

# Palliative Care in Multiple Myeloma

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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## Abstract

With the advent of more effective treatments for multiple myeloma, many patients are maintained longer on chronic therapy and thus have greater need for palliative care to manage symptoms of the disease and side effects of therapy. Although some patients and health-care providers view palliative care as having a role only at the end of life, ideally this should begin at diagnosis and continue throughout the course of the disease. A majority of patients with multiple myeloma present with and experience acute or chronic pain, so ongoing pain assessment is required for effective management of symptoms by either pharmacologic approaches (e.g., opioid and non-opioid medications) or nonpharmacologic approaches (e.g., radiation therapy, vertebroplasty/kyphoplasty). Peripheral neuropathy can also occur in myeloma patients due to the disease or its treatment, and effective management is essential to maintaining the patient's quality of life. Gastrointestinal side effects, postherpetic neuralgia, and renal failure also can arise as a result of the disease or therapy, and should be monitored and treated promptly. While not widely studied in multiple myeloma, many patients report cognitive impairment, often arising from treatment, which can adversely affect quality of life for patients and their caregivers. Fatigue is present in about 80% of patients with multiple myeloma and should be managed proactively. Finally, psychosocial care, including spiritual support and screening/treatment for distress and depression, can help maintain emotional and physical well-being. Advanced practitioners are in a position to address these needs with patients and their caregivers, provide education, monitor symptoms, and integrate supportive care throughout the disease continuum.

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Approximately 26,850 individuals will be diagnosed with myeloma in 2015 within the United States (Howlader, 2014). Many of these patients will present with myeloma-related complications, including bone involvement, pain, anemia, and renal insufficiency. In addition, patients may experience treatment-related complications, including peripheral neuropathy as well as gastrointestinal and steroid side effects (Bertolotti et al., 2008). As patients live longer and are maintained on chronic therapy, the need exists to promptly

identify and treat symptoms that emerge at the time of diagnosis and throughout the continuum of care. This article will outline the definition of palliative care/supportive care, discuss management of common complications and side effects observed in myeloma patients, as well as review issues related to spirituality and psychosocial care in patients living with myeloma.

### DEFINITION OF PALLIATIVE CARE

The World Health Organization (WHO) defined palliative care in 2002 as improving the quality of life in patients living with life-threatening illnesses by relieving suffering of physical, psychological, and spiritual symptoms (Connor & Bermedo, 2014). More recently, the Worldwide Palliative Care Alliance (WPCA) published the Global Atlas of Palliative Care (GAPC), which further expanded upon the WHO definition of palliative care (Connor & Bermedo, 2014). The GAPC recommends early intervention based on symptoms rather than a specific time point so that individuals living with chronic conditions are able to receive palliative care (Connor & Bermedo, 2014). The incorporation of multiple disciplines throughout the continuum of care is essential while patients receive treatment for their illness.

Many patients and healthcare providers view palliative care as occurring at the end of an individual's life. However, studies conducted in patients with advanced cancer have demonstrated not only improvement in quality-of-life measures, but also improved survival (Smith et al., 2012). Thus, the American Society of Clinical Oncology (ASCO), the Institute of Medicine (IOM), and the National Comprehensive Cancer Network (NCCN) now recommend implementation of palliative care at the time of diagnosis in patients with an incurable cancer and/or high symptom burden (IOM, 2000; Levy et al., 2012; Smith et al., 2012).

In order to avoid the stereotype of palliative care as occurring only at the end of life, the term "supportive care" is replacing palliative care. For the purpose of this paper, the term supportive care will be used to describe care focused on improving quality of life through the management of symptoms from the time a patient is diagnosed with myeloma to the end of his/her life.

### SYMPTOM MANAGEMENT IN PATIENTS LIVING WITH MYELOMA

A study by Boland et al. (2014) was conducted to determine holistic health-care needs in 32 previously treated myeloma patients. All patients were required to have had a previous autologous stem cell transplant, at least one previous episode of relapsed disease, currently with stable disease, and either receiving no therapy or maintenance therapy for at least 3 months (Boland et al., 2014). The study utilized the Sheffield Profile for Assessment and Referral for Care to determine the holistic needs of this group of patients. Investigators found that despite myeloma being in remission, many of the patients reported pain, distress over side effects, fatigue, and concern for family members (Boland et al., 2014). This study demonstrates the importance of incorporating symptom management at all stages of diagnosis, including patients who are in remission, in order to improve their quality of life.

### ACUTE AND CHRONIC PAIN

Approximately two-thirds of patients diagnosed with myeloma present with pain. Myeloma patients may experience pain as a result of vertebral compression fractures, lytic bone lesions, nerve root compression, peripheral neuropathy, and rarely from central nervous system involvement (Niscola et al., 2010a). Approximately 60% of patients report severe pain throughout their disease trajectory, and this may increase to 100% at the end of life. In patients with myeloma, pain is often multifactorial, including bone disease, postherpetic neuralgia, infection, procedures, peripheral neuropathy, nerve root compression, mucositis, osteonecrosis of the jaw, skin lesions, and extramedullary disease. In some cases, pain may be unrelated to myeloma, but due to other diseases occurring in the general population such as arthritis or degenerative disc disease (Niscola et al., 2010).

The three main types of pain seen in cancer patients are visceral, somatic, and/or neuropathic pain (Niscola et al., 2010a). Visceral pain occurs as a result of injury to internal organs or blood vessels such as intestinal distention or mucositis. It is often described as a diffuse pain that can be difficult to localize. Somatic pain occurs as a result of injury to tissue, bone, or muscle, such as lytic

bone disease, extramedullary disease, infection, or osteoarthritis; it is often described as a sharp and localized pain. Neuropathic pain results from damage to the nerves, leading to abnormal nerve impulses, and is described as burning, electrical shocks, or tingling sensations. Patients with myeloma may develop neuropathic pain as a result of peripheral neuropathy, nerve root compression, or postherpetic neuralgia. Some individuals may experience a mixed pain syndrome due to the presence of neuropathic pain in combination with visceral/somatic pain (Niscola et al., 2010a).

### ASSESSMENT OF PAIN

Management of pain begins with performing a thorough pain assessment, including a description of intensity, location, duration, frequency, triggering factors, and/or relieving factors (Niscola et al., 2010a; Ripamonti, Santini, Maranzano, Berti, & Roila, 2012). Furthermore, assessment of a patient's coping skills is important to gain a better understanding of how the pain is affecting them emotionally. After the initial assessment is performed, an ongoing pain assessment is required prior to administration of pain medications as well as at each clinic visit. Measuring the intensity of pain should be performed using numerical scales or visual analogue scales.

Description of the pain assists in determining whether it is visceral, somatic, or neuropathic, which is useful in determining the management approach. The patient's description and location of the pain is important to determine its source and the appropriate diagnostic work-up. For example, patients who have compression fractures may complain of pain coming around one or both sides of the abdomen as a result of nerve root compression. The diagnostic work-up aids not only in the evaluation of pain, but also assists in determining if an individual would benefit from interventions, such as kyphoplasty/vertebroplasty or palliative radiation (Niscola et al., 2010a; Ripamonti et al., 2012).

### PHARMACOLOGIC MANAGEMENT

Management of pain in patients with myeloma requires a multimodality approach (Niscola et al., 2010a; Ripamonti et al., 2012). Pharmacologic approaches include the use of opioid and non-

opioid medications. The WHO uses a three-step approach in the management of pain (WHO, 1996). However, one limitation of the analgesic step ladder is the recommendation to start with nonsteroidal analgesics or acetaminophen, which may be contraindicated in patients with myeloma due to impaired renal function and/or concerns of these drugs masking fever (Niscola et al., 2010a; Niscola et al., 2010b; Ripamonti et al., 2012).

Treatment of mild to moderate pain may include the use of tramadol, either immediate-release or extended-release formulas. Hydrocodone in combination with acetaminophen may also be used in the treatment of mild to moderate pain, as it comes in varying doses. However, in patients at risk for infection, caution should be used with hydrocodone because acetaminophen may mask fever. In those with moderate to severe pain, initiation of morphine, hydromorphone, or oxycodone may be required (Niscola et al., 2010; Ripamonti et al., 2012).

The NCCN guidelines for management of cancer-related pain recommend starting opioids at a low dose in patients who are opioid-naïve and then slowly titrating the dose (Swarm et al., 2013). In some patients with severe intractable pain, intravenous opioids may be warranted in order to gain rapid control of pain. In patients who are not opioid-naïve, calculating the total dose of narcotics for the preceding 24 hours is needed in order to adjust the dose. Initiation of extended-release formulas may be warranted, particularly in individuals with severe pain. In order to obtain optimal pain relief, consultation with a pain management specialist may be warranted as they may be able to provide additional interventions such as epidural injections, implantable pumps, and/or regional nerve blocks (Niscola et al., 2010a; Ripamonti et al., 2012; Swarm et al., 2013).

Prior to initiating pain medicine, it is important to assess liver and renal function as dose reductions may be required, along with close monitoring with subsequent dose modification (Niscola et al., 2010b). In patients with renal impairment, oxycodone, hydromorphone, methadone, and fentanyl are preferred over morphine (Niscola et al., 2010b).

The NCCN recommends patient and caregiver education when starting pain medicines, includ-

ing taking pain medicine only for pain and not for sleep, anxiety, or mood (Swarm et al., 2013). Patients should also be educated on the importance of taking the long-acting pain medicine as prescribed, rather than on an as-needed basis. Additionally, patients should be informed about the importance of not breaking or crushing long-acting medications. Educating patients regarding the importance of a bowel regimen is essential to prevent opioid-induced constipation (Swarm et al., 2013).

## NONPHARMACOLOGIC MANAGEMENT

### Radiation Therapy

Radiation therapy is an option to assist in controlling pain and in the management of cord compression (Ripamonti et al., 2012). Radiation may be given alone or concomitantly with systemic treatment. In patients receiving doxorubicin or who have recently received doxorubicin, radiation should be avoided due to the risk of radiation recall. In newly diagnosed myeloma patients, radiation therapy is often avoided due to bone marrow toxicity, except in cases of cord compression, as systemic treatment will often improve the pain. In patients with relapsed/refractory disease, radiation can be used for local control of pain (Terpos, Berenson, Raje, & Roodman, 2014).

### Vertebroplasty/Kyphoplasty

Vertebroplasty/kyphoplasty is a minimally invasive outpatient procedure used to improve pain, reduce the amount of analgesics, and improve the quality of life in patients with compression fractures (Khan, Brinjikji, & Kallmes, 2014; Terpos et al., 2014). Vertebroplasty is an outpatient procedure and involves insertion of polymethylmethacrylate into the vertebral body (Hameed, Brady, Dowling, Clynes, & O’Gorman, 2014). Kyphoplasty is similar except an inflatable balloon is inserted into the vertebral body. Once the balloon is inflated, the polymethylmethacrylate is injected into the space. Both procedures are performed under fluoroscopy and have similar complications, including cement leakage (11%–29%) and subsequent vertebral body compression fractures (6.8%–7.3%) above and below the original fracture (Khan et al., 2014).

### Stabilization Devices

Patients with myeloma may experience worsening pain with movement, so it is important to implement strategies that reduce the physical force placed on the bone and corresponding muscles. The impact of limited mobility on the quality of life of patients with cancer has been documented in the literature (Hacker, 2009). Furthermore, studies have demonstrated improvements in physical and psychological domains after an exercise program was implemented in patients with cancer (Knobf, Musanti, Dorward, 2007; Rome, Jenkins, Lilleby, 2011). Therefore, patients with myeloma should be encouraged to increase their activity levels (Rome, Jenkins, Lilleby, 2011). Patients with pain may require assistive devices to increase their independence and mobility. A wide array of devices are available through physical therapists, including but not limited to assistive devices, compensatory strategies, therapeutic exercises, orthotics, and positioning (Cheville & Basford, 2014).

## PERIPHERAL NEUROPATHY

Peripheral neuropathy (PN) occurs in patients with myeloma as a result of the disease and its systemic treatment. In previously untreated patients, investigators reported that 52% had small-fiber neuropathy while 9% had large-fiber neuropathy (Tariman, Love, McCullagh, & Sandifer, 2008). The exact mechanism of PN in untreated patients is unknown but may be related to amyloid deposition in the nerves, binding of the monoclonal protein, metabolic factors, cord compression, or comorbid conditions such as diabetes (Tariman et al., 2008). The incidence of therapy-induced PN ranges from 3% to 65% in patients living with myeloma (Richardson et al., 2012). Symptoms of PN includes alteration of sensation, numbness/tingling, altered gait, difficulty with balance, and pain. These symptoms may be distressing to patients and reduce their quality of life; therefore, management should be focused on minimizing pain, improving ambulation, and avoiding injury (Garg & Bhatnagar, 2014).

Treatment of PN includes both pharmacologic and nonpharmacologic interventions with the goal of improving quality of life. As in the management of acute and chronic pain, it is essential to establish the patient’s goals prior to im-

plementing interventions. Additionally, titration of analgesics should depend upon the patient's goals, pain intensity, and adverse effects (Garg & Bhatnagar, 2014).

### Pharmacologic Management

Pharmacologic management of PN includes the use of anticonvulsants, tricyclic antidepressants, opioids, and topical agents (Garg & Bhatnagar, 2014). Gabapentin and pregabalin are helpful in the management of PN but often require titration to reach therapeutic levels. Side effects of gabapentin and pregabalin may include dizziness (9%–42%), edema (5%–12%), fatigue (7%–11%), ataxia (3%–15%), and loss of coordination (2%–10%; Garg & Bhatnagar, 2014; Pfizer, 2013, 2015a,b). Depending on the severity of side effects, doses may need to be titrated to reduce symptoms. Antidepressants such as amitriptyline and duloxetine may also be effective for the treatment of PN (Garg & Bhatnagar, 2014). Similar to anticonvulsants, doses may need to be titrated to minimize adverse effects (Garg & Bhatnagar, 2014). Topical lidocaine patches can be used for local pain relief, particularly in patients who develop postherpetic neuralgia (Gan et al., 2013).

### Nonpharmacologic Management

A small feasibility study of acupuncture conducted among 19 myeloma patients with thalidomide- or bortezomib-induced neuropathy demonstrated improvements in patient-reported outcomes and time function tests (Garcia et al., 2014). Patients received a total of 20 acupuncture treatments over a 9-week period. Improvement was seen in pain levels (Brief Pain Inventory-Short Form), functional assessment (FACT-G), postural stability, walking test, and button test. However, no improvement was observed in risk for fall or in neuroconductive studies (Garcia et al., 2014). Similar findings were reported by Bao et al. in 27 myeloma patients with treatment-related neuropathy who received acupuncture treatment; investigators reported improvements in FACT-G scores and NPS (Neuropathy Pain Scores; Bao et al., 2014). However, similar to the above studies, neuroconductive studies failed to demonstrate improvement.

These studies suggest acupuncture may be a viable treatment option for myeloma patients

with treatment-related PN. Both studies continued pharmacologic treatment concurrently with acupuncture, so patients should be encouraged to continue their neuropathy medications. Unfortunately, most insurance companies do not pay for acupuncture treatment, so this may be cost prohibitive for some patients.

## POSTHERPETIC NEURALGIA

Herpes zoster occurs as a result of reactivation of the varicella virus within the sensory ganglia (Gan, Tian, & Tey, 2013). Multiple risk factors have been identified for the development of herpes zoster including older age, chronic kidney disease, immunosuppression, and a family history of zoster. Patients with multiple myeloma may be at risk for developing herpes zoster due to multiple risk factors, such as immunosuppression, older age, and in some cases chronic kidney disease (Gan et al., 2013). Furthermore, bortezomib has been shown to increase the incidence of herpes zoster (13% vs. 5%;  $p = .0002$ ) in patients with multiple myeloma (Chanan-Khan et al., 2008). Therefore, prophylaxis with antivirals is recommended in all patients receiving a proteasome inhibitor (Gan et al., 2013).

Unfortunately, a major complication of herpes zoster is a painful vesicular rash, which often occurs along a single unilateral dermatome (Gan et al., 2013). While treatment with antivirals such as valacyclovir or acyclovir reduces the vesicular eruption, the pain associated with herpes zoster may persist even after the rash has resolved. The incidence of postherpetic neuralgia ranges from 9% to 34% in individuals who develop herpes zoster. There are a few risk factors for the development of post herpetic neuralgia including older age, acute pain, severity of rash, involvement of more than one dermatome, and involvement of the eye (Gan et al., 2013).

### Pharmacologic Management

Management of postherpetic neuralgia may require the use of topical and/or systemic pain medication (Gan et al., 2013). Topical agents such as lidocaine patches and capsaicin cream can be used in patients with mild pain or as an adjunct to systemic neuropathic pain medication. In patients who require systemic pain medicine, neuro-

pathic agents such as anticonvulsants or tricyclic antidepressants should be initiated first. If pain persists with the addition of a neuropathic agent, then adding opioid analgesics should be considered. For those patients who do not obtain relief from the above medications, referral to a pain management specialist is recommended (Gan et al., 2013).

## GASTROINTESTINAL SYMPTOMS

Gastrointestinal (GI) symptoms such as nausea, vomiting, diarrhea, and constipation are common treatment-related adverse events. These symptoms are rarely caused by the disease itself, with the exception of hypercalcemia-related constipation. Gastrointestinal symptoms will vary depending upon the treatment regimen being used but in most cases are mild and easily managed. In some cases, however, they may become dose limiting and require a dose reduction or change in treatment regimen. Most of the myeloma treatment regimens are not particularly emetogenic except high-dose melphalan or regimens that are more dose intensive such as DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide). More commonly, patients will experience constipation and/or diarrhea associated with the use of various immunomodulators (IMiDs) and proteasome inhibitors.

Patients experiencing treatment-related diarrhea should maintain a high fluid intake, and over-the-counter anti-motility agents or fiber-binding agents are often needed on a daily basis. Patients experiencing refractory diarrhea should be evaluated for an infectious cause such as a *C. difficile* infection. Those experiencing constipation as a result of their treatment should maintain a high fluid intake and a high-fiber diet. Stool softeners and laxatives may also be recommended. For those patients taking narcotics for painful bone lesions, opioid-induced constipation can be a significant problem and will nearly always necessitate daily use of stool softeners, laxatives, and stimulants (Gay & Palumbo, 2010).

Nearly every multiple myeloma treatment regimen utilizes steroids, and dyspepsia or heartburn is a common side effect. Untreated, dyspepsia can contribute to nausea and vomiting over time, and may lead to the formation of peptic ulcerations. While an over-the-counter antacid may provide

temporary relief, a proton pump inhibitor is the treatment of choice (Snowden et al., 2011).

Mucositis is an uncommon side effect with the majority of myeloma treatment regimens, although it can be a significant issue following administration of high-dose melphalan for autologous stem cell transplant. A number of studies have shown that the use of oral cryotherapy several hours prior to and following administration of high-dose melphalan significantly decreases the severity and duration of mucositis (Bensinger et al., 2008).

## RENAL FAILURE

Renal impairment is observed in 20% to 50% of myeloma patients, with up to 13% requiring dialysis (Faiman et al., 2011; Grzasko, Morawska, & Hus, 2015). Renal impairment occurs as a result of immunoglobulin light chains combining with Tamm-Horsfall proteins (THP) in the nephrons to produce casts. This results in obstruction of the renal tubules, leading to decreased creatinine clearance. The light chains excreted in the urine are known as Bence-Jones protein. Other factors impacting the kidneys include release of proinflammatory cytokines, inflammation within the kidneys, dehydration, hypercalcemia, infection, and use of nephrotoxic agents (Faiman et al., 2011; Grzasko et al., 2015).

Patients presenting with worsening renal function should be assessed for urinary tract infections, hydronephrosis, nephrotoxic medications, hypovolemia, hypercalcemia, and progressive disease. Once the cause of the renal impairment has been determined, correction of the underlying causative factor should be instituted immediately (Faiman et al., 2011; Grzasko et al., 2015). Additionally, medications should be reviewed and dose-adjusted based on creatinine clearance. If the renal impairment is due to progressive disease, then prompt treatment is recommended. However, if the patient has refractory disease, it is important to discuss goals of care and the advantages/disadvantages of dialysis. In some cases, patients may elect to not pursue dialysis, particularly if they have received numerous treatment options and are considered to have refractory disease. In patients who elect to not receive dialysis, a referral to a home or inpatient hospice is recommended.

## COGNITIVE IMPAIRMENT

Many patients undergoing treatment for cancer report cognitive impairment, which is often described as “chemo brain” or “chemo fog.” Commonly reported symptoms include difficulties with short-term or working memory, attention span, concentration, processing speed, learning new skills, and multitasking. While studies have shown that many of these changes are mild, cumulatively they can have significant impact on quality of life.

Little is known about the causes of the cognitive complaints, but a wide range of hypotheses have been described, including direct neurotoxic effects, hormonal changes, oxidative stress, cytokine release, metabolic abnormalities, immune dysfunction, vascular injury, and general age-related changes. Different agents and modalities likely cause impairment through unique and possibly multiple mechanisms (Wefel, Witgert, & Meyers, 2008). Patients with myeloma are living longer and are therefore exposed to an increasing variety of treatment modalities, including steroids, immunomodulatory agents, chemotherapy, radiation, and autologous stem cell transplants. In addition to these physical causes, patients experience psychological stressors that may contribute to this problem. Stressors include the cancer diagnosis, change in routine, hospitalizations, and worry about relapse and death. Thus, the risk for cognitive impairment may be compounded as patients progress through a succession of treatments.

The majority of studies that have evaluated cancer-related cognitive impairment have been in patients with breast, colorectal, or prostate cancer, as these three represent the majority (60%) of all cancers in the US. Of these, breast cancer has received the most attention and has generated the most data (McDougall Jr., Oliver, & Scogin, 2014). It is not clear if the results from these breast cancer studies directly translate to multiple myeloma. For example, patients with breast cancer are on average 10 years younger than those with multiple myeloma. In addition, cognitive issues described in the breast cancer population may be exacerbated by other problems that are more common in patients having multiple myeloma. Two such issues include anemia and a greater general use of opioids as well as nonopioid agents such as gabapentin, nortriptyline,

and amitriptyline for pain relief (Von Ah, Storey, Jansen, & Allen, 2013).

While a number of studies have examined cognitive impairment in patients undergoing treatment for hematologic malignancies, patients with multiple myeloma were not well represented in these study populations. Only a few studies have specifically looked at this problem in patients diagnosed with multiple myeloma, and most studies have evaluated patients who have undergone an autologous stem cell transplant (Jones et al., 2013; Potrata, Cavet, Blair, Howe, & Molassiotis, 2010). There have been case reports concerning memory loss associated with the use of the IMiD lenalidomide, but no specific studies have examined cognitive functioning in patients undergoing initial therapy, maintenance therapy, or during ongoing therapy for relapsed disease (Rollin-Sillaire et al., 2013).

Many studies have focused on identifying cognitive changes associated with cancer treatment, but studies to identify interventions that are effective in preventing or treating these issues are more limited. In general, clinical interventions can be broadly categorized as pharmacologic (e.g., psychostimulants) or nonpharmacologic (e.g., cognitive-behavioral programs). Of these, nonpharmacologic approaches have demonstrated the most evidence for improving cognitive function, but these studies have been small and no one intervention was able to improve all aspects of cognitive performance (Von Ah, Jansen, Allen, Schiavone, & Wulff, 2011; Von Ah et al., 2013). In many cases, patients can be taught techniques to help themselves with everyday functioning, including using diaries and electronic calendar reminders, leaving themselves notes, identifying shorter and simpler reading materials, and using talking books and DVDs.

In some cases, patients may not want to report their symptoms as it might suggest to them that their disease is progressing and their overall health condition is deteriorating. In addition, some patients may minimize or deny their symptoms due to the social stigma that can be attached to disabilities that challenge cognitive functioning. There are no reliable screening tests for cognitive issues, and patients may need to be referred for a full neurocognitive assessment or to a memory clinic. Bear in mind that many subjective complaints concern-

ing cognitive performance are not always borne out on subsequent cognitive testing, and it is possible that conventional neuropsychological testing may not be sensitive enough to identify the subtle changes experienced by patients receiving chemotherapy (Nelson & Suls, 2013). Also, it is possible that some cognitive complaints may actually be a reflection of anxiety, depression, or fatigue rather than a cognitive decline. Providers working in supportive care should proactively address potential cognitive issues early in diagnosis, and these should be reassessed periodically throughout the disease trajectory.

## FATIGUE

Fatigue is one of the most commonly reported symptoms (80%) in patients with multiple myeloma. The cause of fatigue in these patients is multifactorial and results not only from treatment, but from the disease itself (Booker, Olson, Pilarski, Noon, & Bahlis, 2009). Fatigue rarely occurs in isolation, and in many cancer patients it appears alongside the symptoms of insomnia, depressed mood, and pain (Kirkova, Walsh, Aktas, & Davis, 2010). Thus, effective management of fatigue would also include interventions that target these other symptoms as well. Improved sleep hygiene, excellent pain control, and management of depression and anxiety would all be expected to improve the general symptoms of global fatigue (Coleman et al., 2011; Stepanski et al., 2009). Other common and treatable contributors to general fatigue include thyroid deficiency, low testosterone level, and sleep apnea.

For treatment of general cancer-related fatigue, the NCCN guidelines currently recommend strategies that include energy conservation, increasing physical activity, nutritional counseling, psychosocial interventions, and lastly, consideration of pharmacologic interventions using low-dose corticosteroids or psychostimulants (National Comprehensive Cancer Network, 2015a). As patients with multiple myeloma are often exposed to high doses of corticosteroids, there is little role for the use of these agents in this population. Further, the use of psychostimulants is recommended only when all other treatment- and disease-specific morbidities have been addressed, as studies have shown mixed results when treating

cancer-related fatigue (Spathis et al., 2014). Note, however, that cancer patients do derive benefit from the use of psychostimulants for treatment of other cancer-related comorbidities such as opioid-induced somnolence and depression (Rozans, Dreisbach, Lertora, & Kahn, 2002).

Like many other supportive care issues, treatment options for cancer-related fatigue have been studied in greatest detail in patients with breast and prostate cancer. However, several studies have specifically looked at the relationship between exercise and its effect on fatigue in patients with multiple myeloma. Specially designed physical activity programs not only increase quality of life scores in general but also specifically increase nighttime sleep and concurrently decrease fatigue (Coleman, Hall-Barrow, Coon, & Stewart, 2003; Jones et al., 2004). Even patients having a history of bone lesions or pathologic fractures are able to safely participate in specialized exercise programs. Patients should be provided information that reassures them that increased activity will in fact decrease their fatigue level rather than make them more tired. This is an especially important concept for patients who were not physically active prior to their diagnosis (Craike, Hose, & Livingston, 2013).

Both anemia and poor nutritional status can play a role in cancer-related fatigue. Anemia is a common symptom that is related to the disease process and, as such, may be a short-term problem that is corrected with treatment. Alternatively, it may be a chronic comorbidity (e.g., anemia of chronic disease) or an unavoidable consequence of myeloma treatment that will persist and only be corrected by blood transfusions. Proper nutrition should be addressed both proactively and throughout the course of the disease. Nutritional assessment and counselling should begin as soon after diagnosis as possible and should continue throughout the course of the disease. The assessment should focus on both the current nutritional status of the patient and anticipated nutrition-related symptoms or needs (Rock et al., 2012).

## SPIRITUALITY

Spirituality is an important aspect of a person's care throughout their disease. In the United States, over 90% of individuals report a belief in



God, and over 70% reported religion as an important influence in their lives (Delgado-Guay, 2014). Spirituality is defined as “that dimension of a person that is concerned with ultimate ends and values...Spirituality is that which inspires in one the desire to transcend the realm of the material,” (O’Brien, 1982) whereas religion is “a construct of human making, which enables the conceptualization and expression of spirituality.” Regardless of culture, spirituality and religion play an important role in the lives of most individuals (Delgado-Guay, 2014).

In patients with advanced cancer, 98% reported themselves as spiritual and 98% as religious (Delgado-Guay, 2014). Furthermore, 99% reported spirituality/religion assisted them in coping with their illness, and 100% found it as a source of strength. Spirituality and religion may assist in alleviating symptoms, with 69% reporting it helped with physical symptoms and 84% reporting a positive impact on emotional symptoms. While for many patients spiritual needs are met by pastors, rabbis, priests, personal spiritual leaders, or chaplains, there are those whose spiritual/religious needs are not being met, resulting in higher rates of depression, less meaning, and less peace (Delgado-Guay et al., 2011; Pearce, Coan, Herndon, Koenig, & Abernethy, 2012; Phelps et al., 2012).

In a meta-analysis, researchers evaluated 293 published articles that studied the effects of religious/spirituality (R/S) on social health (social roles/relationship) in patients with a diagnosis of cancer (Sherman et al., 2015). Researchers found that religion/spirituality had an effect on social health, with the affective R/S dimension being the strongest predictor (emotional dedication). Furthermore, those patients who reported a sense of peace/calmness and/or harmony from the spiritual pursuits had higher levels of social health (Fisher  $z$  effect size = .33), whereas those who struggled or felt alienated from their R/S reported decreased levels of social health (Sherman et al., 2015).

Another meta-analysis of the effects of R/S on physical health outcomes on patients with cancer found that affective R/S was associated with physical well-being, functional well-being, and physical symptoms such as fatigue, pain, sleep, and others ( $p < .001$ ; Jim et al., 2015).

The impact of spirituality is not limited to patients but also includes caregivers. In a study of 43 patients in an outpatient palliative care clinic, caregivers reported their religious and spiritual beliefs helped them to cope with their loved one’s illness (Delgado-Guay et al., 2013). Spiritual pain was reported by 58% of caregivers, leading to increased anxiety, depression, denial, behavioral disengagement, dysfunctional coping strategies, and a decrease in quality of life.

Spirituality and religion are important in the lives of individuals with cancer. While no studies have been undertaken in those living with myeloma, studies have been conducted in patients with other incurable cancers. These studies have demonstrated that patients want their health-care providers to address spiritual and religious concerns in the context of their care. Nurses are in a position to address spiritual needs both in the inpatient and outpatient setting. Additionally, it is important to ask patients about their religious and spiritual preferences in terms of management of their disease and to integrate these into their treatment plan. For patients with spiritual needs, referral to a chaplain is warranted.

## PSYCHOSOCIAL CARE

In 1997, the NCCN developed guidelines related to screening for distress in cancer patients and, if needed, providing them with access to appropriate psychosocial care. Since that time, psychosocial care has become increasingly recognized as an integral component of quality care in the management of all patients having a cancer diagnosis. In 2007, the IOM furthered this concept by proposing a model for delivering psychosocial care in oncology practices (Institute of Medicine, 2008). In general, these guidelines include four components:

- Screening for distress and psychosocial needs
- Developing and implementing plans to address these needs
- Connecting those in need to appropriate psychosocial resources and support care services
- Reevaluating the effectiveness of the plans and process

Early, timely evaluation and management of distress helps prevent crisis events and im-

proves medical management of patients. Patients with high levels of distress are at increased risk for nonadherence to treatment plans and have difficulty participating in and making treatment decisions (National Comprehensive Cancer Network, 2015b). Furthermore, patients in distress use more medical resources, have a poorer quality of life, and may experience decreased survival compared with patients in whom distress has been appropriately managed (Temel et al., 2010).

For cancer patients in general, the prevalence of distress varies with the type and stage of cancer and a host of other variables. About one third of newly diagnosed cancer patients experience significant psychological distress. To date, only two studies have assessed supportive care needs in patients with multiple myeloma (Lamers et al., 2013; Molassiotis, Wilson, Blair, Howe, & Cavet, 2011b). In each study, nearly one quarter (24% and 25%) of patients experienced symptoms of depression. Symptoms of anxiety were seen in 27% and 8% of patients, respectively, with the difference in prevalence likely related to the method of screening used in each study. Both studies noted that anxious and depressed patients had more than double the unmet supportive care needs than patients who did not report distress. In the study by Lamers et al. (2013), more than half of patients desired some type of psychosocial intervention regardless of whether they were experiencing distress or not. For patients with multiple myeloma who are undergoing stem cell transplant, levels of anxiety and distress are significantly higher (40% each) than noted in previous studies. Not surprisingly, in this group of transplant patients, depression served as a useful predictor for deficits in other functional domains as well (Sherman et al., 2003).

For patients with myeloma, a key cause of distress is the uncertainty related to having an incurable disease that is punctuated by multiple life-threatening relapses associated with increased symptom burden and disability. Additional sources of distress include treatment side effects and disease symptoms, fatigue, changing family roles, lifestyle changes, loss of control, and financial concerns (Molassiotis, Wilson, Blair, Howe, & Cavet, 2011a). In addition, specific medications used to treat the disease, such as thalidomide and high-

dose steroids, may also be nonpsychological contributors to symptoms of distress.

Standardized distress screening is recommended for all cancer patients at the time of diagnosis and at important transition points (Jacobsen & Wagner, 2012). For patients with myeloma, Zabora et al. (2014) have proposed a specific roadmap that identifies critical points for distress screening and opportunities for psychosocial intervention if indicated. Important transition points include the time of diagnosis, before and after initial treatment, and at each relapse and change of treatment. Following each screen for distress, a more in-depth psychosocial needs assessment should be conducted if indicated. When needs are identified, referral should be made to appropriate psychosocial resources, and timely follow-up is critical to see that needs are met.

At each transition point, goals of care should be addressed, and providers should engage in end-of-life planning early in the course of the disease. This allows patients to plan their financial legacy and will in order to make the ultimate transition from aggressive life-prolonging therapy to palliative end-of-life care much less stressful.

Like patients, family and caregivers can also benefit from both ongoing psychosocial monitoring and support, and their needs should be attended to at a similar level as the patient. Molassiotis et al. (2011) report that caregivers of patients with myeloma experience high levels of anxiety and depression, and they further report a slightly higher number of unmet needs compared with patients. These individuals have supportive care needs similar to patients but also have unique needs. They often have their own chronic illnesses to attend to, and risk neglecting their own health care and other needs to attend to their loved ones. Interestingly, patients who are farther from their diagnosis often desire more support for caregivers, their family, and children. This suggests that at diagnosis, patients are concerned primarily with their own needs, whereas later in the course of the disease the focus is on their loved ones and caregivers (Lamers et al., 2013).

Interventions for identified psychosocial needs include both psychological and pharmacologic interventions. Many psychological interventions can be applied globally at each transition point and include education, cognitive-behavioral

interventions, support groups, and short-term psychotherapy. While education should be universally applied at all transition points, patients may have very specific preferences or dislikes relative to other interventions. Peer support groups are typically preferred by patients who feel the need to connect with persons having similar experiences. On the other hand, some patients resist the idea of psychological counseling as it may provoke a stigma of mental illness. In contrast to the global interventions, more specific interventions such as financial counseling may be needed to manage distress at transition points. In these instances, social workers with specialty oncology training can be invaluable. For practices with more limited on-site resources, there are local (community-based), regional, and national resources available for patients and caregivers (Forsythe et al., 2013). Finally, antidepressants and anti-anxiety drugs have shown benefit for the treatment of depression and anxiety in patients with cancer, and these may be considered as well (National Comprehensive Cancer Network, 2015b; Zabora et al., 2014).

## CONCLUSION

In conclusion, patients living with myeloma may exhibit a variety of symptoms throughout the course of their disease, with varying degrees of severity. Palliative management of symptoms requires a multidisciplinary approach, which may include pain management, integrative medicine, neurology, nutrition, psychiatry, social work, and supportive care. As survival of patients with myeloma has increased, there is an accompanying risk of experiencing an even greater number and degree of disease- and treatment-related side effects. Through early identification and intervention, the severity of these symptoms and side effects may be ameliorated at all stages of the disease trajectory. In those patients who have received numerous treatment regimens without obtaining a significant response, discussion regarding palliative end-of-life care and referral to hospice is appropriate. ●

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