOF], 2010) estimates that 80% of women and 20% of men older than age 50 are affected by osteoporosis. In addition, one in two women and one in four men will experience a fracture secondary to osteoporosis. Studies have shown that not only does the risk for subsequent fractures increase after the first event, but the quality of life and impact on independent activities of daily living is dramatically reduced following a fracture (NOF, 2010). The median age for diagnosis of MM is 66 years (Kyle & Rajkumar, 2007). MM and other comorbid conditions (see Figure 2) increase the risk of age-related osteoporosis and fracture.

### Other Comorbid Conditions

**Renal osteodystrophy:** Bone loss associated with chronic renal disease is one of the most common osseous complications of patients with MM. The bone changes from chronic kidney disease or renal osteodystrophy can begin in adults several years prior to the appearance of any symptoms. Management of myeloma-related renal complications are described in Faiman, Mangan, Spong, Tariman, and the International Myeloma Foundation Nurse Leadership Board (2011). Patients with either osteoporosis or renal osteodystrophy experience increased risk of fractures and resultant joint and bone pain, but renal osteodystrophy does not necessarily respond to bisphosphonates (Legg, 2005).

Kidneys have a significant role in the maintenance of bone mass throughout one’s life by maintaining calcium and phosphorus levels in the blood. Patients with kidney disease may develop hypocalcemia leading to increased stimulation of the parathyroid glands to release PTH. The excess PTH results in osteopenia, and constant removal of calcium over time will weaken the bones (Legg, 2005).

The kidneys also regulate serum calcium by producing calcitriol, a form of vitamin D produced by healthy kidneys that helps the body absorb dietary calcium. In kidney failure, calcitriol production is decreased and the resulting hypocalcemia stimulates the parathyroid gland to release more PTH, which contributes to further osseous calcium loss. Nurses need to be aware that routine monitoring for serum PTH and vitamin D should take place in patients with chronic kidney disease (Legg, 2005).

**Gonadal insufficiency:** Gonadal failure can be a natural part of aging or therapy related and can affect both men and women. Postmenopausal women have a higher risk of developing osteoporosis and risk of fracture. The loss of estrogen results in a higher rate of bone loss (Everitt et al., 2006). Bone mineral density (BMD) in women is estimated to decrease at over 2% annually for the first five years following menopause, and then the rate slows, whereas the rate of bone loss in men begins in midlife and is further reduced from 0.5%–1% per year (Guise, 2006). Selected therapies, both surgical and medical, that result in gonad failure and contribute to the risk of osteoporosis and risk of fracture are listed in Table 3.

**Depression:** Major depressive disorders occur in about 16% of the general population, but more frequently in those diagnosed with cancer (Mezuk, Eaton, & Golden, 2008; Mezuk, Eaton, Golden, & Lee, 2008). People who suffer from major depressive disorders have a lower BMD than those in control groups. The association of depression, osteoporosis, and risk of fracture is unclear. Physiologically, hormone levels that promote osteoclastic function and decrease osteoblastic function, including interleukin-6, tumor necrosis factor-alpha, PTH, C-reactive protein, and cortisol, also are elevated in those who have major depressive disorders. Secondary risk factors may play the greatest role because an association exists between depression and unhealthy behaviors (e.g., smoking, alcohol use, fatigue resulting in inactivity) (Mezuk, Eaton, & Golden, 2008).

**Diabetes:** People suffering from type 1 diabetes have decreased BMD and increased risk of fracture, and those with type 2 diabetes also are at a higher risk for suffering a fracture even if their BMD is normal or increased (Adami, 2009). However, the mechanism for bone loss in these patients is complex, involving a combination of factors such as malnutrition, alcoholism, and an increased risk of fracture.
The association of osteoporosis and various malignancies and antidepressants have been implicated in increased risk of osteoporosis and fracture. Selective serotonin reuptake inhibitors and tricyclic antidepressants (Faiman et al., 2008) may result in osteopenia or osteoporosis by inhibiting or stimulating bone resorption, inhibiting calcium absorption, and increasing calcium excretion.

Steroids: Glucocorticoids (dexamethasone or prednisone) remain a backbone of antimyeloma therapy. Steroids kill myeloma cells directly and may enhance the efficacy of other myeloma drugs when used in combination. However, steroid use may result in osteopenia or osteoporosis by inhibiting or stimulating bone resorption, inhibiting calcium absorption, and increasing calcium excretion. Steroid use also is associated with avascular necrosis or osteonecrosis (Faiman et al., 2008).

Antidepressants: Antidepressant medications such as selective serotonin reuptake inhibitors and tricyclic antidepressants have been implicated in increased risk of fractures. Current use of antidepressants plays a greater role in risk of fracture than previous use and may be age- and life-stage dependent (Mezuk, Eaton, & Golden, 2008).

Bone Marrow Transplantation

Multiple small studies evaluating BMD following autologous and allogeneic bone marrow transplantation report that bone loss is a common side effect. Few long-term studies are available, but disturbance in bone metabolism and reduced BMD is measurable years after the procedure. The mechanism is not completely understood, however, alteration of the osteoprotegerin/RANKL system may play a significant role (Ebeling et al., 1999; Kang et al., 2000; Kerschan-Schindl et al., 2004; Lee, Cho, et al., 2002, Lee, Kang, et al., 2002). Interestingly, one small study (Kielholz et al., 1997) of 29 patients who underwent autologous bone marrow or peripheral blood transplantation following high-dose chemotherapy showed that they did not have significant osteopenia despite high-dose steroids, prolonged inactivity, and decreased estrogen levels. The lowest BMD was seen in men who had the lowest testosterone levels. Because this was a follow-up study of patients who were five years post-transplantation, these unexpected results may be from recovery of endocrine function during that time. With such a small cohort of patients, however, additional investigation is warranted before making any conclusions (Kielholz et al., 1997).

Diet

Although diet is considered a secondary risk factor for osteoporosis and risk of fracture, the peak bone mass, which is reached in youth, is not modifiable in adults. About 90% of bone mass is established within the first two decades of life and, most significantly, during puberty (Cashman, 2007). Vitamins and nutrients important for bone mineralization and skeletal development are listed in Table 4. Vitamin D and calcium are required during development and throughout life and, most significantly, during puberty (Cashman, 2007). Vitamin D is measurable years after the procedure. The mechanism is not completely understood, however, alteration of the osteoprotegerin/RANKL system may play a significant role (Ebeling et al., 1999; Kang et al., 2000; Kerschan-Schindl et al., 2004; Lee, Cho, et al., 2002, Lee, Kang, et al., 2002). Interestingly, one small study (Kielholz et al., 1997) of 29 patients who underwent autologous bone marrow or peripheral blood transplantation following high-dose chemotherapy showed that they did not have significant osteopenia despite high-dose steroids, prolonged inactivity, and decreased estrogen levels. The lowest BMD was seen in men who had the lowest testosterone levels. Because this was a follow-up study of patients who were five years post-transplantation, these unexpected results may be from recovery of endocrine function during that time. With such a small cohort of patients, however, additional investigation is warranted before making any conclusions (Kielholz et al., 1997).

Diet

Although diet is considered a secondary risk factor for osteoporosis and risk of fracture, the peak bone mass, which is reached in youth, is not modifiable in adults. About 90% of bone mass is established within the first two decades of life and, most significantly, during puberty (Cashman, 2007). Vitamins and nutrients important for bone mineralization and skeletal development are listed in Table 4. Vitamin D and calcium are required during development and throughout life to promote bone health (Everitt et al., 2006). Maximizing serum vitamin D levels, as measured by 25-hydroxyvitamin D (25-OHD), contributes to an increase in BMD and is associated with improved muscle strength, resulting in a 20% decreased

- Anticonvulsants (phenytoin or phenobarbital)
- Cytotoxic drugs and immunosuppressants (cyclosporine A, tacrolimus)
- Drugs causing hypogonadism (aromatase inhibitors, methotrexate, antimetabolite chemotherapy, depomedroxyprogesterone acetate, and gonadotropin-releasing hormone agonists such as buserelin, leuprolide, and nafarelin)
- Drugs causing sedation or confusion (pain medication, sleep aids, antianxiety drugs, or antihistamines)
- Glucocorticoid excess (current or previous use for more than three months)
- Heparin (long-term), lithium or aluminum, and I-thyroxine over-replacement

Table 3. Bone Loss and Cancer Therapy

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>TUMOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy (cyclophosphamide, methotrexate, and alkylating agents)</td>
<td>Various malignancies (e.g., breast cancer, multiple myeloma, osteosarcoma, Hodgkin or non-Hodgkin lymphoma)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Various malignancies and autoimmune disorders</td>
</tr>
<tr>
<td>Hormone therapy (androgen-deprivation therapy, selective estrogen-receptor modulators, and aromatase inhibitors)</td>
<td>Prostate, testicular, ovarian, and breast cancer</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>Various malignancies</td>
</tr>
<tr>
<td>Stem cell transplantation</td>
<td>Various malignancies</td>
</tr>
<tr>
<td>Surgical (bilateral orchiectomy and oophorectomy)</td>
<td>Prostate, testicular, ovarian, and breast cancer</td>
</tr>
</tbody>
</table>


Clinical Journal of Oncology Nursing • Supplement to Volume 15, Number 4 • Maintaining Bone Health 15
Table 4. Factors That Reduce Osteoporosis and Risk of Fracture

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>ITEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet or dietary supplements</td>
<td>Calcium, copper, magnesium, phytoestrogens, vitamin C (with caveats about potential interaction with bortezomib), vitamin D, vitamin K, and zinc</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>Estrogen, statins, and thiazides</td>
</tr>
<tr>
<td>Weight-bearing activity</td>
<td>–</td>
</tr>
</tbody>
</table>

Note. Based on information from Adami, 2009; Mauck & Clarke, 2006; Mezuk, Eaton, & Golden, 2008; Mezuk, Eaton, Golden, Wand, et al., 2008.

Evidence-Based Recommendations to Manage and Maintain Bone Health

Comorbidities and concomitant risk factors, such as age, gender, medications, and mobility, should be considered when developing a treatment plan and will influence the approach taken for each patient (see Figure 4). In addition to mobility and exercise, which are discussed in depth in another article in this supplement (Rome et al., 2011), nurses can assist patients to manage their bone health by maintaining proper diet and nutrition, undergoing radiation treatment or surgical procedures when necessary, and safely taking bisphosphonates and pain medications where appropriate.

Diet and Supplements

Only general recommendations exist in regard to diet, supplements, and bone health in MM. Clinicians should encourage patients to eat well-balanced diets comprising fruits, vegetables, protein, and carbohydrates. Most nutritional supplements are safe in moderation; however, based on preclinical evidence, the Nurse Leadership Board suggests the following compounds be used with caution by patients receiving bortezomib. Vitamin C interferes with the ability of bortezomib to kill human cancer cell lines in culture, apparently by binding to bortezomib and inactivating it (Zou et al., 2006). Alpha lipoic acid, often recommended for the treatment of peripheral neuropathy, has been shown to interfere with antmyeloma effects of bortezomib in myeloma cell lines (Steinberg et al., 2009). In addition, preclinical (in vitro and in vivo) research demonstrated tumor cell death caused by bortezomib may be negated by the use of green tea (Golden et al., 2009). Although additional research is warranted, and no clinical evidence exists, the International Myeloma Foundation Nurse Leadership Board recommends avoidance of vitamin C, alpha lipoic acid, and green tea on the day of bortezomib therapy.

Calcium and vitamin D supplementation is advised for all patients with osteopenia or osteoporosis, particularly if they are receiving bisphosphonates such as pamidronate or zoledronic acid. The NOF’s recommendations for calcium and vitamin D supplementation are provided at http://nof.org/aboutostoporosis/prevention/calcium.

In summary, for people older than age 50, 1,200 mg of calcium and 800–1,000 IU of vitamin D daily are recommended. Those younger than age 50 do no require as much, with 1,000 mg of calcium and 400–800 IU of vitamin D daily recommended. Of note, however, individuals with hypercalcemia or renal insufficiency should not take calcium replacement (NOF, 2010), both of which may be concerns for patients with MM. A discussion with a healthcare provider should take place.

Radiation as Treatment for Bone Disease

Care of patients receiving radiation for local pain and tumor control includes alleviating side effects related to the radiated field. The potential for side effects is dose dependent. External beam doses can range from 600–800 cGy hemi-body irradiation for palliation of generalized pain, 3,000 cGy for a localized painful bone lesion, and to 4,500 cGy for tumor control. Patients receiving lower-dose radiation for pain palliation have less potential for side effects, but all should be monitored closely (Terpos & Dimopoulos, 2005). For example, patients with head and neck radiation may have trouble eating and swallowing and may experience mouth sores. For these patients, good oral hygiene is necessary to prevent mouth sores and decrease the risk of infections. Pain medication may be indicated if severe mouth sores or radiation burns to the skin develop. Individuals who receive mediastinal, thoracic, or lumbar spine radiation may develop...
### Medical Follow-Up

<table>
<thead>
<tr>
<th>Blood and laboratory tests (assessment of myeloma activity)</th>
<th>Monthly while on therapy to assess response, then at discretion of clinician. Follow-up every three months, even for stable disease. The National Comprehensive Cancer Network (NCCN) provides guidelines for testing, including calcium and creatinine.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone health–monitoring laboratory tests</td>
<td>Vitamin D and fractionated alkaline phosphate. Hormone levels such as parathyroid and thyroid hormone; testosterone for men; and estradiol, follicle-stimulating, and luteinizing hormone for women.</td>
</tr>
<tr>
<td>Radiology and imaging</td>
<td>Bone survey should be performed annually or with new onset of pain or fracture to monitor for new bone lesions. Bone density tests should be performed if other risk factors are present for osteoporosis. Magnetic resonance image, positron-emission tomography, and computed tomography should be conducted at healthcare provider’s discretion.</td>
</tr>
</tbody>
</table>

### Medications and Supplements

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Very good partial response (VGPR) or better, take monthly for one year; for less than VGPR, take monthly for two years. Stop during remission; restart at relapse.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium supplements</td>
<td>Younger than age 50, use about 1,000 mg per day; for those 50 and older or postmenopausal, use 1,200 mg per day. Calcium supplements should not be used if blood calcium is elevated or kidney function decreased. Consult with an endocrinologist.</td>
</tr>
<tr>
<td>Systemic treatment</td>
<td>For treatment of active disease, maintenance, and disease progression. Treatment options vary and schedule is dependent on regimen prescribed.</td>
</tr>
<tr>
<td>Vitamin D supplements</td>
<td>Younger than age 50, use 400–800 IU per day; for those 50 and older, use 800–1,000 IU per day. Need for additional supplementation is based on blood levels. Consult with an endocrinologist.</td>
</tr>
</tbody>
</table>

### Pain Management

<table>
<thead>
<tr>
<th>Balloon kyphoplasty or vertebroplasty</th>
<th>Painful spinal fractures as a result of osteoporosis or multiple myeloma. May be conducted at the time of a fracture or to prevent further compromise with worsening fractures. Evaluations by orthopedists or spine specialist may be needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications</td>
<td>Pain medications are variable. The World Health Organization provides guidelines for management. Consider evaluations by orthopedists, physical therapists, or pain management clinic professionals.</td>
</tr>
<tr>
<td>Radiation</td>
<td>Should be prescribed for curative intent (palliative to control pain and decrease tumor size). Radiation should be used with caution because it may lead to bone marrow fibrosis and scarring. Coordinate with the radiation oncologist.</td>
</tr>
<tr>
<td>Surgical fixation</td>
<td>Treat impending or actual fracture. Consult with orthopedists.</td>
</tr>
</tbody>
</table>

### Self-Care and Health Maintenance

<table>
<thead>
<tr>
<th>Exercise and activity</th>
<th>At diagnosis, conduct a baseline safety evaluation. Weight-bearing activity promotes bone strength. Consultation with a physical medicine or spine specialist may be recommended to determine activity allowance.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition and hydration</td>
<td>Counsel patients on importance of maintaining a balanced diet and adequate fluid intake. Excess weight can worsen bone pain and muscle fatigue, poor diet can worsen fatigue, and dehydration can worsen fatigue and cause renal dysfunction. Consult with a nutritionist.</td>
</tr>
<tr>
<td>Oral hygiene and dental care</td>
<td>Counsel good oral hygiene and have dental checkups every six months. Avoid invasive dental work if possible. If needed, antibiotics may be prescribed prior to invasive dental procedure. Remind patients to inform their dentist about the use of a bone-strengthening medication.</td>
</tr>
</tbody>
</table>

### Situations that require immediate medical attention include:

- Sudden onset of pain (may indicate a new fracture); back pain with sudden change in sensation in lower or upper extremities or loss of bowel or bladder control (may indicate spinal nerve damage); noticeable changes in mental status such as increased somnolence, confusion, or irritability; or severe constipation, nausea or vomiting, and excessive thirst and urination.

### Guides for monitoring and maintaining bone health:

- Include blood tests and radiologic imaging; bone health is maintained with medications, supplements, and physical activity; and pain management is important for maintaining physical activity and improving quality of life.

---

**Figure 4. Long-Term Survivor Bone Health Plan for Clinicians Treating Patients With Multiple Myeloma**
nausea, loss of appetite, or vomiting. Assessment of hydration and calorie counts and evaluation by a dietician may be necessary if intake is compromised. All patients receiving cumulative external beam radiation therapy may be at risk for radiation dermatitis and are encouraged to keep their skin well hydrated with nonalcohol lotions applied after radiation (Berkey, 2010).

Other common side effects of radiation include fatigue and pain. Patients should be made aware of fatigue as a side effect and be educated about managing their activities. Pain medication may be warranted because individuals are required to remain in an uncomfortable position during the radiation treatment. Opioid or nonopioid analgesics may enhance comfort during and after radiation treatment. A baseline and ongoing pain assessment is integral to the patient’s plan of care.

**Vertebroplasty or Kyphoplasty**

Several studies suggest balloon kyphoplasty and vertebroplasty are effective in reducing pain scores associated with vertebral compression fracture, but each procedure has associated risks. Potential risk is related to the cement injection resulting in extravasation and causing nerve damage or other neurologic issues. General risks include those associated with any surgical procedure, namely increased risk of bleeding and infection. Although minimal blood loss occurs with vertebroplasty and balloon kyphoplasty, this risk increases if patients are thrombocytopenic or are receiving low molecular weight heparin, heparin, warfarin, or antiplatelet agents, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs). Although specific recommendations are not documented, practices followed by Nurse Leadership Board members at their institutions include stopping aspirin and NSAIDs seven days prior to the procedure. Management should be patient specific. Therapeutic anticoagulation should be bridged from warfarin to low molecular weight heparin or heparin, and this should be stopped within six hours of the procedure. Baseline complete blood count, including platelets, white blood count differential, and coagulation studies such as prothrombin time, international normalized ratio, and partial thromboplastin time may be indicated.

Infection risk could rise because of a low white blood cell count as a result of marrow infiltration by myeloma or as a result of the treatment itself. Clinicians should assess complete blood count with white blood cell differential if patients are receiving myelosuppressive antimalma treatment.

Mobility and exercise can be encouraged almost immediately after the procedure. The cement used creates an internal cast hardens within minutes. Patients can resume their usual activities and, if this procedure proves effective at decreasing pain, patients can be weaned off pain medications gradually. The use of slings and orthotic braces are not usually encouraged unless used in preparation for planned surgical intervention because they may reduce mobility and lead to osteopenia (Tariman & Estrella, 2005).

**Bisphosphonates**

Bisphosphonates should be administered monthly for a total duration of two years in individuals with lytic lesions or osteoporosis. The International Myeloma Working Group suggests that using pamidronate or zoledronic acid decreases the risk of skeletal-related events, but the optimal duration of bisphosphonates therapy is unknown (Durie et al., 2007). In patients achieving very good partial response or better from their initial treatment as defined as greater than a 90% reduction in serum or urine paraprotein, bisphosphonates should be given on a monthly basis for one year. Although clear evidence does not exist for modified administration, the International Myeloma Working Group members have agreed that patients should continue bisphosphonates use if they have active bone disease or achieve less than a very good partial response to treatment. If, after two years, the patient does not have evidence of active bone disease, bisphosphonate use may be discontinued. Bisphosphonates should be resumed at the time of relapse if they were discontinued (Durie et al., 2007; Kyle et al., 2007).

Although the aim is to reduce skeletal-related events, bisphosphonates can have adverse effects. Side effects of bisphosphonates include acute phase reactions, a small but increased risk of osteonecrosis of the jaw (ONJ), and renal impairment (Maxwell, Swift, Goode, Doane, & Rogers, 2003). Acute phase reactions present as flu-like symptoms after the bisphosphonate infusion. These symptoms can be decreased with the use of acetaminophen. Other side effects include nausea, fatigue, and bone pain.

Monitoring and surveillance for ONJ is necessary. ONJ is an uncommon but serious condition usually involving the maxilla or mandible that may occur with prolonged use of bisphosphonates. The incidence is relatively low, at 2%–10%. Signs of ONJ may include jaw or tooth pain, and exposed bone may be identified on physical examination. If ONJ symptoms occur, initial treatment should be with antibiotic therapy and not surgical procedures (Cafro et al., 2008). ONJ is thought to be an infectious process, and the use of antibiotic prophylaxis for dental procedures has been studied. The Italian Myeloma Group evaluated patients receiving either amoxicillin-clavulanate 2 g per day by mouth, levofloxacin 500 mg per day by mouth, beginning a day prior, up to three days after a dental procedure, or standard care (no antibiotics). In patients receiving antibiotic prophylaxis with amoxicillin-clavulanate, a decreased incidence of infection with dental procedures such as cleaning, implants, and extractions was noted. More studies are required to validate these findings (Montefusco et al., 2008).

Prevention of ONJ is important, and good dental hygiene is integral to the prevention of ONJ in patients with MM. Patients should receive baseline and routine dental examinations every six months. In addition, dentures should fit well because poorly fitting dentures increase the risk of ONJ (Vahtsevanos et al., 2009). Patients should advise their dental care providers when they are receiving bisphosphonates.

Renal impairment is common in patients with MM. Precautions concerning the use of bisphosphonates in patients with renal impairment are discussed in Faiman et al. (2011).

**Pain Management**

Damage to bones as a result of MM often causes pain; effective doses of analgesia should be administered for patient comfort and to increase mobility and quality of life. A good pain history is essential to assessing the quality and character of a patient’s
Multiple myeloma is treated as a chronic disease and management extends over time. It is important that you keep a history of your general myeloma information and information specific to bone involvement and treatment. Bone health and kidney health are closely related, so it also is important that you are aware of your kidney function. You are your own best advocate.

**My myeloma diagnosis:**
- Ig (G, A, M, E, or D): light chain ___________ (kappa or lambda).
- Date of diagnosis:

**My kidneys are affected:**
- Yes
- No

If yes, my creatinine is _______ and creatinine clearance or glomerular filtration rate is _______ ml per minute.

**My bones are affected:**
- Yes
- No

Bone strengthening (bisphosphonate) medication(s) used:
- Pamidronate (First dose: _____ Last dose: _____ Frequency: _____)
- Zoledronate (First dose: _____ Last dose: _____ Frequency: _____)
- Other: (First dose: _____ Last dose: _____ Frequency: _____)

**Symptoms that require immediate medical attention include:**
- Sudden onset of pain (may indicate a new fracture)
- Back pain with sudden change in sensation in lower or upper extremities or loss of bowel or bladder control (may indicate spinal nerve damage)
- Noticeable changes in mental status such as increased somnolence, confusion, or irritability; or severe constipation, nausea or vomiting, excessive thirst, and urination (may indicate increased calcium in blood)

The following guidelines will help monitor and maintain your bone health, including blood tests and radiographic imaging. Bone health is maintained with medications, supplements, and physical activity. Pain management is important for maintaining physical activity and improving quality of life.

### Medical Follow-Up

**Blood and laboratory tests** (performed at least annually)
- Last date tested: ___________

**Radiology and imaging** (performed annually and with new onset of pain or fracture)
- Last date tested: ___________

**Medications and Supplements**

**Bisphosphonates:** If your disease status is very good partial response rate (VGPR) or better, monthly use for one year is recommended. If your disease status is less than VGPR, monthly use for two years is recommended.

**Pain medication:** Monitor changes in your pain, such as an increase or decrease based on a pain scale of 1 (least pain) to 10 (worst pain).

**Calcium supplements:** Younger than age 50 should take about 1,000 mg per day; those age 50 and older or post-menopausal should take 1,200 mg per day.

**Vitamin D supplements:** Younger than age 50 should take 400–800 IU per day; those age 50 or older should take 800–1,000 IU per day

**Self-Care and Health Maintenance**

**Maintain a balanced diet and hydration (fluid intake):** Try to drink two to three liters (quarts) of fluids per day

**Oral hygiene:** Practice good oral hygiene and have dental examinations every six months

**Exercise and activity:** Regular exercise based on tolerance. No lifting of more than 20 pounds.

**Note:** This patient education tool may be reproduced for noncommercial use.
pain. The pain assessment includes asking a patient about the following.

• Onset: When did it start? Was trauma involved?
• Location: Where is it located?
• Quality: Dull, sharp, burning, or stabbing?
• Duration: How long have you had this pain?
• Character: Is it present when you sit or move? All the time or some of the time?

In addition, patients should be asked to rate their pain according to a pain scale. One of the most common scales is a 1–10 rating system with 1 as minimal pain and 10 as the worst pain. Treatment of the pain with analgesics can be accomplished by using the World Health Organization (2009) pain ladder. Additional management strategies include the use of bisphosphonates and systemic antmyeloma therapy that may have a marked effect on bone pain.

Bone pain from MM can be challenging to control because it usually occurs when patients change position or walk and is often called “incident pain.” Three main types of analgesia are used to treat bone pain and other types of pain related to MM and include nonopioid analgesics, opioid analgesics, and adjunct medications. Nonopioid analgesia includes acetaminophen, NSAIDs, and aspirin. Use of NSAIDs is discouraged because of the risk of renal injury. Many opioid analgesics exist and also can decrease pain, but at the expense of sedation and the risk of constipation. Neuropathic pain often is present after nerve-related injuries such as in peripheral neuropathy, post-herpetic neuralgia, or spinal canal compromise and often is described as “burning or shooting” in character. Medications such as gabapentin or pregabalin, or tricyclic antidepressants such as amitriptyline, can be helpful in decreasing this type of pain (Levy, 1996). Systemic antmyeloma therapy and the use of bisphosphonates will not be effective in reducing pain in some patients, and this group may require bracing or surgical intervention.

Effective pain management is imperative because the psychosocial aspects of pain can lead to depression and anxiety. In addition, uncontrolled pain will result in immobility and muscle and bone wasting, in turn leading to increased risks of atelectasis, pneumonia, and venous thromboembolism. Healthcare providers must recognize this, diligently monitor pain scores, and prescribe analgesia to combat these deleterious side effects (Coleman, 2000).

Patient and Family Education

Nurses play an important role in educating patients as well as promoting functional independence. Activity can decrease fatigue as well as improve mood and prevent insomnia. However, even simple activities can be difficult for patients with pain. All patients must have effective pain management. Patients should be educated regarding the use of NSAIDs and narcotics as educated patients are more likely to adhere to their therapy. Because bone disease can be debilitating throughout the continuum of treatment, a dire need exists to instruct and educate patients and their caregivers regarding the signs and symptoms of depression and anxiety. Interdisciplinary collaboration may be required in the education of the patient. All patients will have varying needs for education regarding their bone health; emphasis on the benefits of treatment will assist patients in adhering to their therapy.

Educational opportunities include the following.

• Using evidence-based recommendations to promote behaviors that enhance bone health
• Instructing patients on how to rate pain using a pain scale
• Informing patients about symptoms of hypercalcemia, a complication of bone disease that includes lethargy, nausea, confusion, thirst, and constipation
• Ensuring the need for bisphosphonate use; advocating good oral hygiene while patients are receiving bisphosphonates
• Referring patients to a clinical social worker or psychiatrist to identify anxiety and depression if necessary
• Counseling to encourage continued adherence to pharmacologic regimens and exercise programs

Useful resources and tools for patients and caregivers, as well as nurses and other healthcare providers, can be obtained from the International Myeloma Foundation at www.myeloma.org.

Conclusion

Recent research in myeloma and the advent of novel agents has led to increased response rates and improved survival. Bone disease as a prognostic indicator and therapies directed at bone disease may alter future treatment regimens and outcomes. Supportive care and the management of bone disease are of the utmost importance to alleviate bone-related sequelae, enhance mobility and disease response, and promote quality of life. Oncology nurses and other healthcare providers play a crucial part in assessing and managing myeloma, along with educating patients, as they live longer and continue to experience both disease- and treatment-related complications.

The authors gratefully acknowledge Brian G.M. Durie, MD, and Robert A. Kyle, MD, for critical review of the manuscript; Lynne Lederman, PhD, medical writer for the International Myeloma Foundation, for preparation of the manuscript; and Lakshmi Kamath, PhD, at ScienceFirst, LLC, for assistance in preparation of the manuscript.

Author Contact: Teresa S. Miceli, RN, BSN, OCN®, can be reached at miceli.teresa@mayo.edu, with copy to editor at CJONEditor@ons.org.

References


Effect of lenalidomide-based regimens on bone remodeling in patients with relapsed/refractory multiple myeloma [Abstract 0192]. Presented at the European Hematology Association 13th Congress in Copenhagen, Denmark.


