

# Bone Health, Pain, and Mobility

## Evidence-based recommendations for patients with multiple myeloma

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**BACKGROUND:** About 85% of patients with multiple myeloma develop bone disease. In these patients, lytic bone lesions can cause fractures, poor circulation, blood clots, pain, poor mobility, and decreased quality of life.

**OBJECTIVES:** This article presents consensus statements to guide nurses in the assessment and management of bone disease, pain, and mobility in patients with multiple myeloma at varying points in their disease trajectory.

**METHODS:** Members of the International Myeloma Foundation Nurse Leadership Board reviewed previously provided recommendations, current recommendations based on literature review, and evidence-based grading.

**FINDINGS:** Oncology nurses play a key role in maximizing bone health, minimizing skeletal injury, maximizing pain control, and improving quality of life in patients by enhancing patient mobility and safety. Clinician assessment accompanied by effective interventions reduces patient injury and optimizes functioning in patients with multiple myeloma.

### KEYWORDS

multiple myeloma; pain; bone health; functional mobility

### DIGITAL OBJECT IDENTIFIER

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**WITH IMPROVEMENTS IN SUPPORTIVE CARE AND TREATMENT,** patients with multiple myeloma (MM) are living longer (Kumar et al., 2014). For patients with MM, bone pain is a hallmark symptom that affects function, mobility, and quality of life (QOL) (Rajkumar, 2009). Health-related QOL includes physical and mental health perceptions (e.g., energy level, mood) and their correlates, as well as health risks and comorbidity, functional status, social support, and socioeconomic status (Centers for Disease Control and Prevention, 2016). In this updated evidence-based consensus statement, the International Myeloma Foundation (IMF) Nurse Leadership Board (NLB) presents the most recent information about bone health and functional mobility, along with evidence-based recommendations for the management of bone pain in MM survivors, with a focus on promoting patient QOL. The IMF NLB uses Melnyk and Fineout-Overholt's (2011) levels of evidence as a systematic framework for the appraisal and grading of the consensus statements and evidence-based recommendations for MM- and treatment-related symptoms. Melnyk and Fineout-Overholt's (2011) rating system has seven levels that are inclusive of evidence from qualitative studies, case-control and cohort studies, reports of expert committees, and opinion of authorities.

### Bone Health in Multiple Myeloma Survivors

Since the 2011 IMF NLB consensus care plan (Miceli, Colson, Faiman, Miller, & Tariman, 2011), the published literature about bone health maintenance has focused on preventing skeletal events through early disease detection. Because most patients with high-risk smoldering MM (which has the potential to evolve into active disease and is considered a premalignant plasma cell proliferative disorder that requires monitoring) progress to active MM within two years, the latest diagnostic criteria for active myeloma now require at least one myeloma defining event (MDE), of which bone disease is one possible type of event (Rajkumar et al., 2014) (see Figure 1). As a result, patients who were classified by previous criteria as having high-risk smoldering MM are now classified as having active MM if they have one MDE (Rajkumar, Larson, & Kyle, 2011). The updated criteria promote starting treatment prior to end-organ damage, such as bone disease (Rajkumar, 2011a; Rajkumar et al., 2014). Consequently, there is growing support for more sensitive diagnostic imaging to identify early bone

disease. Early detection and treatment of MM to prevent bone damage, along with already understood methods to promote bone health, are critical to patient QOL. A patient education tip sheet for managing bone health can be found in Figure 2.

### Evidence-Based Recommendations to Manage and Maintain Bone Health

#### LEVEL OF EVIDENCE I

- Based on the International Myeloma Working Group (IMWG) criteria, active MM should be diagnosed when there is more than one lesion with a diameter greater than 5 mm detected by whole-body magnetic resonance imaging (MRI), even in the absence of end-organ damage (Dimopoulos et al., 2015; Rajkumar et al., 2014). For lesions involving the skull and ribs, the metastatic bone survey may still play an important role in evaluating bone disease. However, the more sensitive imaging techniques, such as 2-deoxy-2 [fluorine-18] fluoro-D-glucose positron-emission tomography (F-FDG-PET), MRI, and whole-body computed tomography have greater diagnostic and prognostic value (Regelink et al., 2013).
- MRI is highly sensitive for early detection of myeloma bone marrow infiltration. The IMWG recommends that all individuals with smoldering or asymptomatic MM be evaluated for bone lesions with whole-body MRI (Rajkumar et al., 2014; Terpos et al., 2013).
- An IV bisphosphonate medication (BPM) every 3–4 weeks is recommended for all newly diagnosed patients with MM. BPM

#### FIGURE 1.

#### DIAGNOSTIC CRITERIA FOR ACTIVE MULTIPLE MYELOMA DISEASE: MYELOMA-DEFINING EVENTS

To meet the definition for a diagnosis of active multiple myeloma warranting treatment, a person must have at least 10% clonal bone marrow plasma cells, or biopsy-proven bone or soft tissue (extramedullary) plasmacytoma, and any one or more of the following features attributable to the disease process:

- Calcium elevation: Greater than 1 mg/dl above the upper limits of normal, or greater than 10.5 mg/dl
- Renal insufficiency: Creatinine greater than 2 mg/dl or creatinine clearance less than 40 ml per minute
- Anemia: Hemoglobin less than 10 g/dl or 2 g below baseline
- Bone disease: Diffuse osteoporosis; one or more osteolytic lesions on skeletal imaging

#### ADDITIONAL DIAGNOSTIC CRITERIA ADDED TO THE 2014 INTERNATIONAL MYELOMA WORKING GROUP CRITERIA

- Greater than 60% clonal bone marrow plasma cell
- Serum free light chain ratio (involved:uninvolved) of 100 or greater
- More than one focal lesion (5 mm or greater) detected by magnetic resonance imaging

**Note.** Based on information from Durie et al., 2003; Rajkumar et al., 2011a, 2014.

## “Early detection and treatment of multiple myeloma to prevent bone damage is critical to patient quality of life.”

may be stopped or its frequency decreased after 12–24 months at the provider’s discretion for patients who have no evidence of bone disease and have achieved a complete response to MM therapy (Terpos et al., 2013).

- With long-term use of BPM, patients are at risk of developing osteonecrosis of the jaw (Miceli et al., 2011; Terpos et al., 2013). For this reason, IMWG guidelines include dental evaluation prior to initiation of therapy and minimum annual dental evaluations after the initiation of BPM. Patients should avoid dental extractions, if possible. If osteonecrosis of the jaw develops, BPM should be held until relapse of the MM occurs.
- Close monitoring of renal function is required, and serum creatinine should be assessed before each BPM treatment; the dose should be held if there is evidence of renal dysfunction as defined as a creatinine clearance less than 30 ml per minute. Patients with a creatinine clearance of 30–60 ml per minute should receive reduced doses of zoledronate with no change to infusion time, whereas pamidronate should be given via a four-hour infusion (Terpos et al., 2013).
- Calcium and vitamin D supplements should be prescribed to promote bone health if no clear contraindications are noted (National Osteoporosis Foundation, 2017). This is relevant to patients with MM because 60% are vitamin D deficient and in need of supplementation to prevent bone resorption, decrease parathyroid hormone levels, and maintain bone health (National Osteoporosis Foundation, 2017; Terpos et al., 2013).

#### LEVEL OF EVIDENCE III

- Balloon kyphoplasty or vertebroplasty is recommended for vertebral compression fractures (Dudeney, Lieberman, Reinhardt, & Hussein, 2002; Hadjipavlou, Tzermiadianos, Katonis, & Szpalski, 2005; Lane et al., 2004).
- Low-dose radiation therapy (as much as 30 Gy) and orthopedic consultation are recommended for the management of vertebral compression fractures, impending or actual long bone fractures, and associated pain (Miceli et al., 2011; Terpos et al., 2013).

- In one prospective cohort study, osteolytic lesions were detected using F-FDG-PET in patients, particularly in patients with smoldering MM, without pain or destructive lesions on metastatic bone survey (Siontis et al., 2015).

## Pain Prevention and Management in Multiple Myeloma Survivors

The prevention and management of pain is a priority for the NLB, which has addressed the topic in several publications (Miceli et al., 2011; Richards & Brigle, 2016; Tariman, Love, McCullagh, & Sandifer, 2008). Physician counterparts within the IMWG also place a priority on pain management in several of their publications (Johnson et al., 2011; Moreau et al., 2011; Richardson et al., 2012; Terpos et al., 2013). Tip sheets for patients and for healthcare providers can be found in Figures 3 and 4.

### Primary Sources of Multiple Myeloma Pain

Pain can be acute or chronic in patients with MM. Acute pain is of short duration, has an identifiable cause, and functions to warn people about and protect them from tissue damage. In most clinical situations, acute pain resolves. In contrast, chronic pain lasts longer than expected for typical recovery time following tissue

injury. In general, chronic pain continues for longer than one to six months or recurs at intervals over time. Patients with MM may experience acute pain, chronic pain, or both, because both types can occur simultaneously depending on the disease state and any ongoing diagnostic procedures or treatments (Miaskowski, 2010).

In many instances, pain associated with MM may be prevented and treated. For this reason, members of the healthcare team should continuously assess patients for pain and modify treatment regimens based on current symptoms. Treatment options are numerous; however, pain management requires constant shared communication between the healthcare team and the patient. Referral to a pain specialist or palliative care service may be necessary if pain persists despite multiple unsuccessful management attempts (Miceli et al., 2011).

### Sources of Pain

Cancer can cause pain through several mechanisms, making pain one of the most feared and prevalent symptoms in all patients diagnosed with cancer (Faiman, 2016). Because MM involves bone disease, bone pain is one of the most common symptoms of MM (Kyle & Rajkumar, 2009). In addition, patients with MM may also experience neuropathic and procedural pain. Identifying the

**FIGURE 2.**

## PATIENT EDUCATION TIP SHEET: MANAGING BONE HEALTH IN MULTIPLE MYELOMA

### KEY POINTS

Most patients with multiple myeloma will develop bone lesions, leading to pain, possible fractures, and decreased mobility. Maintaining bone health is important for reducing pain and the risk for fractures, as well as for maximizing mobility. Side effects from treatment, like neuropathy or muscle weakness, can affect your ability to move safely. Your healthcare provider may change your medication dose or schedule to help manage your symptoms.

### PREVENTION OF FRACTURES

Make sure you have tests done if they are recommended by your healthcare provider.

- Laboratory tests (e.g., complete blood count, creatinine)
- Bone health monitoring laboratory tests (e.g., vitamin D, alkaline phosphatase, calcium, specific hormones for men and women)
- Radiologic imaging (e.g., positron-emission tomography, computed tomography, magnetic resonance imaging, bone survey, bone density test)

Take medications and supplements if they are prescribed or recommended by your healthcare provider.

- Bisphosphonates (e.g., zoledronic acid, pamidronate)
- Supplements (e.g., calcium, vitamin D); your healthcare provider may check your kidney function while you are taking these.
- Pain medication for bone pain

Maximize your nutrition.

- Review a dietary plan with your healthcare provider.

- Meet with a nutritionist if recommended by your healthcare provider.
- Perform good daily oral hygiene and have a dental examination every six months. Be sure to inform your dentist if you are taking a bone-strengthening medication.

Maximize your functioning.

- Talk to your healthcare provider about a plan for daily physical activities, including activities that help with balance, strength, and fitness.
- If needed, use devices to help you with mobility, including a cane or walker.
- If needed, use pain medication to help decrease your pain and improve your mobility.
- Improve your sleep quality to promote your well-being and decrease your pain and fatigue.

Be aware of symptoms that require immediate attention.

- 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 sleepiness, confusion, or irritability
- Severe constipation, nausea or vomiting, and excessive thirst and urination
- Falling, tripping, or loss of balance

**Note.** Based on information from Denlinger et al., 2014; National Comprehensive Cancer Network, 2017b, 2017d; Rock et al., 2012; Schmitz et al., 2010.

underlying source of pain may help optimize treatment for each patient with MM.

### Bone Disease as a Source of Pain

MM has a higher incidence of bone involvement than any other malignant disease. For this reason, pain is a presenting characteristic in a high proportion of patients diagnosed with MM. Osteoporosis, osteolytic bone lesions, pathologic fractures, and vertebral compression fractures are common findings at diagnosis and throughout the course of MM. An estimated 80%–90% of all patients with MM experience pain from bone involvement, and 60% develop pathologic fractures (Delgado-Calle, Bellido & Roodman, 2014; Greenberg et al., 2014; Kyle & Rajkumar, 2009).

### Neuropathic Pain

Neuropathic pain is caused by abnormal somatosensory processing in the peripheral or central nervous system (Dworkin et al., 2010). It is less common than pain caused by bone involvement but can be unrelenting and influence patient QOL. Neuropathic pain can

present as peripheral neuropathy (PN) at the time of MM diagnosis or may be related to comorbid conditions, such as amyloidosis, cryoglobulinemia, spinal cord impingement, or autoimmune mechanisms (Mohty et al., 2010). Symptoms of PN are also common in patients diagnosed with disorders such as diabetes, peripheral vascular disease, nutritional deficiency, alcoholism, postsurgical changes, and inherited diseases (Staff & Windebank, 2014; Yorek, 2015). Postherpetic neuralgia (PHN), another cause of neuropathic pain, is a direct result of reactivation of the varicella-zoster virus (VZV), which may occur in patients with MM because of stress, weakened immunity from active disease, or treatment (Faiman, 2016).

### Procedural Pain

Patients with MM may undergo multiple necessary procedures throughout their diagnostic evaluations and treatment courses. Although necessary for assessment of disease activity and treatments, procedures—such as tumor biopsy, central line placement, surgical interventions, venipuncture, and bone marrow biopsies—are all sources of recurrent, acute pain (Rajkumar et al., 2014).

#### FIGURE 3.

#### PATIENT EDUCATION TIP SHEET: PREVENTING AND MANAGING MULTIPLE MYELOMA PAIN

##### KEY POINTS

Most patients with multiple myeloma have pain at some time. The pain can be caused by bone disease, including fractures, or by neuropathic pain caused by nerve damage. In addition, you may experience pain during medical tests or treatments, including when you have your blood drawn or an IV placed.

To best treat pain, it is important to undergo a thorough assessment by your healthcare provider. Tell your healthcare team important information, such as where the pain is located and how it feels. Include descriptions of how intense it is, how long it lasts, when it started, and what makes it worse or better. Let them know what has been tried to relieve the pain—what has worked, what has not. As part of the assessment, you will need to undergo a physical examination and may need radiologic imaging (i.e., x-ray, magnetic resonance imaging, positron-emission tomography) if you have muscle or bone pain.

Medications may be prescribed to treat bone disease and decrease bone pain. Starting on anti-myeloma therapy and using bisphosphonate therapy can treat and prevent bone disease.

The use of IV bisphosphonates (pamidronate or zoledronic acid) can reduce pain and prevent skeletal events secondary to bone involvement. Procedures like vertebroplasty or kyphoplasty, local radiation, or even surgery may be used to treat pain and prevent further bone damage.

Treatment of neuropathic pain is difficult and, therefore, prevention is important. For patients receiving bortezomib therapy, subcutaneous administration is associated with lower rates of peripheral neuropathy than IV administration. Dosing and scheduling adjustments can also be made to prevent worsening of symptoms. You should also receive antiviral medication (e.g., acyclovir) to prevent activation of varicella-zoster virus, more commonly known

as shingles. Pain medications, such as narcotics and other classes of drugs, may be prescribed for acute and ongoing pain. Any medication should be taken as prescribed for best effect.

Procedural pain may be difficult to avoid because procedures and interventions are needed for assessment of disease response and activity. If you experience pain or anxiety related to procedures, be sure to ask your healthcare team if there are medications available to reduce the pain and relieve anxiety. Share laboratory test results with healthcare providers, such as your hematologist and your primary care provider, to avoid unnecessary repetition of blood draws.

##### TIPS AND REMINDERS

- Be sure to inform your healthcare team of new onset of pain or pain that is not helped by treatment.
- Keep a calendar to remember when you are due for your next bisphosphonate treatment.
- If you are taking narcotics to treat your pain, be sure to stay on a bowel regimen to prevent constipation.
- Take medications for pain as prescribed, adjusting doses only after discussion with your healthcare team.
- If proteasome inhibitors (such as bortezomib, carfilzomib, or ixazomib) are part of your treatment plan, be sure you are receiving antiviral medication to prevent shingles.
- Physical activity can help with pain management. Consider a physical therapy evaluation to promote safe activity and strengthening.

**Note.** Based on information from Denlinger et al., 2014; Moreau et al., 2011; National Comprehensive Cancer Network, 2017a, 2017b, 2017c, 2017d; Rock et al., 2012; Schmitz et al., 2010.

Patient-focused approaches to limiting the number of blood draws can be achieved by consolidating laboratory tests from different care providers (e.g., primary care, hematology) into single blood draws (Rajkumar et al., 2014). In addition, conscious sedation may be provided in some institutions for invasive procedures, such as bone marrow biopsies, alleviating this recurrent source of pain and procedure-related anxiety (Hjortholm et al., 2013).

## Evidence-Based Recommendations to Manage Pain

### LEVEL OF EVIDENCE I

- Pain can adversely affect QOL in patients with cancer and should be prevented, when possible, or effectively managed

to reduce physical and emotional distress (Mesgarpour et al., 2014; Miaskowski, 2010).

- Comprehensive pain assessment starts with a detailed history, examination of the painful site(s), and a diagnostic evaluation, which may include radiologic imaging, to find a source of musculoskeletal pain. The next steps are to determine the effect of pain on the patient's QOL and overall function, and to determine what interventions are needed to relieve the pain (Miaskowski, 2010).
- Patients should be questioned about the impact of pain, specifically on their functional status and activities of daily living. Patients should also be questioned about any previous coping strategies they may have had that worked, any financial issues

### FIGURE 4.

## HEALTHCARE PROVIDER TIP SHEET: PAIN MANAGEMENT IN MULTIPLE MYELOMA

With improvements in supportive care and treatment, patients with MM are living longer. Because pain is a major symptom of MM, pain prevention and management are important for patient quality of life.

### SOURCES OF PAIN

- Bone disease: Osteoporosis, osteolytic bone lesions, pathologic fractures, and/or vertebral compression fractures are common findings at MM diagnosis and throughout the course of the disease.
- Neuropathic pain: Neuropathic pain is not as common as pain caused by bone involvement; however, it can be difficult to treat and influence quality of life. Neuropathic pain can present as PN, which may be present at diagnosis or related to treatment. Postherpetic neuralgia, another cause of neuropathic pain, is a direct result of reactivation of VZV.
- Procedural pain: Throughout their illness, patients with MM undergo multiple procedures that can cause acute pain. Routine blood work and frequent bone marrow biopsies are sources of recurrent, acute pain.

### ASSESSMENT, PREVENTION, AND MANAGEMENT

To best treat pain, it is important to perform thorough assessments at baseline and at each encounter. The healthcare team should collect information regarding pain location, intensity, and duration, as well as when it started and what makes it worse or better, including treatments. A physical examination should be performed, and radiologic imaging (i.e., x-ray, magnetic resonance imaging, positron-emission tomography) may be needed to evaluate new musculoskeletal pain.

Medications may be prescribed for bone disease. Anti-myeloma therapy and use of bisphosphonate therapy can treat and prevent bone disease. The use of IV bisphosphonates (pamidronate and zoledronic acid) can reduce pain and prevent skeletal events secondary to bone involvement. Analgesic medications, such as narcotics, may be prescribed to better manage pain and allow for improved mobility. Procedures like local radiation, vertebroplasty or kyphoplasty, or even surgical fixation may be used to treat pain and prevent additional bone damage.

Treatment of neuropathic pain is difficult and, therefore, prevention is important. For patients receiving bortezomib therapy, subcutaneous administration is associated with lower rates of PN than IV administration. Dosing and scheduling adjustments can also be made to prevent worsening of symptoms. Patients

receiving bortezomib or ixazomib therapy should also receive antiviral medication (e.g., acyclovir) to prevent activation of VZV. Pain medications, such as narcotics and other classes of drugs, may be prescribed for acute and chronic pain.

Procedural pain may be difficult to avoid because procedures and interventions are needed for assessment of disease response and activity. Patients may experience pain or anxiety related to procedures. Be sure to discuss the use of premedications to reduce procedural pain and anxiety. When possible, consolidate the collection of blood for different laboratory tests into as few blood draws as possible to minimize the number of painful venipunctures.

### TIPS AND REMINDERS

- Remind patients to inform the healthcare team of new onset of pain or pain that is not well managed before they start any self-treatment with over-the-counter medications.
- Assess pain at each visit or encounter.
- Ensure that the primary provider prescribes medications for pain, adjusting doses based on the patient's response.
- If narcotics are prescribed to manage pain, make sure a bowel regimen is also prescribed to prevent constipation.
- If the patient is receiving bortezomib, carfilzomib, or ixazomib as part of the treatment plan, be sure an antiviral medication to prevent shingles is also prescribed.
- Bortezomib given by subcutaneous injection is associated with lower risk of PN than IV administration.
- Physical activity can help with pain management. Consider recommending that the provider prescribe a physical therapy evaluation to promote safe physical activity and strengthening.
- Make sure that the patient receives premedications for painful or anxiety-producing procedures, such as bone marrow biopsy or magnetic resonance imaging.

MM—multiple myeloma; PN—peripheral neuropathy; VZV—varicella-zoster virus

**Note.** Based on information from Denlinger et al., 2014; Moreau et al., 2011; National Comprehensive Cancer Network, 2017a, 2017b, 2017c, 2017d; Rock et al., 2012; Schmitz et al., 2010.

as a result of their functional status, and any concerns about opioid use to manage pain (Greco et al., 2011; Ripamonti, Santini, Maranzano, Berti, & Roila, 2012).

- Clinicians can initiate measures to quickly relieve acute pain while the patient is undergoing evaluation to determine the specific etiology of the pain (Portenoy, 2011).
- Interventions to alleviate pain include pharmacologic and non-pharmacologic strategies, which are chosen based on results of the initial pain assessment. Treatment effectiveness is continuously assessed and changes made based on the clinical situation and the patients' response (Miaskowski, 2010).
- Neuropathic pain can progress from being mildly uncomfortable to being incapacitating and limiting function and QOL in patients with MM. Healthcare providers must prevent neuropathic pain when possible and, if present, to diagnose and treat it. PN is a neuropathic pain and is associated with various medications, including thalidomide and bortezomib (Mohty et al., 2010; Moulin et al., 2014).

#### LEVEL OF EVIDENCE II

- Conduct a comprehensive assessment to determine the type of pain being experienced and the best interventions for any patient with MM. The initial step in assessing pain is derived from the patient's self-report, including the description, intensity, duration, etiology, and characteristics of pain. In addition, any aggravating and alleviating factors should be determined. The effectiveness of interventions already attempted, such as medications, rest, activities, heat, or cold compresses, should be determined (National Comprehensive Cancer Network [NCCN], 2017a).

#### LEVEL OF EVIDENCE V

- Hjortholm et al. (2013) provide pharmacologic and nonpharmacologic strategies to reduce procedural pain associated with bone marrow biopsy and aspiration. Many of the nonpharmacologic strategies, such as hypnosis, music, and cognitive behavioral therapy, may be used to reduce other sources of procedural pain and anxiety.

### Pharmacologic Interventions for Pain

#### LEVEL OF EVIDENCE I

- Based on the World Health Organization (1990, 2017) analgesic ladder, opioids are the principal analgesics to treat moderate-to-severe pain. Opioids prescribed for chronic pain should be administered on a regular basis. Before an opioid is prescribed and administered, nurses, providers, and pharmacists should have an understanding of the medication's mechanism of action, common starting doses, equivalence to other opioids, duration of effect, half-life, available routes, and associated adverse effects.
- Breakthrough pain medication may be needed at the end of the extended-release medication schedule or with added activity during

the day (McMenamin, 2011; Miaskowski, 2010; NCCN, 2017a). Nonsteroidal anti-inflammatory medications are associated with renal toxicities and, therefore, should be avoided in patients with MM, who are at risk for renal dysfunction (NCCN, 2017c).

- Pharmacologic treatment of metastatic bone disease requires a multi-strategy approach. This includes treatment of the underlying disease, opioid/analgesic medications, and use of bisphosphonate therapy. The use of IV BPM (pamidronate and zoledronic acid) as supportive care for patients with MM may reduce pain, increase calcium levels, decrease skeletal complications secondary to bone involvement, and improve QOL (NCCN, 2017c; Terpos et al., 2013).
- The administration of BPM significantly reduces the number of skeletal events. Either pamidronate or zoledronic acid is recommended for patients with MM who have one or more lytic lesions identified radiologically (Pozzi & Raje, 2011).

#### LEVEL OF EVIDENCE II

- Initial opioid titration for opiate-naïve patients is done at a slower pace than in opiate-tolerant patients (NCCN, 2017a). When long-acting opioids do not adequately control pain, a short-acting or breakthrough medication should be prescribed. Administration of BPM can decrease pain, improve performance, and preserve QOL (NCCN, 2017c).

### Nonpharmacologic Interventions for Pain

#### LEVEL OF EVIDENCE I

- The efficacy of complementary and alternative medicine (CAM) in cancer pain management was systematically reviewed in 2006 (Bardia, Barton, Prokop, Bauer, & Moynihan, 2006). Although the authors mentioned hypnosis, imagery, support groups, acupuncture, and healing touch as promising interventions, given the paucity of rigorous trials, the authors did not recommend these CAM approaches for pain management.
- Two systematic reviews among patients with hematologic cancers revealed limited data to support an improvement in patient QOL associated with yoga and meditation (Felbel, Meerpohl, Monsef, Engert, & Skoetz, 2014; Salhofer, Will, Monsef, & Skoetz, 2016).

#### LEVEL OF EVIDENCE III

- The IMF NLB recommends either vertebroplasty or kyphoplasty for the treatment of vertebral compression fractures. These procedures successfully decrease pain and potentially restore or prevent loss in height. Vertebroplasty is performed by injecting methyl methacrylate into collapsed vertebra, and kyphoplasty is performed by inserting an inflatable balloon followed by the methyl methacrylate injection (Dudeney et al., 2002; Hadjipavlou et al., 2005). Pain relief is generally rapid and can be long-lasting (Lane et al., 2004).
- Localized external radiation is a widely accepted treatment option to control MM pain. The IMF NLB recommends radiation

therapy primarily for the treatment of solitary plasmacytoma, symptomatic spinal cord compression, extremely painful lytic lesion, and for the prevention of pathologic fractures. However, radiation therapy may cause delays in systemic therapies because of the combined toxicity associated with aggressive systemic therapy and radiation (Terpos et al., 2015).

#### LEVEL OF EVIDENCE IV

- CAM may offer several options for patients with symptoms related to MM or MM treatment. In the 2007 National Health Interview Survey, individuals with cancer listed the five most common complementary therapies practiced as vitamin or mineral supplement, prayer for self, intercessory prayer, chiropractic/osteopathic manipulation, and herbal therapies (Anderson & Taylor, 2012).

### Management and Prevention of Neuropathic Pain

#### LEVEL OF EVIDENCE I

- According to a recent systematic review, pain management is the most studied and established role for cannabinoid therapies (Maida & Daeninck, 2016). Most of the information about cannabis use is derived from patients with symptoms of PN (Maida & Daeninck, 2016). In addition, cannabinoids appear to be safe when used in appropriate doses. A meta-analysis reported that about 1 in every 5–6 patients with PN improved with inhaled cannabis (Andreae et al., 2015).
- A systematic review indicated that cannabinoids are effective adjuvants for opioid therapy in patients whose cancer pain is not completely relieved by opioid therapy alone (Tateo, 2017). However, the author cautions that there is a paucity of high-quality studies to support a stronger conclusion about cannabinoids for cancer pain (Tateo, 2017).
- A systematic review revealed that inhaled cannabis is associated with potential pulmonary issues and, therefore, the IMF NLB recommends ingesting cannabis to avoid these detrimental side effects (Tetrault et al., 2007).

#### LEVEL OF EVIDENCE II

- For patients receiving bortezomib therapy for relapsed MM, subcutaneous was equal in efficacy to IV administration and associated with lower rates of PN (Moreau et al., 2011).
- Dosing and scheduling adjustments of potentially neurotoxic agents can also be made to reduce onset or progression of PN symptoms (Richardson et al., 2012). Concomitant prophylactic use of antiviral medication, such as acyclovir, with proteasome inhibitor therapy will prevent activation of VZV and postherpetic neuralgia.

#### LEVEL OF EVIDENCE III

- In general, the studies of CAM therapies are small and not randomized, controlled trials, which makes it difficult to de-

termine the efficacy of specific CAM interventions. However, data suggest that providing CAM therapies with concurrent chemotherapy improves QOL in patients with cancer (Bar-Sela, Danos, Visel, Mashiach, & Mitnik, 2015).

- In a recently published study by Han et al. (2017), patients with MM received methylcobalamin therapy or methylcobalamin and acupuncture to alleviate symptoms of PN. The study reported a decrease in PN pain scores that was greater in the acupuncture than the non-acupuncture group. Using a visual analog scale, the pain scores decreased in 86% of participants in the methylcobalamin plus acupuncture group compared to 78% in the methylcobalamin-only group. In addition, the magnitude of decrease was 5.6 to 3.2 versus 5.5 to 4.3. A decrease of 2 points on an 11-point pain visual analog scale is considered clinically relevant (Farrar, Young, LaMoreaux, Werth, & Poole, 2001; Han et al., 2017).

#### LEVEL OF EVIDENCE IV

- For patients experiencing PN or PHN, coanalgesics often are used in conjunction with opioids to treat neuropathic pain (Fallon, 2013). Coanalgesics, or adjuvant analgesics, have pain-relieving properties in specific clinical situations; however, the primary indications of coanalgesics are not for the treatment of pain. Common coanalgesic medications include antidepressants (nortriptyline, duloxetine, or venlafaxine), anticonvulsants (gabapentin and pregabalin), corticosteroids, and topical agents (capsaicin or local anesthetics) (Fallon, 2013; Moulin et al., 2014; NCCN, 2017a).
- Tricyclic antidepressants are effective and inexpensive medications used to treat neuropathic pain; however, patients should be monitored for cardiotoxicity, urinary retention, orthostatic hypotension, constipation, and drowsiness. Secondary amine tricyclic antidepressants, such as nortriptyline and desipramine, are preferred over tertiary amine tricyclic antidepressants (e.g., amitriptyline, imipramine) because they are better tolerated by older adults (Fallon, 2013; Moulin et al., 2014; NCCN, 2017a).
- Anticonvulsants and antidepressants used for neuropathic pain management should be increased slowly to avoid toxicities (Moulin et al., 2014; NCCN, 2017a).

### Mobility and Safety in Multiple Myeloma Survivors

Mobility and safety practice recommendations were provided by Rome, Jenkins, and Lilleby (2011), which incorporated aspects of health maintenance with promotion of QOL. As previously noted, mobility challenges vary among patients with MM and may change over time. An individual plan of care is based on physical activity, the overall level of functioning, frailty, and fall risk.

Exercise is an effective behavioral intervention with the potential to mitigate multiple side effects and improve physical function in patients with cancer and survivors. Exercise can improve side effects, such as fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction (Mustian,

Sprod, Janelsins, Peppone, & Mohile, 2012), and symptom clusters (Mustian et al., 2016). Many cancer survivors are highly motivated to seek information about nutrition, physical activity, dietary supplement use, and complementary therapies (Rock et al., 2012). Most patients with cancer report that they do not discuss initiating or continuing an exercise program, yet they want healthcare providers to initiate discussions about exercise (Mustian et al., 2012). Clinicians should feel encouraged that lifestyle behaviors are one area survivors can control if they are prompted to change and are provided with resource information. Interventions may include telephone-based health behavior coaching and positive feedback, as well as motivational counseling (Denlinger et al., 2014). Survivors often have heightened motivation, particularly close to the time of diagnosis, and this is perhaps the ideal time to employ an exercise program or other behavioral intervention in the treat-

ment plan (Mustian et al., 2012). Tip sheets for patients and for healthcare providers can be found in Figures 5 and 6.

**Evidence-Based Recommendations to Improve Mobility and Safety**

**LEVEL OF EVIDENCE I**

■ The American Cancer Society, through a group of experts, developed nutritional and physical activity guidelines for cancer survivors (Rock et al., 2012). These guidelines offer detailed information in the following categories: (a) nutrition and physical activity across the cancer continuum; (b) weight management, physical activity, food choices, alcohol intake, and food safety; (c) selected cancer sites; and (d) answers to common questions many survivors have (Rock et al., 2012). These guidelines may be implemented in any clinical practice.

**FIGURE 5.** HEALTHCARE PROVIDER TIP SHEET: MOBILITY AND SAFETY IN PATIENTS WITH MULTIPLE MYELOMA

Evidence suggests that exercise is an effective intervention for reducing side effects such as fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction. An individual plan of care should be based on physical activity, the overall level of functioning, frailty, and fall risk. Perform focused clinical evaluation as appropriate.

- Weight/body mass index
- Vital signs
- Functional status and frailty status
- Barriers to physical activity and safety
  - Environment, including gym access, home, outdoor space, and home safety
  - Financial
  - Physical limitations
  - Time/competing demands and priorities
  - Knowledge/interests
  - Social support

Assess factors and comorbidities that can impede safe activity and exercise with the healthcare team at each patient encounter.

- Cardiovascular and pulmonary disease
- Arthritis and musculoskeletal issues, including steroid myopathy
- Pain, including neuropathy
- Bone health and/or presence of lytic lesions, including the need for assistive devices
- Hematologic problems, including anemia, neutropenia, and thrombocytopenia
- Fatigue and its contributing factors, including endocrine, electrolyte, sleep, and other dysfunctions
- Emotional distress, including depression, anxiety, and substance abuse
- Nutritional deficits
- Medications, including polypharmacy
- Prior and current participation in physical activity and other health behaviors

- Eating habits and patterns
  - Alcohol and tobacco use
  - Physical activity habits and patterns
- Based on results of the mobility and safety assessment, make recommendations along with the healthcare team regarding the level of activity and exercise, including long- and short-term goals (light, moderate, and vigorous exercise). Make periodic reassessment and recommend modifications, if needed.
- All survivors should avoid inactivity or a sedentary lifestyle and should return to daily activities as soon as possible.
  - Survivors who are able should engage in daily physical activity, including exercise, routine activities, and recreational activities.
  - Physical activity and exercise recommendations should be tailored to the individual's abilities and preferences. Even light activity can improve physical functioning in survivors, and clinicians should advise survivors against inactivity.
  - General recommendations
    - Overall volume of weekly activity should be at least 150 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity, or an equivalent combination (light exercise: no noticeable change in breathing pattern; moderate exercise: can talk but not sing; vigorous exercise: can say a few words without stopping to catch breath).
    - Survivors should engage in two to three sessions per week of strength training and stretching that includes major muscle groups.
    - Stretch major muscle groups on a routine basis.
  - Inactive survivors can begin with one to three light- or moderate-intensity sessions of 20 minutes or more per week, with progression based on how well they tolerate the activity.
  - Walking and using a stationary bike are safe for virtually all survivors.

**Note.** Based on information from Denlinger et al., 2014; National Comprehensive Cancer Network, 2017a, 2017b, 2017d; Rock et al., 2012; Schmitz et al., 2010.



- A Cochrane systematic review by Bergenthal et al. (2014) was conducted on the quality of trials on aerobic physical exercise for adult patients with hematologic malignancies, including MM. Based on the findings from this systematic review, the IMF NLB recommends that physical exercise should be incorporated with standard care to improve patient QOL, particularly aspects of physical functioning, depression, and fatigue. Three trials investigated serious adverse events of physical exercise, and found no evidence of an increase in serious adverse events, such as bleeding, fever, thrombosis, pneumonia, and other infections, with exercise (Bergenthal et al., 2014).

#### LEVEL OF EVIDENCE II

- The NCCN guidelines on survivorship propose that structured aerobic and resistance training programs, when initiated after treatment, can improve cardiovascular fitness and strength and can have positive effects on balance, body composition, and QOL (Denlinger et al., 2014; NCCN, 2017b).

#### LEVEL OF EVIDENCE III

- Several studies demonstrated that physical activity can be safely performed by MM survivors, and there is evidence suggesting physical activity may aid in various treatments and alleviate some comorbidities (Coleman et al., 2003; Coon & Coleman, 2004a, 2004b; Groeneveldt et al., 2013; Jones et al., 2004).

#### LEVEL OF EVIDENCE VII

- Care should be provided to frail patients by a range of health-care providers, including geriatricians, psychiatrists, pharmacists, physiatrists, social workers, and dietitians (Tuchman et al., 2014). The goal for these patients is to reduce stressors that can enhance frailty and potentially limit effective treatment. Because of the increased toxicities that may occur in older adult patients with cancer, careful selection of treatment and adjuncts is critical to reduce harm; for example, the risks and benefits of anticoagulation for prevention of venous thromboembolism should be carefully considered in patients already at risk for falls and bleeding (Tuchman et al., 2014).

### Functional and Frailty Assessment

About one-third of patients with MM are older than age 75 years at diagnosis. However, the population is heterogeneous, and tolerability of treatment is not defined by age alone, but rather by a combination of age, physical function, cognitive function, and comorbidities (Pawlyn, Gay, Larocca, Roy, & Ailawadhi, 2016). In addition to a general assessment, patient-specific screening of functioning, fall risk, frailty, and comorbidity indices should be employed (Bila et al., 2015). A variety of tools are available to assess fall risk and were previously described by Rome et al. (2011). The NCCN guidelines on survivorship (Denlinger et al., 2014; NCCN, 2017b) recommend that a risk assessment for exercise-induced adverse events be used based on disease and treatment

#### FIGURE 6.

### PATIENT EDUCATION TIP SHEET: MOBILITY AND SAFETY IN MULTIPLE MYELOMA

#### KEY POINTS

Physical activity can help reduce side effects of multiple myeloma and your therapy, such as fatigue and weakness. By keeping active, you can also reduce your risk of injury from falls. Your healthcare provider can direct you in safe activities that will benefit you and that you can enjoy. The following are some general recommendations.

- Avoid inactivity or a sedentary lifestyle and return to daily activities as soon as possible, unless otherwise directed by your healthcare team.
- Engage in daily physical activity, including exercise, routine activities, and recreational activities.
- Discuss physical activity and weight control with your healthcare provider. This should be a part of your treatment plan. Consider an appropriate exercise program and possible referral to an exercise specialist who will work with your healthcare team.
- Consider nutrition consultation to optimize nutrition.
- Delay exercise if severely anemic and return to exercise when the anemia has improved.
- If you are fatigued, inform your healthcare team and employ energy conservation measures, such as structured daily routine and setting priorities.

- If you experience severe fatigue from your therapy, do 10 minutes of light exercises daily if approved by your healthcare team.
- If you have difficulty sleeping, speak to your healthcare team regarding strategies to promote adequate sleep.
- Avoid public gyms and pools if you have a compromised immune system.
- Avoid chlorine exposure (e.g., swimming pools) if undergoing radiation therapy.
- Avoid pools, lakes, or ocean water if you have an indwelling catheter or other tube coming out of your body. Also, avoid resistance training of muscles in the area of the catheter or tube to avoid it being pulled.
- Your exercise program may need to be modified if you have other medical problems that put you at risk for injury or harm.
- Your exercise programs can be modified for your safety if you have significant neuropathies, balance, or limb problems. For example, a stationary bike may be safer than a treadmill.
- Make sure to let your healthcare team know if you have changes in your ability to move or exercise safely.

**Note.** Based on information from Denlinger et al., 2014; National Comprehensive Cancer Network, 2017a, 2017b, 2017d; Rock et al., 2012; Schmitz et al., 2010.

history, late and long-term effects, and comorbidities. The NCCN guidelines recommend that the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) be considered as an assessment tool (Bredin, Gledhill, Jamnik, & Warburton, 2013).

Patients with MM are at moderate risk for exercise-induced adverse events because of PN, bone metastases, poor bone health, arthritis, and musculoskeletal issues. Stability, balance, and gait should be assessed in these patients, and exercise plans should be tailored to the condition of each patient (e.g., stationary bike and water aerobics for patients with poor balance). Patients with MM should also be assessed for fracture and spinal cord compression risk. These moderate-risk survivors can often follow general recommendations, but with specific medical clearance and referrals to trained personnel for their exercise programs (Denlinger et al., 2014).

A comprehensive geriatric assessment (CGA) for those aged 65 years or older should be routinely conducted. CGA appraises objective health, including comorbidities and functional status, that can impact prognosis and treatment (NCCN, 2017c). Functional status includes activities of daily living and instrumental activities of daily living. With MM treatment and adjunct therapies, functional status can improve or worsen. Therefore, functional status assessment should be ongoing and include fall and gait assessment; medication review; and psychological, physical, and cognitive function (NCCN, 2017c).

The IMWG conducted a pooled analysis of 869 newly diagnosed older adult patients, all of whom had undergone a CGA (Palumbo et al., 2015). The CGA consisted of three tools: the Katz activities of daily living (Katz & Akpom, 1976), the Lawton instrumental activities of daily living (Lawton & Brody, 1969), and the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987). The analysis revealed that the frailty score predicted mortality and risk of toxicity in older adult patients with myeloma. A patient's chronologic age, performance status, and physician's clinical judgment were not sufficient to classify patient frailty. Instead, CGA is a more sensitive predictor of clinical outcomes and, therefore, performing CGA can optimize treatment.

### Evidence-Based Recommendations to Manage Frailty

#### LEVEL OF EVIDENCE VII

- Larocca and Palumbo (2015) published a narrative review of the literature and proposed an approach to MM assessment and treatment with a focus on patient frailty. They recommend the use of CGA to assess patients with MM in everyday clinical practice. Ideally, CGA results can be used to direct clinical decision making, tailor therapy, and ultimately to reduce risk of toxicity and improve treatment tolerance (Larocca & Palumbo, 2015).
- The IMF NLB recommends incorporating a CGA score to measure patient frailty in future clinical trials (Palumbo et al., 2015).

#### IMPLICATIONS FOR PRACTICE

- Explain that bone disease, pain, and reduced mobility are experienced by most patients with multiple myeloma at varying points in the disease trajectory.
- Improve bone health, reduce pain, and maximize mobility and functioning of patients with multiple myeloma by providing astute assessments and interventions along with the healthcare team.
- Maximize patient outcomes by employing evidence-based practice in the care setting.

### Implementing an Activity Plan of Care

Behavioral support interventions can assist cancer survivors in making behavior changes required for the implementation of a successful exercise program. Supervised exercise, support groups, telephone counseling, motivational interviewing, and cancer survivor-specific print materials may help overcome personal barriers (Rock et al., 2012; Smith et al., 2015). Barriers to physical activity in patients with MM may include side effects of therapy, pain, fatigue, fear of infection, and low self-motivation (Craike, Hose, Courneya, Harrison, & Livingston, 2013). Other factors that may be associated with noncompliance in patients with MM include history of fracture, spinal cord compression, and radiation. These individuals may require additional supervision to implement a safe and successful exercise program (Shallwani et al., 2015). When implementing a plan, it is important to consider personal interests and goals. Ask questions such as, "What activities do you enjoy, and are currently able to do?"; "What benefits will you get from activity—physical benefits, social benefits, keeping busy, etc.?" and "What is your goal—weight loss, pain management, improved mobility and flexibility?" Addressing perceived benefits, barriers, and personal needs and goals will enhance compliance and lead to a more successful program (Craike et al., 2013).

A structured, individualized program that includes supervision and in-home follow-up can promote durable participation for patients with MM (Groenveldt et al., 2013). MM survivors, particularly those with bone disease, may require specialty consultation to advise them on restrictions for weight lifting or impact sports before implementing a plan. The American College of Sports Medicine (ACSM) provides minimum activity guidelines (Schmitz et al., 2010), but implementing these guidelines for individuals within their community may present challenges, including lack of appropriate services. To overcome challenges in connecting survivors to appropriate programs in their community, healthcare professionals should anticipate questions from exercise professionals and collaborate closely with them. In addition, healthcare professionals should feel comfortable following the ACSM guidelines and prescribing exercise to cancer survivors (Rome et al., 2011; Schmitz et al., 2010; Wolin, Schwartz, Matthews, Courneya, & Schmitz, 2012).

### Evidence-Based Recommendations to Implement an Activity Plan of Care

#### LEVEL OF EVIDENCE I

- The IMF NLB recommends that oncology nurses help maximize patients' QOL by ensuring that mobility and safety is assessed

and that the plan of care includes appropriate interventions and resources for survivorship. Every survivorship care plan should include recommendations for a healthy lifestyle, such as regular health screening, sun safety, immunizations, physical activity, dietary habits, and weight management (Denlinger et al., 2014).

- To reach the goal of improved patient outcomes with QOL, the IMF NLB recommends that nurses continuously assess and tailor patient interventions to manage pain, protect bone health, and maximize functional abilities (Denlinger et al., 2014).

## Conclusion

Patients with MM are affected in many ways by physical changes, comorbidities, and treatment effects. In particular, patient QOL can be negatively affected by bone disease, pain, and limited mobility. Ongoing research and outcomes from that research provide healthcare providers with evidence to guide practice and patient care. Oncology nurses can help improve outcomes for patients with MM by conducting assessments at every encounter, regardless of care setting; playing a role in symptom prevention; managing medication side effects; and implementing plans of care that promote safety, mobility, and QOL in conjunction with the healthcare team.

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