# Multiple Myeloma

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### *Faculty*

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### *Faculty Disclosure*

Contributing faculty, Jacqueline Houtman, RN, MA, CDP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

### *Audience*

This course is designed for nurses and allied healthcare professionals involved in the care, treatment, and education of patients with the diagnosis of multiple myeloma.

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### Course Objective

Multiple myeloma is the second most prevalent hematologic cancer after non-Hodgkin lymphoma. While great strides have been made to improve survival rates with this disease, and positive outcomes have been attained, multiple myeloma remains an incurable disease. The purpose of this course is to provide healthcare professionals in contact with multiple myeloma patients the information necessary to provide optimum care, treatment, and patient education.

### Learning Objectives

*Upon completion of this course, you should be able to:*

1. Review the history of multiple myeloma.
2. Describe the pathophysiology and differentiation of multiple myeloma.
3. Discuss the etiology, epidemiology, and clinical presentation of multiple myeloma.
4. Review multiple myeloma-associated physiology, including normal plasma cell formation, the significance of immunoglobulins, and bone homeostasis.
5. Discuss the diagnostic workup associated with multiple myeloma.
6. Describe the staging of multiple myeloma with prognostic indicators.
7. Discuss the role of glucocorticoids and bisphosphonates in the treatment of patients with multiple myeloma, incorporating regimens for relapsed/refractory disease with recognition of anticipated side effects.
8. Outline the role and action of the immunomodulators in the treatment of multiple myeloma, including side effects and patient education.
9. Discuss stem cell transplantation as a treatment option for multiple myeloma.
10. Discuss disease-related complications and potential oncologic emergencies associated with multiple myeloma, including interventions and treatment.


Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

## INTRODUCTION

Multiple myeloma (MM) is a systemic malignancy of the plasma cells and accounts for approximately 1% of all cancers diagnosed in the United States. The high degree of variability within this malignancy can result in a broad spectrum of treatments, which requires oncology nurses to look at the whole clinical picture. Patients with asymptomatic (smoldering) disease require no treatment; for patients with active disease, immediate treatment with chemotherapy, immunomodulators, or proteasome inhibitors incorporated with renal dialysis may be required to halt the aggressive disease process. Stem cell transplantation is also a treatment option for eligible individuals. Unlike some other forms of hematologic malignancies, patients with MM are not reliant upon achieving a complete remission in response to treatment in order to survive. The drug resistance that inevitably develops with this disease has the potential to be rechallenged with newer, more effective treatment modalities [1; 2; 3].

As an incurable malignancy, the effects of MM encompass the patient, family, and caregiver. While the medical profession has much to offer during the disease trajectory, an equally important component of care is the responsibility patients assume for their health. Measurable and achievable patient goals should be established from the time of diagnosis. The intent behind this vested patient involvement is not to create an overwhelming burden for the patient but to educate and empower patients to promote their own well-being and achieve the optimum quality of life.

## HISTORY OF THE DISEASE

As early as 1844 the as-yet unidentified disease of multiple myeloma was documented by descriptions of fragile soft bones ("mollities and fragilitas ossium") [4; 5]. Building on the discoveries of British physician William Macintyre, who noted that unusual proteins in urine also contributed to this disease, Dr. Bence Jones researched these findings even further, publishing his discoveries in 1848. This was undoubtedly momentous in medical history; Bence Jones proteinuria, or light chains, subsequently emerged as the first tumor marker on record [6]. As research continued, identification of lesions in bone from the infiltration of multiple plasma cells signified a more complex disease process. By 1873, this disease was officially termed multiple myeloma [7]. Moving into the early 1900s, x-ray imaging revealed lytic lesions from bone destruction. Evidence pointed to the bone marrow itself as the producer of plasma cells capable of destroying the bone. Improved technology coupled with refined laboratory testing of serum and urine and advances in bone marrow aspirations and biopsies over the next 50 years yielded results. Immunoglobulins (Ig) were classified by immunoelectrophoresis. In 1956, Bence Jones proteins were subtyped as kappa and lambda, so named in honor of the researchers Korngold and Lipari [8].

Despite significant accomplishments, it was not until 1958, with more than a century elapsing since the initial discovery of this disease, that the first chemotherapy treatment for MM, melphalan, became available. Measures of success were reported four years later, in 1962, with melphalan being recognized as first-line treatment for the disease.

Melphalan was followed by the addition of prednisone, cyclophosphamide, vincristine, doxorubicin, and dexamethasone. By 1992, melphalan and prednisone, the gold standard in treatment for decades, paralleled all other combined modalities. Thalidomide, lenalidomide, carfilzomib, pomalidomide, doxorubicin (liposomal), and bortezomib have been approved in treatment regimens prescribed for refractory and relapsed disease and as first-line and maintenance treatments [9; 10; 11]. Combinations of these and other agents have continued to prove efficacious.

The first staging system to determine prognosis and the eligibility for treatment was introduced by Durie and Salmon in 1975 [12]. As noted, due to the nature of this disease, not every patient with MM requires treatment.

For the many thousands of patients diagnosed with MM, the impetus to find newer and improved therapies continues. Without question, the last 30 years have seen major changes in treatment options, but the greatest strides in improving survival rates have been made since the late 1990s. There has been a re-evaluation of the criteria associated with determining appropriate first-line treatment and initiation of stem cell transplantation. Stem cell transplants, whether autologous or allogeneic, single or tandem, are available for eligible patients, generally up to 65 years of age (though this is not an absolute rule) [13]. Allogeneic transplants are not considered a standard treatment for MM but may be done as part of a clinical trial [14]. In 2005, a simplified staging system was introduced defining organ involvement with prognostic indicators. In 2015, a working group of the International Myeloma Foundation (IMF) published the Revised International Staging System (R-ISS) [15]. The R-ISS incorporates two further prognostic factors: genetic risk and level of serum lactate dehydrogenase [6]. Work continues in this arena to incorporate gene profiling to assess high-risk patients with MM [6].

Multiple myeloma is by no means a "new" disease. This malignancy continues to present a challenge not only to those diagnosed with the disease but also to healthcare providers whose shared commitment is to fulfill the goal of achieving the best outcomes for the patient.

## PATHOPHYSIOLOGY

There is often confusion regarding the classification of MM as a malignancy. Although there is extensive bone destruction throughout the skeletal system created by malignant plasma cells, MM is not considered a bone cancer. It is considered a hematologic malignancy, with some similarities to leukemia in the areas of treatment and subsequent complications of impaired immunity [16]. While leukemic cells circulate in the blood, the malignant plasma cells associated with MM remain within the bone marrow compartment. These plasma cells proliferate in bone marrow [16].

Multiple myeloma is defined as a malignancy of plasma cells, specifically terminally differentiated B-lymphocytes. When plasma cells mutate or become aberrant, the Igs produced by plasma cells are homogenous or monoclonal. The myeloma cells produce and secrete the characteristic monoclonal protein (M protein) detected in serum or urine [16]. Various terms denote this paraprotein: protein spike, M spike that has been likened to a church spire, myeloma protein, and "sticky-m" protein. Identification of the M spike is detected by electrophoresis, a laboratory test that separates and identifies proteins [16]. When more light chains are produced than match the heavy chains, light chains are excreted by the kidneys and detected in the urine. This is termed Bence Jones proteinuria [6].

The overabundance of ineffective plasma cells incapable of providing humoral immunity results from MM. It is proposed that the mutation occurs in the genes responsible for Ig production, with genetic changes occurring late in the B-cell differentiation [6]. When B cells fail to mature and are incapable of performing their function by binding to invading pathogens or antigens, they undergo apoptosis or programmed cell death. The process of plasma cell maturation is termed "antigenic selection" [17; 18; 19].

## MULTIPLE MYELOMA DIFFERENTIATION

MM manifests itself not only in various stages, which may or may not require treatment, but also in premalignant and malignant forms.

### MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant state. In most cases, the condition is asymptomatic and no treatment is required; patients may remain stable for many years. Approximately 1% to 2% of patients with MGUS will progress to MM each year [20]. In total, MGUS is detected in 3.2% of all patients 50 years of age or older. Most cases of MGUS are diagnosed as a result of abnormal findings on a routine blood test. Laboratory values for patients with MGUS are only slightly abnormal, with less than 10% plasma cells detected in the bone marrow and M protein less than or equal to 3 g/dL [20]. As noted, there are typically no symptoms associated with the disease. The absence of lytic lesions, anemia, hypercalcemia, and renal insufficiency distinguishes it from MM. Patients should be observed for progression, with follow-up in six months and then on a yearly basis [1; 21; 22].

### NONSECRETORY

Nonsecretory MM is a malignant form of the disease characterized by an absence of M protein secreted in either serum or urine (light chains). In patients with nonsecretory MM, plasma cells have become so de-differentiated that they are incapable of producing protein; hence, none are released into blood or urine. These patients present with anemia, lytic lesions, renal impairment, and hypercalcemia [1; 21; 22].

### PLASMACYTOMA

Plasmacytoma is a mass of plasma cells found outside bone marrow, usually in the respiratory or digestive tract. When a plasmacytoma is found in bone, it is referred to as intramedullary; plasmacytoma outside of bone, in soft tissue, is categorized as extramedullary [6]. When there are multiple plasmacytomas, this condition also is called myeloma [6]. Approximately 55% of patients with a plasmacytoma will develop MM [1; 6; 21; 22; 23].

### SMOLDERING, INDOLENT, ASYMPTOMATIC

Asymptomatic MM, also referred to as indolent or smoldering MM, is a nonmalignant form of the disease. Although the clinical presentation is similar to that of MGUS, with an absence of anemia, lytic bone lesions, hypercalcium, and renal impairment, it presents a greater risk of transformation to MM. Smoldering MM is characterized by a serum M-protein level of 3 g/dL and at least 10% of plasma cells in bone marrow [6].

Treatment may not be required for many years [6]. If symptoms develop, erythropoietin may be administered for anemia and bisphosphonates may be prescribed for hypercalcemia. It is imperative that patients follow up with an oncologist on a regular basis to monitor for any disease progression [1; 6; 21; 22].

## EPIDEMIOLOGY/ETIOLOGY OF MULTIPLE MYELOMA

### EPIDEMIOLOGY

Multiple myeloma is the second most common hematologic malignancy, and 1.8% of all cancers diagnosed in the United States are myeloma [24]. In 2024, an estimated 35,780 individuals will be diagnosed with MM and an estimated 12,540 individuals will die as a result of the disease [24]. The median age at diagnosis is 69 years. There is evidence that demographic factors may affect the risk of developing the disease. MM occurs twice as frequently in blacks as whites and at a higher ratio in men than in women [24; 25]. The 5-year survival rate after diagnosis is approximately 59.8%, with a range of less than 6 months to more than 10 years [25].

### ETIOLOGY

Research is inconclusive as to the definitive causes of MM. However, there are many theories regarding its etiology. Many researchers believe that MM is most likely the result of many risk factors acting together. Exposure to ionizing radiation as a risk factor is evidenced by an increased incidence among atomic bomb survivors and some individuals exposed to lower levels of radiation [26]. Herbicides, pesticides, and insecticides have been studied for their possible implication in the development of the disease. One supporting factor for this research is the apparently higher rates of disease among farmers and leather and wood workers. In addition, the prolonged use of hair colorants has been suggested as a precipitant. Finally, the relationship between specific viruses, including human herpes virus 8 (HHV-8), and MM has been studied [1; 19; 26].

## CLINICAL PRESENTATION

It is not unusual for a diagnosis of MM to be determined during a routine physical examination in patients who have presented to the physician's office with totally unrelated symptoms [16]. Blood work usually initially reveals anemia or renal insufficiency, warranting further investigation. In the majority of patients, MM manifests itself between the fifth and seventh decades of life. Many patients attribute their symptoms of lower back or rib pain, fatigue, weakness, and feeling out of breath on exertion to the normal aging process. Patients report their back pain is not relieved at night when resting and increases with a change in position. Neurologic involvement, with paresthesias and sensory loss in the extremities, may also be a presenting symptom [20; 23; 27]. Patients may voice some frustration during the prediagnosis period, reporting frequent office visits for upper respiratory or recurrent urinary tract infections that never completely resolve.

Upon initial diagnosis, approximately 80% of the patients have pathologic disease with punched out areas of bone due to lytic lesions; some will have evidence of fractures [6; 16]. Anemia, which may be quite severe, is the most common cause of weakness in patients with MM [16]. Seventy percent of patients presenting with this disease have anemia, and approximately 20% will have an elevated serum creatinine, showing signs of acute or chronic renal impairment [28]. Obviously, a more advanced stage of disease will reveal increased organ involvement or damage, evidenced by hypercalcemia and lytic bone lesions. For patients presenting with a more aggressive disease, this poses a serious problem requiring prompt intervention to halt the disease process [1; 2; 20]. Higher-risk patients are candidates for clinical trials at the discretion of the clinician [20]. The hallmarks of the disease—calcium elevation, renal insufficiency, anemia, and bone disease—are known by the acronym CRAB [6; 29].

## AN OVERVIEW OF MULTIPLE MYELOMA-RELATED PHYSIOLOGY

### PLASMA CELL FORMATION

The emphasis placed upon the need for thorough hand washing and regular oral hygiene in patients with impaired immune systems is evidence of the fact that skin and mucous membranes provide physical barriers against infection. These physical barriers, along with cell-mediated and biochemical components, make up the nonspecific or innate immune system. Additional immunity is provided by lymphocytic Igs, major components of the adaptive immune system; this system learns, stores information, and prepares itself for antigen invasion.

Bone marrow is one of the primary organs of the immune system. The pluripotent stem cell in bone marrow produces two very distinct cell lines: the myeloid and lymphoid stem cells. The myeloid stem cells differentiate into platelets, erythrocytes, eosinophils, macrophages, basophils, and neutrophils. While the lymphoid stem cell may appear to be more simplistic, differentiating into only two lines of cells (the T or B lymphocytes), these cells have the mammoth task of providing immunity at the cellular and humoral level. Cellular immunity is provided, in part, by the T lymphocytes, or T cells. When T cells encounter foreign cells within the body, they are able to act directly and destroy the cells from within. Humoral immunity, or Ig-mediated immunity, is provided by B lymphocytes, or B cells, which attack antigens on the cell surface. At any given time, millions of B cells circulate in blood and lymph on surveillance for pathogens invading the body. These B cells have not reached the mature stage of a plasma cell. Plasma cells do not have the capability of fighting infection until an antigen enters the body and an antibody-antigen response occurs. The malignancy of these plasma cells constitutes MM [1; 22; 27; 30].

### THE FUNCTION OF B AND T LYMPHOCYTES

On the surface of every B cell is a protein, the B cell receptor (BCR), that distinguishes this cell from other lymphocytes. The BCR is a membrane-bound Ig (antibody) that enables the B cell to become activated when an antigen is recognized. An antigen equates to any foreign substance invading the body that is capable of mounting an immune response; viruses, bacteria, fungi, particles of food, transplanted organs, cancer cells, and blood product transfusions all have the potential to fit the antigen criteria.

One of the functions of T cells is to assist B cells to differentiate into either mature plasma cells or memory B cells. Memory B cells, as the name indicates, respond rapidly to a repeat of a previously encountered exposure (the primary trigger creating the initial response).

Differing from B cells, T cells are incapable of recognizing or attaching to pathogens until dendritic cells, macrophages, or B cells, collectively known as antigen-presenting cells, have ingested the antigen. These antigen-presenting cells secrete enzymes that break up and fragment the antigen into a chain of peptides. These peptides within the B cell become attached to an identification molecule, either the human leukocyte antigen (HLA) or the major histocompatibility complex (MHC) class 11 protein. This is necessary for the body to identify foreign substances and recognize self from nonself. The HLA molecule transports the peptides to the surface of the B cell. On the T cell surface are T-cell receptors; these cells are now capable of recognizing and locking onto the HLA molecules on the B cell, just as a key fits into a lock. When the T and B cells have matching structures, the B cell activated by the T cell matures into a plasma cell, capable of producing Igs for humoral immunity. Under examination with a microscope, lymphocytes look similar, but are distinguished with the use of monoclonal antibody dyes, which identify the molecules on the cell

surface. Cells are labeled according to the "cluster of differentiation" (CD) antigen to distinguish one from another. To illustrate this, CD4 is the main receptor for HIV; CD34 is expressed on all early stem cell precursors [1; 17; 27].

## IMMUNOGLOBULINS

With the knowledge that MM is a malignancy of plasma cells, a review of Igs produced by plasma cells is appropriate. Approximately 5% of cells within the bone marrow are plasma cells. As previously discussed, plasma cells are mature B cells; in the absence of disease of these lymphocytes, plasma cells are responsible for humoral immunity [1].

The most commonly discussed immunoglobulins are probably IgG, IgA, IgD, IgE, and IgM. The three simplest of the five are IgG, IgD, and IgE, all of which are monomers, or single-unit structures in the shape of a Y. Each monomer has an identical structure consisting of four glycoprotein chains. Two heavy (H) chains, which have the most amino acids and therefore the highest molecular weight, and two light (L) chains, with the least amino acids and subsequently lower molecular weight, make up the top portion of the Y. The L chains are subtyped as kappa and lambda. The lower portion of the Y is a continuation of the H chains. Compatible bonds of disulfide form a connection between the four glycoprotein chains. A hinge connects the top of the Y to the bottom, granting flexibility of movement within the Ig for antibody-antigen binding sites. The two tips or ends of the Y on both the H and L chains have an antigen-binding fragment, known as Fab. Fab is the variable, as opposed to the constant, region of antibody. Antibody molecules differ greatly from one another on the Fab portion, providing specificity for binding to antigens. The stem of the Y is the constant region of the Ig, referred to as the constant fragment (Fc). The Fc portion determines the class, subclass, and activity of antibody, which are then denoted as IgG, IgM, IgD, IgE, or IgA [17; 18; 27; 31].

### Specific Antibody Function

Of the five immunoglobulin isotypes found in mammals, the most common is IgG, which comprises 75% of Ig in blood [6]. IgG is detected in blood and tissues and is the antibody responsible for fetal and infant immunity during the time before an infant develops its own immunity [31; 32].

IgA is the second most common Ig and is formed as a dimer, a more complicated structure. In general, IgA is found in the mucous membranes in the mouth, saliva, tears, nose, digestive tract, and lungs. It provides defense against micro-organisms by preventing antigens from attaching to epithelial cell surfaces [31; 32].

The third most common antibody is IgM. IgM is a huge structure compared to the other isotypes, as it is formed as a pentamer of five molecules joined together. This isotype is detected in the blood [31; 32]. IgM (rarely myeloma) is typically associated with Waldenström macroglobulemia [6].

IgG and IgM are the only immunoglobulins able to fix complement. Complement is a series of approximately twenty proteins able to complete opsonization, which consists of coating antigens for recognition and providing binding sites for phagocytes. A first encounter with an antigen produces an immediate primary response. If there has been a recent exposure to sepsis, high levels of antibodies will be detected. Secondary antibody response occurs when previously encountered antigens are re-encountered.

IgE is released in reaction specific to a particular antigen. When an allergen is encountered, IgE has primed both basophils and mast cells to release histamine in blood. Atopic individuals have increased IgE levels. This type of antibody may also be released in cases of parasitic infestation.

The final antibody is IgD, which is detected in the blood. The function of IgD has recently begun to be elucidated [33; 34]. Mature B cells undergo alternative mRNA splicing to express IgD and IgM

receptors with identical antigenic specificity. Studies have shown that IgD helps the peripheral accumulation of physiologically autoreactive B cells through its functional unresponsiveness to self-antigens and prompts readiness against foreign antigens. Other studies have clarified how and why certain mucosal B cells become plasmablasts or plasma cells that specialize in IgD secretion. Secreted IgD enters the circulation to "arm" basophils and mast cells with IgD antibodies that are reactive against mucosal antigens and to stimulate the release of immunoactivating, proinflammatory, and antimicrobial mediators [33; 34].

## BONE FORMATION

The destruction of bone associated with MM results in lytic lesions, with the potential for fractures. The sites most frequently involved are the vertebrae, ribs, pelvis, sternum, skull, and the long bones, such as the humerus and femur. The development of hypercalcemia due to these lytic lesions and compounded by renal impairment necessitates a review of bone formation [1; 35; 36; 37].

From fetal development through infancy to early adulthood, skeletal development evolves through a process termed modeling and remodeling. Two types of bone form: cortical bone, which provides support for strength, and trabecular bone, which is the main base for the formation of bone and hematopoiesis while also providing support.

During puberty, remodeling replaces the modeling process. By 21 years of age, an adult has attained maximum bone mass and strength. Modeling and remodeling in bone cells is governed by several mechanisms: genetic regulation, cell differentiation, hormonal and dietary influences, and mechanical stimuli (e.g., exercise, stress on bone). Bone is formed, resorbed, and subsequently repaired through a continual process of remodeling. While remodeling continues into old age, the rates of resorption and new bone formation change. By 30 years of age, bone resorption, predominantly in trabecular bone, exceeds bone formation [1; 35; 36].

Bone matrix is a mesh of collagen fibers that provides strength to bones. Deposits of calcium and phosphate are essential to strengthen this matrix. For bone mineralization, calcium, phosphorus, alkaline phosphatase, and the correct pH must be in balance. At the cellular level, osteoblasts, osteocytes, and osteoclasts are responsible for remodeling. Osteoblasts lay down new bone matrix of collagen fibers; fatigued mineralized bone cells are resorbed by osteoclasts. MM has an enormous impact on these cells with resultant destruction of bone, hypercalcemia, and subsequent complications.

### Bone Homeostasis

Bone homeostasis under the normal physiologic process is achieved when there is a balance between bone resorption and bone formation. The cells responsible for remodeling (i.e., osteoblasts, osteocytes, and osteoclasts) participate in three phases of bone homeostasis:

- Resorption
- Reversal
- Formation

#### *Resorption*

As noted, osteoclasts are the bone cells responsible for resorption or removing fatigued mineralized bone to prepare the bone surfaces for osteoblasts to lay down new bone matrix. Osteoclasts originate from hematopoietic stem cells, specifically the monocyte/macrophage lineage. In order to differentiate and become activated, cytokines produced by bone marrow stromal cells and by osteoblasts produce macrophage colony-stimulating factor (M-CSF). Osteoclasts express receptor activator of nuclear factor kappa B (RANK) on their surface; its ligand, RANKL, is expressed on marrow stromal cells and osteoblasts. When RANK and RANKL interact, promoting the differentiation of osteoclasts, the resorption process begins.

Osteoclasts have a life expectancy of three to four weeks. They are large, multi-nucleated cells found on the surface of cortical bones, forming Howship lacunae, or tunneling into trabecular bone, forming Haversian canals. Osteoclasts adhere firmly to bone surface engulfed in a membrane that seals off the area, over a "ruffled border," and begin resorption. Osteoclasts can remove only a limited area of mineral and matrix before the next step, the reversal process, begins. How osteoclasts receive the signal to halt the process is unknown; the possibility that elevated calcium triggers this halt has been suggested, or the matrix itself may secrete a substance. One very important established factor in this process is the osteoprotegerin (OPG) decoy receptor. Osteoprotegerin prohibits RANK/RANKL binding, preventing osteoclast development. Therefore, OPG and RANKL regulate how much bone is broken down, maintaining a necessary balance [35; 36; 38; 39; 40; 41].

### *Reversal*

With the completion of bone resorption, mononuclear cells, presumed to be monocyte/macrophages located on the bone surface, lay down material on which the osteoblasts will adhere. It is possible that osteopontin may play a major role here; there is still much research underway in this area [42; 43; 44; 45].

### *Formation*

The third and final phase of the growth of new bone occurs during formation. Osteoblasts, the major component of formation, arise from pluripotent stem cells, which differentiate into fibrous tissue, adipocytes, cartilage, or muscle. The periosteum and marrow stromal cells have osteoblast progenitor cells; these cells are committed to differentiate into osteoblasts and are instrumental in acting as receptors for bone growth factors and remodeling. In a slow process over time, the bone matrix fibers introduced by the osteoblasts strengthen and completely fill in the area cleared away by osteoclasts. Flattened lining cells then cover this new area, and a resting phase ensues until the cycle repeats itself.

### *Bone Maintenance*

Calcium stored within bone promotes calcium homeostasis. Decreased serum calcium prompts a signal to the parathyroid hormone to allow the release of calcium from bone, which results in an increase in the level in blood. Conversely, with an elevated serum calcium, the thyroid releases calcitonin to counteract the effects of the parathyroid and promote the storage of calcium within bone. Parathyroid hormone, in its role as calcium regulator, is essential to promote absorption of calcium from the gastrointestinal tract and maintain the balance within the kidneys [36; 41]. This becomes disrupted in patients with hypercalcemia.

### Bone Marrow

Bone and bone marrow, while having very distinct functions, also work interdependently. Along with the process of skeletal changes, bone marrow undergoes its own changes. The hematopoietic (red) marrow of infancy is replaced gradually by yellow or fatty marrow. For every 10 years of life, the cellularity of marrow decreases by approximately 10%. In adults, red marrow is found in the sternum, ileum, ribs, and vertebra [35].

### Bone Destruction

The destruction of bone caused by the invasion of plasma cells produces a multitude of problems. In MM, homeostasis is lost or uncoupled, and this results in destroyed bone, with osteolytic lesions leading to fractures, pain, and the release of calcium into the circulation, perpetuating renal insufficiency and hypercalcemia. The pathology of bone destruction in those with MM begins by MM cells expressing RANKL, prompting osteoclasts to resorb bone. MM cells then secrete macrophage inflammatory protein 1α (MIP 1α), which stimulates osteoclast formation. A gene (*dickkopf1*) and protein (DKK1) are expressed, inhibiting osteoblasts. Vascular endothelial growth factor (VEGF) mimics M-CSF to help in the differentiation of osteoclasts, thereby increasing resorption. MM cells are in close proximity to marrow stromal cells, which induces release

of cytokine IL-6. IL-6 promotes MM cell survival, either by promoting growth or blocking apoptosis. Finally, bone matrix is destroyed, releasing IL-6 and promoting MM cloning. Plasma cells release PTH-related protein, which increases bone resorption [19; 35; 36; 41; 46].

## DIAGNOSIS

When a diagnosis of MM is suggested, referral to an oncologist/hematologist is imperative. Several factors will determine where the majority of the patient's diagnostic workup will be completed. The patient's functionality and the stage of disease upon initial presentation will influence these decisions. If the patient has the ability to attend the physician's office as an outpatient for lab testing and the various x-ray departments for imaging, this is one option. If, conversely, the patient is experiencing pain prohibiting mobility, with fractures requiring stabilization or the degree of spinal cord involvement requiring urgent intervention, inpatient hospitalization will be ordered. Any clinical presentations of hypercalcemia, anemia, early renal impairment, or sepsis can be addressed and subsequently corrected while work to make a definitive diagnosis with staging is completed. With the diagnosis of MM established, a treatment plan will be discussed and may include chemotherapy and chronic blood transfusion support, with potential for dehydration correction, IV antibiotics, and routine bisphosphonate treatments. This may also be an opportune time to consult a surgeon for the placement of a central venous access device.

The benefit patients derive from the accompaniment of a supportive family member or caregiver when attending office visits cannot be overemphasized. The ideal person will be someone committed to being involved and willing to act as spokesperson for relaying information to other family members. This is especially significant when the diagnosis has been established, completed test results are on hand, and the oncologist sits down with the patient to discuss an appropriate treatment plan. Having a notepad readily available and writing questions to ask at future appointments helps keep the communication open between the patient and oncologist. Not every patient will have the desire to keep track of their lab work; as time passes and patients become more familiar with their disease, they may request copies of their lab results or choose to keep a journal. This provides not only an opportunity for education but helps foster a sense of responsibility on the part of the patient. Time spent with the patient and caregiver after they have received the diagnosis is paramount to the care the patient will require. Whatever treatment plan is decided upon, understanding the need to remain mobile, drink adequate fluids, keep current with appointments, and adhere to medication regimens will all contribute to the patient's well-being and promote his or her quality of life [1; 22].

### DIAGNOSTIC STUDIES

Approximately two to three days are required to complete and receive the results from all of the following diagnostic tests when diagnosing MM. Initial diagnostic tests include [20; 36; 43; 47; 48]:

- Complete history and physical
- Complete blood count (CBC) with manual differentiation and peripheral smear (looking for rouleaux formation)
- Complete metabolic panel (CMP), which includes blood urea nitrogen (BUN), creatinine, calcium, albumin, and lactate dehydrogenase (LDH)
- Serum protein electrophoresis (SPEP)
- Quantitative Ig
- Urine for urinalysis, culture, and sensitivity
- Urine protein electrophoresis (UPEP) with immunofixation
- 24-hour urine collection (looking specifically for Bence Jones light chains)
- Free light chains in serum
- Immunofixation electrophoresis (IFE)

- Skeletal survey (whole body)
- Whole body magnetic resonance imaging (MRI)
- Whole body computed tomography (CT) scan
- 18Fluorodeoxyglucose (F-FDG) positron emission tomography (PET)/CT scan
- Bone marrow biopsy with aspiration

EVIDENCE-BASED PRACTICE RECOMMENDATION

For people with newly diagnosed myeloma or smoldering myeloma who have not had whole-body imaging with one of the following, the National Collaborating Centre for Cancer recommends whole-body imaging be considered to assess for myeloma-related bone disease and extra-medullary plasmacytomas with MRI, CT, or fluorodeoxyglucose positron emission tomography CT.

(https://www.nice.org.uk/guidance/ng35. Last accessed March 14, 2024.)

**Level of Evidence**: Expert Opinion/Consensus Statement

A nuclear bone scan is not appropriate as part of the workup, as technetium-99 highlights new bone, not lytic lesions. MRI is considered the gold standard for imaging myeloma infiltration of marrow and is able to detect bone involvement before bone destruction without radiation exposure [49; 50]. The International Myeloma Working Group considers 18F-FDG PET/CT a valuable tool for the workup of patients with both newly diagnosed and relapsed or refractory MM due to its high degree of sensitivity and specificity in assessing bone damage and detecting extramedullary sites of proliferating clonal plasma cells [48]. If the diagnosis of a plasmacytoma is part of the initial workup, a biopsy of the tumor mass will be included in the diagnostics. Obtaining an accurate 24-hour urine sample is important. A more accurate collection may be obtained if completed during hospitalization, as opposed to the patient completing this at home.

### Cytogenetic Profiling

Advances in technology (e.g., high-throughput sequencing) and the associated shift toward precision medicine in oncology have revolutionized the diagnosis and treatment of MM in the last decade. Modern diagnostic workups are incomplete without cytogenetic testing, including interphase fluorescence in situ hybridization (FISH) in purified plasma cells or in combination with immunofluorescent detection of light-chain-restricted plasma cells (cIg-FISH) [29; 51; 52]. Standard cytogenetic testing uses samples grown in the lab from bone marrow (or blood) plasma cells, a process that takes weeks [53]. FISH testing uses the actual biopsied plasma cells and fluorescent dyes that attach to specific areas of particular chromosomes to identify abnormalities, and the results are available within one or two days.

In respect to MM, there are several specific gene mutations that can help to predict a patient's prognosis and response to a particular type of therapy. Cytogenetic irregularities seen in MM are of two main types: immunoglobulin heavy-chain (IgH) translocations and genomic imbalances (i.e., chromosomal gains and losses) (***Table 1***) [52; 53]. IgH translocations are found in approximately 40% of MM cases, but abnormal cytogenetic findings are not necessarily indicative of poor prognosis. In fact, a t(11;14) translocation is associated with a positive or neutral prognosis [52; 53].

Monosomy 13/13q deletions are found in 50% of malignancies [54; 55; 56]. Although these are linked with short survival (even with chemotherapy), 80% of patients with monosomy 13 also have t(4;14), another strong factor for poor outcome. Armed with data from clinical trials that show patients with the t(4;14) translocation have more favorable outcomes when treated with proteasome inhibitors, clinicians can now make better informed treatment decisions for this cohort [57; 58]. Rare chromosomal deletions (e.g., 17p deletions) are associated with extremely poor prognoses; mean survival after diagnosis is four months [59].

| COMMON CYTOGENETIC ABNORMALITIES IN MULTIPLE MYELOMA | |
|---|---|
| **IgH Translocations** | **Genomic Imbalances** |
| t(4;14)[a]<br>t(6;14)<br>t(11;14)<br>t(14;16)[a]<br>t(14;20)[a] | 1q gains[a]<br>17p deletions[a]<br>Monosomy 13<br>Hyperdiploid<br>Nonhyperdiploid[a] |
| [a]Associated with unfavorable prognosis and poor outcomes | |
| *Source: [20; 52; 53]* | *Table 1* |

Other genetic tests used in research or clinical trial settings include comparative genomic hybridization, mapping arrays based on single nucleotide polymorphisms, and gene expression profiling. However, these tests are typically unavailable in clinical settings due to technologic limitations [51]. Although the molecular markers currently lack validation, these whole-genome techniques are expected to become an important feature of diagnosis and treatment in the near future.

**Bone Marrow Aspiration and Biopsy**

Bone marrow aspiration and biopsy are performed for diagnostic purposes. They are initially performed as part of the plasma cell dyscrasia workup and then periodically to monitor the response to treatment and disease progression [6]. Investing time in preparing the patient for bone marrow aspiration and biopsy and obtaining a good specimen with the first endeavor is time well spent. A signed informed consent form must be obtained, and patients should be prepared for the procedure, including the fact that they will be positioned on their stomachs.

Red marrow is the target for biopsy. Realizing that the marrow will have decreased by approximately 50% in adults, with the remainder being adipose tissue, there is little to be gained from sampling marrow from various sites for comparison [21; 60]. The iliac crest is usually selected for the aspiration and biopsy and is reportedly the least uncomfortable from all the sites [21; 60]. The posterior iliac crest is the preferred site; the anterior iliac crest is an alternative if the patient is unable to lie prone or is obese [21; 60]. In patients with MM, the sternum is never the optimum site for the bone marrow aspiration because the bones are too fragile and the procedure would present a heightened risk of perforating the sternum and damaging the underlying organs.

Prior to the procedure, the lab will have been notified in order to have a technician available at the bedside. The technician will set up the slides for the marrow smears, as the aspirate and biopsy specimens clot quickly. The screening of the marrow will include cellularity, morphology, maturation, cytogenetic testing, immunophenotyping, and molecular analysis [21; 60].

Approximately 10 to 15 minutes prior to the bone marrow biopsy, the patient will be administered an analgesic and possibly an anxiolytic. A nail imprint or indentation with a pen (no ink) will mark the area selected. The area is cleansed, draped, and numbed with local anesthetic, and the bone marrow biopsy is performed. The patient may experience pain when the needle penetrates the periosteum and cortical bone; a more intense discomfort occurs when the marrow is aspirated [60].

A pressure dressing will be applied to the bone marrow site, and the patient will be instructed to lie on their back (a rolled up towel works well to reinforce pressure) for at least one hour. Periodic checks to assess for any bleeding, ensuring the site remains dry and the dressing intact, for 48 hours will help to reduce the risk of infection [21; 60].

## STAGING

Staging of MM is a necessary step to enable the clinician to determine a prognosis, which is based on four major factors: disease stage, disease aggressiveness, host characteristics (e.g., age, performance status, comorbidities), and response to therapy [61]. When patients receive the news of a cancer diagnosis, undoubtedly their first reactions are fear and a belief that the diagnosis translates to death.

Compounded with this is the knowledge that MM is an incurable malignancy. It is imperative from the moment this information is presented that healthcare professionals provide reassurance and explain to patients that while MM may not be curable, there are treatments available.

The first universally accepted staging system for MM emerged in 1975 from Durie and Salmon. This system is still available and in use, but a more concise tool, the International Staging System (ISS), has been developed. The ISS evolved from data collected between 1981 and 2002 from 10,750 symptomatic, untreated patients with MM residing in North America, Asia, and Europe. Researchers found the ISS to be easier to use and more precise in predicting prognosis than the Durie/Salmon staging system [62]. As stated, in 2015 a working group for the International Myeloma Foundation published the R-ISS, which incorporates the additional prognostic factors of genetic risk (as assessed by molecular FISH) and cytogenic abnormalities identified in bone marrow myeloma cells [6].

For comparative purposes, the Durie/Salmon staging system categorizes disease into three stages. The six criteria for stage I or stage III (stage II is neither III nor I) are based on values of: hemoglobin, serum calcium, lytic bone lesions, values of IgG and IgA, Bence Jones urine light chains, and myeloma cell mass. The detection or absence of bone lesions, proteins, and cell mass with variable increases in normal values determines the necessity for treatment options. In contrast to the six criteria from Durie/Salmon, the R-ISS measures three variables, with predictions for median survival [2; 6; 62].

A study conducted by the European Myeloma Network (EMN) found that a main limitation of the R-ISS is that most patients (62%) are classified into the intermediate-risk category (R-ISS stage II), possibly including patients with large variations in risk of progression/death [52; 63]. The EMN proposed a revised R-ISS (the R2-ISS), which further divides the intermediate-risk group into low- and high-risk groups. The group conducted a study to determine how many R-ISS patients would be redistributed with the R2-ISS and how the R-ISS compared with the R2-ISS [63]. After evaluating overall survival in R-ISS stage II patients according to the new R2-ISS score, the EMN found that R-ISS stage II patients represent a very heterogeneous population in terms of survival that can be discriminated through the revised (R2-ISS) scoring system [63]. The study has only been validated in patients with newly diagnosed MM enrolled in clinical trials [52; 63].

## THE REVISED INTERNATIONAL STAGING SYSTEM

The R-ISS, formerly the ISS and the International Prognostic Index (IPI), organizes disease into three stages that correlate with estimated survival (***Table 2***) [6]. The R-ISS staging system is based on three values in the blood: serum albumin, serum microglobulin, and serum lactate dehydrogenase (LDH).

In stage I, serum ß-2 microglobulin is less than 3.5 mg/L, the serum albumin is equal to or greater than 3.5 g/dL, and the serum LDH is normal. Stage II disease is defined as serum ß-2 values of 3.5–5.5 mg/L, regardless of the serum albumin value. MM is also considered stage II when serum ß-2 microglobulin is less than 3.5 mg/L and the serum albumin is also less than 3.5 g/dL. In stage III, the serum ß-2 microglobulin level is greater than 5.5 mg/L and the serum LDH is high [2; 64; 65; 66]. Serum albumin level is not part of stage III criteria.

Stage I disease has historically been associated with an average survival time of 62 months; stage II survival is an estimated 44 months, and stage III is 29 months [67]. However, overall survival times have increased with newer chemotherapy agents and treatment algorithms. The estimated survival times indicated by disease stage are often very disturbing to patients and families. MM has many variables within the disease process. The disease itself produces complications, compounded with the side effects from specific treatments. It is important to point out that survival is not predetermined and that individuals have lived with the disease for up to 10

| REVISED INTERNATIONAL STAGING SYSTEM FOR MULTIPLE MYELOMA | | | | |
|---|---|---|---|---|
| **Stage** | **Serum Albumin** | **Serum ß-2 Microglobulin** | **Serum Lactate Dehydrogenase** | **Chromosomal Abnormalities** |
| I | ≥3.5 g/dL | <3.5 mg/L | Normal | Standard risk |
| II | Any other combinations of prognostic factors | | | |
| III | NA | >5.5 mg/L | High | High risk |

*Source: [64; 65]* *Table 2*

years. Patients require support to understand that, with ongoing research, evolving treatments provide new hope and longer survival times [1].

New, more effective risk classification systems are being developed and evaluated. One such system is microarray-based gene expression profiling (GEP), which has been used to assess risk in patients with myeloma both at diagnosis and at relapse. Approximately 15% of newly diagnosed patients assessed with GEP in clinical trials have shown a high-risk GEP signature [6]. While GEP has the potential to refine risk prognosis beyond standard cytogenetics, its use is currently limited by the lack of a uniform platform and widespread unavailability [6].

## TREATMENT MODALITIES

Staging systems are useful for providing prognostic information, but they are not of great benefit when planning a treatment strategy for patients with MM due to the inter-stage diversity [29; 68]. For example, while one patient may be classified ISS stage III due to renal failure, another may be stage III due to high tumor burden, as both cause high serum ß-2 microglobulin. The treatment approach would be significantly different in each patient. Another prognostic indicator, response to therapy, is of course not useful for guiding the initial treatment decision. Initial therapy is typically determined based primarily on disease aggressiveness markers (i.e., cytogenetic, molecular, and proliferative features) and host factors and is adapted to each patient's risk [68].

A risk-adapted, personalized approach is the most rational way to treat MM as it helps to ensure that patients are not undertreated (for aggressive disease) or overtreated (for indolent disease that will be slow to relapse), and there are many effective agents and combinations with differing indications and safety profiles [29]. Individuals with aggressive disease, younger biologic age, and few comorbidities typically receive intensive therapy (i.e., continuous high-dose therapy with autologous stem-cell transplant). Patients with nonmalignant smoldering or asymptomatic MM may require no immediate active treatment (e.g., no chemotherapy or immunomodulators) or therapy that is less intense and/or in intervals. Furthermore, treatments are tailored to variations in host and disease characteristics, sparing patients from excessive toxic effects.

As discussed, advances made in the last decade, including technologic innovation, identification of multiple genes involved in the development and proliferation of malignant plasma cells, and an understanding of the importance of the bone marrow microenvironment and its role in sustaining the malignancy, have allowed the use of a risk-adapted, precision approach [6; 29]. The Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) is a continually updated guideline designed to provide recommendations for initial therapy, transplant, and maintenance therapy in the rapidly evolving, complex field of MM treatment [29; 69].

| mSMART 3.0 CLASSIFICATION OF ACTIVE MULTIPLE MYELOMA | |
|---|---|
| **Risk Level** | **Cytogenetic and Biologic Markers** |
| High[a]<br>Double-hit myeloma: Any two high-risk genetic abnormalities<br>Triple-hit myeloma: Three or more high-risk genetic abnormalities | FISH testing:<br>• t(4;14)<br>• Del 17p<br>• t(14;16)<br>• t(14;20)<br>• *p*53 mutation<br>• 1q Gain<br>R-ISS stage III<br>High plasma cell S-phase[b]<br>Gene expression profiling (if available): High-risk signature |
| Standard[a] | All others, including trisomies, t(11;14)[c], and t(6;14) |
| [a]Trisomies may ameliorate<br>[b]Cut-offs vary<br>[c]t(11;14) may be associated with plasma cell leukemia | |
| *Source: [69]* | *Table 3* |

The guideline is a consensus of more than 20 Mayo Clinic physicians and is widely used in clinics and clinical trials. The recommendations are based on a collection of evidence from previous clinical trials that demonstrates safe, effective treatments for MM in patients with differing tumor biology factors, patient-related factors, and tumor burden factors. The result of this risk stratification is better long-term outcomes.

Tumor burden is assessed during staging, and the presence or absence of extramedullary disease (i.e., malignancy other than in bone marrow) is also investigated. Aside from age, patient-related factors integral to treatment include renal function and performance status. The Eastern Cooperative Oncology Group (ECOG) performance status scale is useful for evaluation and treatment planning. The ECOG gauges the patient's level of disability and their ability to perform activities of daily living, including job/work activities and self-care [70]. The estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease formula, is the recommended method for the assessment of renal function in patients with MM with stabilized serum creatinine [71]. The RIFLE (risk, injury, failure, loss and end-stage kidney disease) and Acute Renal Injury Network criteria are appropriate for defining the severity of renal impairment in individuals with acute renal injury. Tumor biology factors include a variety of cytogenetic and biologic markers that have been found to correlate with disease aggressiveness; these are used to classify a patient's disease into a risk group (***Table 3***) [69].

The majority (60%) of patients with MM are categorized as standard risk, while high-risk patients comprise 20% [29; 68]. For patients with symptomatic disease, treatment should begin as soon as possible. Modalities include [20; 29]:

- Stem cell transplant
- Chemotherapy (oral or IV)
- Glucocorticoids
- Bisphosphonates
- Immunomodulators
- Proteasome inhibitors

Various combinations of these modalities are often used. Fortunately, many patients with MM do not have to depend upon a complete remission in response to treatment in order to survive. Median overall survival rates for patients with disease classified as standard-risk, intermediate-risk, and high-risk are 8 to 10 years, 4 to 5 years, and 3 years, respectively [29].

Patients younger than 70 years of age are considered eligible for stem cell transplantation and potentially an initial treatment of high-dose chemotherapy. However, many patients with MM are elderly and/or their comorbidities and poor overall performance status prohibit this type of rigorous regimen. [9; 22; 28; 29; 52; 72; 73; 74]. Biologic age (versus chronologic age), which takes into consideration organ function, nutritional status, and other host characteristics, guides candidacy for stem cell transplantation, and the choice of therapy is significantly impacted by this decision [68]. Treatment algorithms for transplant-eligible patients with active disease in each risk group are suggested in the mSMART guideline [29]. It is important to note that the choice of therapy often depends upon the availability of agents and the familiarity of the clinic and clinicians with the available modalities.

Oncology nurses working with inpatients on a medical/oncology unit may never receive orders to administer high-dose chemotherapy to patients with MM, but having knowledge of what this entails is applicable to patient care. Many of the regimens described for transplant candidates are also options for nontransplant candidates. For example, as in transplant-eligible patients, three-drug regimens are preferred by the National Comprehensive Cancer Network (NCCN). Patients ineligible for initiation of treatment with a three-drug regimen can be started with a two-drug regimen, with a third drug added after performance status improves. A two-drug regimen is preferred for elderly and/or frail patients [52]. The preferred regimens for primary therapy of nontransplant patients include [52; 75]:

- Bortezomib/lenalidomide/dexamethasone (for frail patients)
- Daratumumab/lenalidomide/dexamethasone
- Lenalidomide/low-dose dexamethasone (for frail, elderly patients)
- Bortezomib/cyclophosphamide/dexamethasone (for patients with acute renal insufficiency)

A randomized phase III trial that compared the bortezomib/lenalidomide/dexamethasone regimen to the lenalidomide/dexamethasone regimen reported superior results with the three-drug regimen [76]. Results of two trials found that the two-drug regimen (lenalidomide/low-dose dexamethasone) was well-tolerated and effective in nontransplant and elderly patients [77; 78].

Other recommended regimens include [52; 75]:

- Daratumumab/bortezomib/melphalan/prednisone (regimens containing melphalan are rarely used in North America)
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone (for patients with renal insufficiency and/or peripheral neuropathy, ixazomib may be substituted for carfilzomib in select patients)
- Lenalidomide/cyclophosphamide/dexamethasone

Daratumumab-containing regimens include daratumumab for IV infusion or daratumumab plus hyaluronidase-fihj for subcutaneous injection [52]. Daratumumab in combination with hyaluronidase-fihj received FDA approval in 2020 for treatment of newly diagnosed or relapsed/refractory MM [79].

Bortezomib/dexamethasone and cyclophosphamide/lenalidomide/dexamethasone may be useful in certain circumstances (e.g., frail, elderly patients) [52; 75]. Lenalidomide and bortezomib are recommended for maintenance therapy [52].

As with transplant patients, nontransplant patients are stratified by risk. As stated, melphalan-containing regimens are no longer considered the standard of care for nontransplant patients; however, they may be useful in certain circumstances [52]. For example, for nontransplant patients who are not high risk, oral melphalan and prednisone offer an easier mode of administration, with fewer side effects [52; 80]. This regimen, which is repeated every 42 days, consists of [75]:

- Melphalan 9 mg/m$^2$ oral dose given on days 1–4
- Prednisone 60 mg/m$^2$ given on days 1–4

However, there are several variations of this regimen [75]. Oral melphalan is administered on an empty stomach, either two hours prior to a meal or three hours following a meal. Food decreases the absorption of the drug [75]. Dexamethasone as a single agent may also be prescribed. The oral dose is 40 mg on days 1–4, 9–12, and 17–20. This cycle is repeated every four weeks [81]. As with transplant patients, nontransplant patients are stratified by risk and several additional combinations are suggested. Newer chemotherapy therapies are being researched, with the continued emphasis on prolonging survival, reducing toxicities from the various agents, and the ease of administration.

## GLUCOCORTICOIDS

Glucocorticoids, also termed corticoid steroids, adrenocortical steroids, or steroids, are prescribed in various forms for patients with MM. As discussed, glucocorticoids may be given alone, usually prednisone or dexamethasone, or in combination with chemotherapy. Steroids are used increasingly with immunomodulators and emergently in the treatment of patients diagnosed with spinal cord compression.

### Action of Glucocorticoids

Glucocorticoids act in several ways. They reduce inflammation by inhibiting cytokines and suppress the action of immune system. This prevents white blood cells (WBCs) from migrating to a site of infection, in turn reducing swelling and pain and increasing circulation to the area. The agents also potentiate the effects of chemotherapy and immunomodulators.

Patients taking glucocorticoids should be monitored closely, as the drugs may mask underlying infections. They also decrease the body's ability to fight infection, as WBCs remain in the circulation rather than at the site of inflammation.

Unfortunately, the side effects associated with glucocorticoids can negatively influence patients' quality of life. As with any medication, responses differ; some patients tolerate steroids well, while others find the side effects intolerable. The longer the period patients remain on the steroids, the more pronounced the side effects become. Possible side effects associated with glucocorticoids include [22]:

- Mood swings (e.g., depression, mania, steroid-induced psychosis)
- Facial or abdominal bloating
- Increased appetite with subsequent weight gain
- Increased sodium and water retention
- Gastrointestinal (GI) perforation (use cautiously in patients with peptic ulcer disease)
- Lengthened healing times
- Increased susceptibility to infection
- Elevated blood glucose
- Fragile "onion" skin
- Osteopenia as a result of decreased absorption of calcium

When patients are educated regarding their medications and possible side effects and have an awareness of what to expect, this invariably guides their attitude and willingness to comply with their treatment. Patients should be encouraged to take steroids after a meal or with food to reduce the risk of gastric irritation; steroids should never be ingested on an empty stomach. Taking the medication as early as possible in the day may help to relieve feelings of hyperactivity and promote a good night's sleep.

Daily weight should be monitored and recorded; patients are instructed to report any sudden weight increase, shortness of breath, or edema to their healthcare provider immediately [22]. When nurses administer dexamethasone as an IV push, it is best to administer the drug slowly to avoid the unpleasant (although transient) perineal irritation that occurs with too rapid administration of this agent.

## BISPHOSPHONATES

Areas of bone loss resulting in lytic lesions, bone pain with the potential for fractures, and hypercalcemia can all occur in patients with MM and drastically impact quality of life. Lytic lesions in bone never repair; therefore, halting bone destruction and preventing skeletal events are an integral part of symptom management in these patients [1; 82; 83].

Oral bisphosphonates typically prescribed for osteoporosis, such as ibandronate and alendronate, are unsuitable for bone destroyed by osteoclast activity from the influences of malignant plasma cells. Oral bisphosphonates are poorly absorbed by the GI tract, and their absorption is reduced considerably when taken with food or fluids [41; 84]. When the essential rapid mechanism of a bisphosphonate is required, as in the treatment of hypercalcemia, or when the standard regimen of dosing every three to four weeks to prevent further bone loss is not successful, bisphosphonates in the IV form are used.

The exact action of bisphosphonates is not fully understood. It is known that bisphosphonates bind to the bone surface and interrupt the resorbing activity of osteoclasts and that osteocyte and osteoblast apoptosis is also prevented [85]. Laboratory studies have indicated that bisphosphonates may be capable of producing anti-tumor effects—possibly by inhibiting tumor cell angiogenesis, invasion, proliferation, and survival—but this is still under investigation. The NCCN guidelines recommend the use of bisphosphonates for all patients receiving therapy for symptomatic MM, regardless of documented bone disease. (Denosumab is preferred in patients with renal disease [52].) The mSMART guidelines recommend that bisphosphonate therapy only be used in patients with smoldering MM in the setting of a clinical trial. The routine use of bisphosphonates is not recommended [69]. The International Myeloma Working Group's 2021 guideline regarding MM-related bone disease recommends the use of bisphosphonates (zoledronic acid preferred) in all patients with MM [86].

There are two bisphosphonates currently approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of MM: zoledronic acid and pamidronate. Zoledronic acid is administered once every three to four weeks at a dose of 4 mg over 15 minutes as IV infusion [75]. Zoledronic acid is more costly than pamidronate but is 100 times more potent. Renal function should be monitored for elevated creatinine and albumin levels. In patients who develop renal deterioration with no other apparent cause, bisphosphonate therapy with zoledronic acid or pamidronate should be withheld until the serum creatinine returns to within 10% of the baseline level. Intermittent evaluation (every three to six months) for the presence of albuminuria is recommended. Patients with pre-existing mild-to-moderate renal impairment should receive a reduced dosage of zoledronic acid [52]. Use in patients with severe renal impairment is not recommended [20; 52]. Alternately, a pamidronate dose of 90 mg is administered over four to six hours by IV infusion once every three to four weeks. Pamidronate is used more frequently in patients with MM than zoledronic acid [75; 83]. The monoclonal antibody denosumab may be used when renal dysfunction precludes the use of bisphosphonates [20].

Patients may be maintained on bisphosphonates for a period of two years before the efficacy of the drug is re-evaluated [52]. There are reports of patients remaining on the medication for as long as six years [2; 83].

Side effects that may arise during the use of bisphosphonates include [22; 66; 87]:

- Bone pain
- Fever
- GI symptoms: nausea, vomiting, diarrhea (usually transient and do not require treatment)
- Medication-related osteonecrosis of the jaw (MRONJ): temporary or permanent loss of blood supply to the jaw bone (usually the mandible) resulting in necrotic areas

MRONJ is a serious and more significant issue. It is characterized by loose teeth and areas of exposed jaw bone, with resulting pain and infection. This condition is more likely to occur with more potent bisphosphonate therapy (e.g., IV zoledronic acid) and with longer duration of therapy [75; 83; 88].

EVIDENCE-BASED PRACTICE RECOMMENDATION

In light of the slight risk of osteonecrosis of the jaw associated with bisphosphonate (or other osteoclast inhibitor) administration, the American College of Radiology recommends considering a pretreatment dental evaluation to assess dentition and potential risk prior to starting a bisphosphonate.

(https://acsearch.acr.org/docs/3091670/Narrative. Last accessed March 14, 2024.)

**Level of Evidence**: Expert Opinion/Consensus Statement

### Patient Education

Patient education is vital for patients with MM taking bisphosphonates. Regular oral hygiene should be stressed. A thorough dental check-up prior to starting bisphosphonate treatment is strongly recommended, with extraction of unsalvageable teeth [52; 75]. Invasive dental work while taking bisphosphonates should be avoided or completed before treatment begins [83; 88].

Patients should be advised that blood work will be monitored for creatinine and albumin. The findings of this blood work will guide dose adjustments. Oral supplements of calcium and vitamin D should be continued per the physician's recommendation [87].

## IMMUNOMODULATORS

### Thalidomide

Thalidomide was originally used in Europe during the 1950s and early 1960s as a treatment for morning sickness and insomnia in pregnant women. Thalidomide did not appear to present any risks. Respiratory depression was not an issue; the belief that the placenta acted as a protective barrier between mother and fetus supported the safety aspect. For approximately five years, women in Europe and Canada could obtain this over-the-counter drug. The FDA never approved the use of thalidomide due to concerns related to peripheral neuropathy, and it was not available in the United States. In the 1960s, it began to become evident that the drug was linked to severe teratogenic side effects. Thalidomide produced at least 10,000 infants born with deformed internal organs, missing arms and legs, and flipper-like attachments at shoulder and hip areas that replaced digits (phocomelia) [89].

These fetal deformities heightened the awareness of the need for improved and adequate drug safety regulations, including the realization that the effects for animals and humans are not always the same. In this case, a medication that appeared to be safe in animals proved teratogenic in humans [89; 90; 91]. However, thalidomide was also found to have anti-inflammatory and immunomodulatory properties. Both of these mechanisms make the drug useful in medicine today.

Thalidomide reappeared in the medical arena in the late 1990s. In July 1998, the FDA initially approved thalidomide to treat the skin disease erythema nodosum leprosum, which is associated with Hansen disease (leprosy). The anti-inflammatory properties also make thalidomide a useful medication for rheumatoid arthritis. Oncology nurses may be familiar with this immunomodulator for its use in the treatment of advanced breast cancer, hepatocellular tumors, Kaposi sarcoma, and renal cell cancer. Patients with acquired immunodeficiency syndrome (AIDS) receive thalidomide as palliation for cachexia, as it can reportedly stimulate appetite and promote sleep. For hematologic malignancies, thalidomide is generally prescribed for Waldenstöm macroglobulinemia and myelodysplastic syndrome (MDS) [75; 92; 93; 94; 95].

With the introduction of thalidomide for myeloma treatment in 1997, the options for treatment expanded and additional novel agents followed soon after [6]. Nearly all patients in the United States receive induction therapy that includes at least one novel agent. Most patients receive combination bortezomib/lenalidomide/dexamethasone [6]. The NCCN guideline states that combination regimens that include thalidomide may be useful in certain circumstances [52]. However, the agent is no longer widely used in the United States due to the availability of next-generation immunomodulatory drugs and their relatively favorable side effects profile compared to thalidomide [6; 52].

### *Safety Regulations Related To Thalidomide*

Since 1998, at least 130,000 patients in the United States have received thalidomide under the strict governance of the System for Thalidomide Education and Prescribing Safety (STEPS) program—now called Thalidomide REMS [96]. The Thalidomide REMS program mandates safety practices in the prescription, administration, and monitoring of patients taking thalidomide. Thalidomide may be prescribed to women of childbearing age and men who are still possibly sexually active, which means the risk for severe fetal defects exists. Patients, prescribing practitioners, and pharmacists are all required to register with Thalidomide REMS, undergo an education process, and their verbal understanding and written consents are obtained. Only registered practitioners who complete the mandated training receive an authorization number; pharmacists are required to follow up with a verification number when prescriptions are filled. Patients are allowed a maximum of seven capsules before a new prescription can be filled. These capsules are considered a 28-day supply and no refills are permitted [96]. On the casing of every thalidomide capsule is a warning related to risks to pregnancy. One 50-mg capsule is sufficient to cause the teratogenic side effects of phocomelia during fetal limb formation. This could potentially occur during the first 20 to 35 days of pregnancy.

Women who take thalidomide must use two acceptable forms of birth control (as directed by their physician) for four weeks before beginning thalidomide, during their treatment, and for four weeks after treatment. The woman must have two negative pregnancy tests prior to beginning thalidomide and will need to be tested for pregnancy in a lab at certain times during her treatment [96]. Women who are two years postmenopausal or have undergone a hysterectomy may be excused from meeting these requirements [96]. Men receiving thalidomide treatment who are sexually active should be counseled to use a condom during treatment or completely avoid any sexual contact with a woman who is pregnant or may become pregnant while taking this medication and for four weeks after completing treatment. Women taking thalidomide cannot breastfeed, and men cannot donate sperm; neither is permitted to donate blood [92; 96; 97; 98].

### *Mechanism of Action*

Within the bone marrow, myeloma cells produce growth factor, known as vascular endothelial growth factor (VEGF), to promote their own existence (neovascularization). VEGF exerts its influence upon marrow cells to secrete cytokines IL-6 and tumor necrosis factor-alpha (TNF-α) [75]. These factors attract additional myeloma cells. With an increased number of cells attached to endothelial cells, a vicious cycle continues, with an increase in VEGF producing a more aggressive disease.

Thalidomide produces several actions to combat the effects of myeloma cells [89; 90; 94]:

- Inhibits angiogenesis by blocking fibroblast growth factor
- Blocks VEGF
- Inhibits plasma cells and marrow cells
- Interrupts cytokine production and pathways
- Down regulates or inhibits TNF-α and IL-6
- Increases effect of glycoproteins, which have antitumor necrosis factor activity

### *Dosing*

Thalidomide is poorly soluble in water and therefore is not manufactured in the IV form. Within four hours of oral ingestion, the maximum serum concentration is reached and the kidneys excrete the breakdown of metabolites [75; 99]. Capsules are produced in 50-mg, 100-mg, 150-mg, and 200-mg doses [75].

In most cases, the goal is to reach a target dose within 14 days of initiating the medication, but each treatment plan is individualized. Patients may have comorbidities that do not accommodate rapid titration of the drug. The usual dose increases are by increments of 50 mg or 100 mg, and the maximum dose is usually 800 mg [75]. The average daily dose is in the range of 200–400 mg. Higher doses may produce a better response, but the toxicities may outweigh the benefits [82]. Routine blood work should be ordered to monitor protein levels and plasma cell counts in order to assess the response to therapy.

There is a great deal of flexibility with thalidomide dosing, which is one benefit of its use. If the side effects warrant dose reduction, the drug may be stopped for a short period and reinstituted at a lower dose [75]. Reportedly, patients have been maintained on thalidomide for two to three years. However, it is not clear if there is a maximum length of time patients can continue to stay on this drug [82].

### *Side Effects*

In addition to teratogenicity, thalidomide is associated with several side effects, including [2; 9; 66; 75; 87; 94; 96; 97; 98; 99]:

- Sedation
- Peripheral neuropathy
- Constipation
- Dry skin or skin rash, pruritis, and rarely, Stevens Johnson syndrome
- Dizziness
- Thromboembolytic events (increased risk of deep vein thrombosis [DVT] with patients on steroids and anthracyclines)

Reversing or minimizing the side effects of thalidomide is generally achievable with a few simple measures. However, if side effects are not addressed in a timely manner, patients are at risk for long-term effects, such as peripheral neuropathy with the potential for permanent residual damage, especially if neuropathy was a prior issue. Problems identified early in the treatment plan may be ameliorated by interruption or reduction of the thalidomide dose, allowing for the addition of medications to counteract the side effects [20].

To reduce the incidence of adverse sedative effects, patients are advised to take thalidomide at bedtime [75; 94; 96]. For patients prescribed higher doses, the recommendation is to take half of the dose at 7:00 p.m. and the remainder at bedtime. It is important to remember that, for patients who are required to make an early start in the morning, safety and the ability to function are paramount. As trivial as this may sound, it adds significantly to patients' quality of life when they are able to achieve as much normalcy as possible.

Constipation, orthostatic hypotension, and skin problems may also arise. Constipation can be remedied by advising patients to take stool softeners or laxatives and to drink plenty of fluids on a regular basis. Patients should also be encouraged to consume a high-fiber diet.

For reports of dizziness or syncope, education similar to that provided to patients who are taking medications for hypertension is applicable. Changing position slowly, sitting on the side of the bed for at least a minute or more before standing, and avoiding sudden movements that could precipitate a rapid drop in blood pressure will help to prevent falls and subsequent injuries.

Dry skin usually requires emollients. Patients should be advised to avoid soaking in hot baths; applying lotion directly after a shower will help to keep skin moist. Light, loose-fitting clothing and staying cool will alleviate some of the symptoms of pruritus [9; 90; 94].

**Lenalidomide**

Patients taking lenalidomide are often encountered in an emergency setting as a result of hospitalization caused by the side effects of this immunomodulatory drug. Common admitting diagnoses in these patients include neutropenia, thrombocytopenia, DVT, or pulmonary embolism [82]. Obtaining a patient's admission history may reveal inclusion of peripheral blood stem cell (PBSC) transplant in the treatment plan, as lenalidomide is prescribed as part of maintenance therapy for these patients [52; 100]. Most patients who have undertaken such a procedure are good historians; many will relate the entire history of their disease, and this personal account of their journey provides valuable and insightful information. In addition, family members often have useful information about disease and treatment histories.

In 2006, lenalidomide combined with dexamethasone (RD or Revlimid/Dex) was approved by the FDA for the treatment of relapsed/refractory MM in patients previously treated with at least one other treatment modality [6]. The FDA expanded approval of lenalidomide in combination with dexamethasone as frontline therapy for patients newly diagnosed with MM [6]. The combination also has been shown to be effective in relapsed or refractory MM [101]. In 2017, Revlimid received FDA approval as maintenance therapy after autologous stem cell transplant. Revlimid is part of standard of care regimens [6; 101]. For previously treated MM, the NCCN recommends the combination lenalidomide/dexamethasone/carfilzomib [52]. Greater numbers of patients are now receiving lenalidomide (or bortezomib) combinations for induction therapy, and, as noted, fewer are receiving thalidomide combinations.

It has been well established that the immunomodulatory actions of thalidomide reduce tumor burden. However, the dose-limiting toxicities associated with thalidomide, such as neuropathy, excessive sedation, and constipation, prompted researchers to formulate a drug with comparable actions but with fewer side effects. Lenalidomide, a derivative of thalidomide, is the result of this research. Lenalidomide is reportedly 50,000% more potent than thalidomide when analyzed in the laboratory [87]. Comparable responses with lenalidomide at lower doses to those of thalidomide have been established; furthermore, lenalidomide displays a different side effect profile [9; 10].

***Revlimid REMS Program***

The teratogenic properties of lenalidomide are unknown; however, with the lessons learned from thalidomide, there is no margin for error. Therefore, a program has been established to monitor patients who take lenalidomide [102].

The Revlimid REMS program has the same governing principles as the Thalidomide REMS program. Registration of prescribers, pharmacists, and patients is required. Contraception (with two forms of contraception or abstinence) for women of childbearing age is mandated four weeks prior to initiating the drug, during any interruption, and four weeks after discontinuing lenalidomide. After treatment begins, weekly pregnancy tests are required for the first four weeks of use, followed by monthly tests in women with regular menstrual cycles. Pregnancy testing should occur every two weeks in women with irregular menstrual cycles [102].

Lenalidomide is present in semen. For men who are sexually active with women of potential childbearing age (even if the men have had a vasectomy), condoms are required during treatment and for four weeks after completing the therapy. Additionally, men should not donate sperm during and for four weeks after treatment or during therapy interruptions [75; 102].

***Mechanism of Action***

Lenalidomide acts in several beneficial ways to combat the MM process. Most importantly, the drug [9; 10; 75; 91]:

- Inhibits angiogenesis by blocking VEGF
- Promotes activity of natural killer cells

- Stimulates T-helper cells
- Increases IL-2 production
- Initiates apoptosis (induced cell death)
- Prevents MM cells binding to bone marrow stromal cells
- Inhibits production of TNF-α and IL-6

### *Dosing*

The general dosing regimen for lenalidomide is 25 mg daily for 21 days. Dexamethasone 40 mg is added on days 1–4, 9–12, and 17–20. This is repeated for four cycles. In the fifth cycle, lenalidomide is given for 21 days, but dexamethasone is administered on days 1–4 only [75; 81; 87].

Lenalidomide is rapidly absorbed. It is available only in the oral form, and the drug is produced in 2.5-mg, 5-mg, 10-mg, 15-mg, 20-mg, and 25-mg capsules. A daily aspirin is prescribed in addition to the lenalidomide and dexamethasone as prophylaxis against thromboembolic events. For patients with an implanted central venous access device, the standard therapy of warfarin 1-mg or 2-mg tablet daily will also be prescribed [75].

For the first three cycles of lenalidomide, lab work, including a CBC with manual differential, will be monitored twice weekly and then on a monthly basis thereafter. Monthly lab work includes creatinine, LFTs, and a thyroid function test. For patients taking warfarin, monitoring the prothrombin ratio/international normalized ratio (PT/INR) is essential. Additional lab work will vary depending on the overall performance of the patient and any existing comorbidities [75; 87].

### *Side Effects*

The major side effects with lenalidomide, all of which require dose reduction or interruption, are the myelosuppressive effects of neutropenia, anemia, and thrombocytopenia. For patients with a combination regimen including doxorubicin and erythropoietin, the heightened risk of thromboembolic events bears very close monitoring. The GI symptoms of constipation, loss of appetite, and diarrhea are usually less significant than the myelosuppressive effects [9; 75; 87]. Side effects may be treated as follows [10; 87]:

- Neutropenia: Growth factors
- Anemia: Transfusion support with packed red blood cells and growth factors
- Thrombocytopenia: Platelet transfusion
- GI symptoms: Laxatives, appetite stimulants, antidiarrheals
- Muscle cramps: Quinine taken at bedtime may relieve leg cramps

Presence of unacceptable side effects calls for dose reduction, interruption, or discontinuation. One very important factor to consider in this equation is the willingness of the patient to accept and deal with the side effects. What one patient may tolerate relatively easily may seem monumental to another. The patient's goal is survival. For some patients, the realization that this is the last treatment option available leaves them little choice; they make the decision to do their best to get through each day.

The FDA warns that patients who receive lenalidomide are at an increased risk of developing additional malignancies, including acute myelogenous leukemia, myelodysplastic syndromes, and Hodgkin lymphoma [103]. While the overall risk is low, patients should be warned of this risk, and physicians should closely monitor those who have been treated with lenalidomide [75].

### Bortezomib

Bortezomib is a proteasome inhibitor and one of the more recently developed targeted therapies available for relapsed or refractory MM. Due to the improved survival seen with this drug, it was approved by the FDA as a first-line/induction treatment in 2008. Bortezomib is approved for use alone or in combination with melphalan and prednisone (VMP) [75]. Other combinations used, though not specifically approved for use in the United States, include lenalidomide/bortezomib/dexamethasone (RVD) and bortezomib/melphalan/prednisone/thalidomide (VMPT) [75].

### *Mechanism of Action*

Proteasomes are essential to cellular metabolism and are present in every cell in the human body. The proteasome/ubiquitin system regulates cell proliferation and apoptosis; damaged cells are broken down, and undamaged proteins are used to make new proteins. In order to destroy cancer cells and prevent cancer cell division, bortezomib as a proteasome inhibitor produces the following actions [2; 72; 93; 104; 105]:

- Blocks release of NFKB
- Inhibits IL-6
- Inhibits VEGF
- Inhibits osteoclast activity
- Inhibits angiogenesis
- Blocks adhesion between bone marrow stromal and myeloma cells (a key factor in myeloma cell survival)
- Causes apoptosis
- Restores drug sensitivity in myeloma cells resistant to chemotherapy

Bortezomib is well tolerated in patients with renal dysfunction; creatinine clearance does not affect the pharmacokinetics of this drug [66].

### *Dosing and Monitoring*

Bortezomib is administered in the outpatient setting as an IV push over three to five seconds. On days 1, 4, 8, 11, 22, 25, 29, and 32 of a 42-day treatment cycle, 1.3 mg/m$^2$ IV is administered for four cycles, followed by 1.3 mg/m$^2$ IV on days 1, 8, 22, and 29 of a 42-day treatment cycle for five cycles [75]. A 72-hour timed interval between administrations is given to allow proteasome activity within the cells to return to normal. If after two cycles there is evidence of progressive disease or after four cycles there is stable disease, dexamethasone may be added. In these cases, dexamethasone 40 mg oral is given on days 1 to 4 and days 9 to 12; bortezomib is administered on days 1, 4, 8, and 11. The cycle is repeated every 21 days for cycles 1 and 2. On cycles 3 and 4, bortezomib 1.3 mg/m$^2$ IV is administered on days 1, 4, 8, and 11; dexamethasone oral 40 mg is administered on days 1 to 4 [75]. A total of eight cycles are given [75].

Pegylated liposomal doxorubicin may also be combined with bortezomib [106]. In this combination regimen, bortezomib 1.3 mg/m$^2$ IV push is administered on days 1, 4, 8, and 11. Pegylated liposomal doxorubicin 30 mg/m$^2$ IV is added on day 4. The cycle is repeated every 21 days [75; 81].

Prior to each treatment of bortezomib, baseline vital signs and a neurologic assessment should be performed to monitor for potential side effects. Any evidence of hypotension, exacerbated even further by dehydration, will be corrected with a bolus of IV saline prior to the treatment.

Routine lab work will include a CBC, CMP, and measurement of folate and vitamin B levels. Patients with a high tumor burden require close monitoring as there is the potential for tumor lysis syndrome to occur [22; 72; 81; 105].

### *Side Effects*

Bortezomib inhibits megakarocyte formation, which may cause thrombocytopenia. However, platelet counts will recover by the next cycle. Other possible side effects include [22; 72; 104]:

- Asthenia (e.g., fatigue, weakness, malaise)
- GI toxicity (e.g., diarrhea, constipation, nausea and vomiting)
- Peripheral neuropathy
- Hypotension
- Sepsis

It should be noted that approximately 15% of patients experience severe (grade 3 or 4) neuropathy with the VMP combination [75]. Supplements such as the amino acids L-carnitine and L-glutamine and vitamins B6 and B12 may offer some neuroprotection. Additionally, an mRNA test is in development that would identify patients with MM at risk for bortezomib-induced peripheral neuropathy. The incidence of neuropathy has been demonstrated to be significantly less with subcutaneous bortezomib than with IV administration [75]. Neuropathy can be reversed in the majority of patients with gabapentin.

### *Patient Education*

Providing patients with calendars that map out the dates for treatment will help prevent any miscommunication regarding appointments. Educating patients and caregivers regarding possible side effects, warning signs, and when to contact a healthcare provider positively impacts the delivery of treatment as planned [72; 105]. It is important that patients divulge any supplements they may be taking to address side effects, as these can interfere with renal function and cause diarrhea [105].

Patients should be instructed to report nausea, vomiting, or diarrhea not controlled by their prescribed medications, as this can quickly lead to dehydration. Patients invariably wait too long to notify their providers when these side effects are an issue. Patients require reminders that it is easier to correct dehydration before it becomes severe.

The neuropathy associated with MM and its treatment is usually sensory as opposed to motor in nature. Any previous treatment regimens should be carefully considered for cumulative side effects, especially related to peripheral neuropathy. If symptoms are severe, a reduction in the dose may be necessary until the neuropathy subsides. Peripheral neuropathy may be treated with pregabalin (150–600 mg/day) for at least three months or gabapentin starting with doses of 100 mg three times per day and increasing to a maximum of 600 mg three times per day. Duloxetine (30–60 mg/day) is considered a valid second-line option [107]. Creams such as capsaicin or cocoa butter have also been reported to be helpful [105]. In patients with suspected disease related to peripheral neuropathy, it is important to rule out amyloidosis in patients presenting with nephrotic syndrome or unexplained cardiac problems [52]. If fatigue is an issue, patients should be advised not to drive and to avoid operating heavy machinery. Hyponatremia has been reported as a side effect after several cycles of bortezomib.

## Carfilzomib

Carfilzomib is a novel, highly selective proteasome inhibitor approved by the FDA for the treatment of MM in 2012 [75; 108]. It is specifically indicated for patients previously treated with at least two other therapies, including bortezomib and an immunomodulatory agent, whose disease progressed within 60 days after the last treatment. It may now be used at first relapse [6].

### *Mechanism of Action*

Like bortezomib, carfilzomib inhibits proteasome, which is responsible for intracellular protein homeostasis. Specifically, it is a potent, selective, and irreversible inhibitor of chymotrypsin-like activity of the 20S proteasome, leading to cell cycle arrest and apoptosis [75]. The high selectivity of this agent leads to fewer adverse systemic effects, such as peripheral neuropathy, that may arise with the use of bortezomib [108].

### *Dosing and Monitoring*

Carfilzomib should be administered intravenously over 2 to 10 minutes, on two consecutive days weekly for three weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17 to 28) [75; 108]. The recommended dose in the first cycle is 20 $mg/m^2$, and, if tolerated, the recommended dose for the second and succeeding cycles is 36 $mg/m^2$ [75]. It is important that patients are well hydrated when taking carfilzomib. An infusion of 250–500 mL normal saline (or other appropriate IV fluid, such as 5% dextrose in water) should be given before and after (if needed) each dose in the first cycle and additional cycles, if necessary [75]. Premedication with dexamethasone is recommended prior to all doses in cycle 1, all doses during first dose escalation cycle, and as needed with future cycles to reduce the incidence and severity of infusion reactions [75]. Patients should be monitored for infusion-related reactions, dehydration, tumor lysis syndrome, heart failure, peripheral neuropathy, and pulmonary symptoms.

### *Side Effects*

Anemia, thrombocytopenia, fatigue, nausea, dyspnea, diarrhea, and pyrexia are among the most common side effects associated with carfilzomib [75; 108]. Other serious adverse effects include [75; 108]:

- Pneumonia
- Acute renal failure
- Congestive heart failure

## Pomalidomide

In 2013, the FDA approved pomalidomide, an immunomodulator in the same class as lenalidomide and thalidomide [109]. Like carfilzomib, it is approved for the treatment of patients previously treated with at least two other therapies, including lenalidomide and bortezomib, whose disease progressed within 60 days after the last treatment [75].

### *Mechanism of Action*

Pomalidomide acts in many of the same ways as other drugs in its class. It has been shown to induce cell cycle arrest and apoptosis directly in MM cells; enhance T cell- and natural killer cell-mediated cytotoxicity; inhibit production of proinflammatory cytokines; and inhibit angiogenesis [75].

### *Dosing and Monitoring*

Pomalidomide should be administered orally (either alone or in combination with dexamethasone) at a dose of 4 mg on days 1 through 21 of repeated 28-day cycles [75; 109]. Cycles are repeated until disease progression or unacceptable toxicity. The absolute neutrophil count should be ≥500 cells/mcL and platelets ≥50,000 cells/mcL prior to initiating new cycles of therapy [75]. For each subsequent drop of neutrophil count to <500 cells/mcL and/or platelets <25,000 cells/mcL, therapy should be interrupted. When counts rise back to appropriate levels, resume dosing at 1 mg less than the previous dose.

### *Side Effects*

In clinical trials of pomalidomide, the most common side effects included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia [75; 109]. Boxed warnings regarding the risk for embryo-fetal toxicity and venous thromboembolism have also been issued [75; 109]. Due to the significant embryo-fetal risks, pomalidomide is only available to those registered with the POMALYST Risk Evaluation and Mitigation Strategy (REMS) Program. Patients of childbearing age are required to use two forms of reliable contraception to prevent pregnancy, and women must have two negative pregnancy tests prior to initiating treatment. Pregnancy prevention should continue for at least four weeks after cessation of therapy. To address the risk of thromboembolic events, individualized anticoagulation therapy should be considered [75].

## Panobinostat

Panobinostat was approved in 2015 for the treatment of patients with MM [110]. This agent is indicated for patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent [75].

### *Mechanism of Action*

Panobinostat acts by inhibiting histone deacetylase (HDAC), causing cell cycle arrest and/or apoptosis [75]. At the time of its approval, it was the only HDAC inhibitor approved for the treatment of MM [110].

### *Dosing and Monitoring*

Oral panobinostat is administered as part of a multiagent regiment with bortezomib and dexamethasone. The initial dose is 20 mg once every other day for three doses each week during weeks 1 and 2 of a 21-day treatment cycle (rest during week 3) for up to eight cycles, or 16 cycles in patients experiencing clinical benefit and acceptable toxicity [75; 111]. If dose reduction is necessary to manage toxicity, the same schedule should be kept, but the dose should be reduced in increments of 5 mg [75].

### *Side Effects*

The most common side effects of panobinostat are diarrhea, fatigue, nausea, edema in the extremities, decreased appetite, fever, vomiting, and weakness [75; 110]. The most common laboratory abnormalities include hypophosphatemia, hypokalemia, hyponatremia, increased creatinine, thrombocytopenia, leukopenia, and anemia [75]. The drug also carries a boxed warning due to the increased risk of severe diarrhea and severe and fatal cardiac events, arrhythmias, and electrocardiogram changes [75; 110].

### Isatuximab

In 2020, the FDA approved isatuximab, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor [75; 112]. Isatuximab is a CD38-directed cytolytic antibody that promotes apoptosis and immunomodulatory activity. In studies, patients who received isatuximab in combination with pomalidomide and low-dose dexamethasone had a 40% reduction in the risk of disease progression or death compared with patients who received only pomalidomide and dexamethasone [112]. In 2021, the FDA approved isatuximab in combination with carfilzomib and dexamethasone (isatuximab-irfc) for the treatment of relapsed/refractory MM in patients who have received one to three prior lines of therapy [113].

### BCMA-Directed CAR T-Cell Agents

There are two chimeric antigen receptor (CAR) T-cell therapies approved by the FDA and included as preferred options by the NCCN Panel for relapsed/refractory MM after at least four prior therapies: idecabtagene vicleucel and ciltacabtagene autoleucel [20].

### *Idecabtagene Vicleucel*

In 2021, the FDA approved idecabtagene vicleucel, the first cell-based gene therapy to treat adult patients with multiple myeloma [114]. The agent is reserved for patients who have not responded to, or whose disease has returned after, at least four prior lines of therapy. Idecabtagene vicleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous chimeric antigen receptor T-cell therapy. Severe adverse effects have been associated with use, including cytokine release syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, neurologic toxicity, and prolonged cytopenia [114]. Because of this, it was approved with a REMS plan requiring that dispensing facilities and their involved staff be specially certified and trained and that patients be informed of the potential serious side effects.

### *Ciltacabtagene Autoleucel*

A second (BCMA)-directed genetically modified autologous chimeric antigen receptor T-cell therapy, ciltacabtagene autoleucel, received FDA approval in 2022 [115]. The safety and efficacy of this agent were evaluated in an open label, multicenter clinical trial that included 97 patients with relapsed or refractory MM who had received at least three prior lines of therapy. Eighty-two percent of patients had received four or more prior lines of therapy [115]. Efficacy was established based on overall response rate and duration of response. The overall response rate was 97.9%. Among the 95 patients who responded to treatment, the median duration of response was 21.8 months. Ciltacabtagene autoleucel carries the same boxed warning for adverse effects as idecabtagene vicleucel and also includes a REMS plan [75; 115].

### Bispecific Antibodies

There are three bispecific antibodies approved by the FDA and included as preferred options by the NCCN Panel for relapsed/refractory MM after at least four prior therapies: elranatamab, teclistamab, and talquetamab [20].

### *Elranatamab*

In August 2023, the FDA granted accelerated approval to elranatamab, the first fixed-dose subcutaneous BCMA-directed agent for treatment of relapsed/refractory MM [6; 75; 116].

### *Teclistamab*

Teclistamab-cqyv is a first-in-class bispecific BCMA-directed T-cell engager [6; 75]. It received FDA approval in 2022 for the treatment of relapsed/refractory MM in patients who have received at least four prior lines of therapy [117]. Teclistamab binds to the CD3 receptor on the surface of T-cells and to BCMA expressed on the surface of MM cells, resulting in T-cell activation, the release of various proinflammatory cytokines, and the lysis of BCMA-expressing MM cells [75]. Teclistamab has a boxed warning for life threatening or fatal cytokine release syndrome (CRS) and neurologic toxicity. Because of these risks, the agent is available only through Tecvayli REMS [117].

### *Talquetamab*

Talquetamab received FDA approval in 2023 for treatment of relapsed/refractory MM [6; 75; 118]. Due to the boxed warning risks of CRS and neurologic toxicity, patients should be hospitalized for 48 hours after all doses within the talquetamab dosing schedule. One to three hours prior to receiving all doses of talquetamab, patients should be premedicated with a corticosteroid, a histamine $H_1$ antagonist, and an antipyretic [75]. Talquetamab is available only through Tecvayli-Talvey REMS [118].

### Other Novel Agents

Selinexor is a first-in-class selective nuclear export inhibitor. It reversibly inhibits nuclear export of tumor suppressor proteins, growth regulators, and mRNAs of oncogenic proteins, resulting in accumulation of suppressor proteins in the nucleus, cell cycle arrest, and cancer cell apoptosis [75]. Selinexor received FDA approval in 2019 (in combination with dexamethasone) for the treatment of relapsed/refractory MM in patients who have received at least four prior therapies. In 2020, the FDA approved the agent (in combination with bortezomib and dexamethasone) for treatment of MM in patients who have received at least one prior therapy [6; 119]. The NCCN Panel included selinexor/dexamethasone under other recommended options for patients with relapsed/refractory MM. Selinexor/bortezomib/dexamethasone once weekly is a category 1 recommendation for previously-treated MM [52]. Adverse reactions reported in approximately 20% of patients include nausea/vomiting, fatigue, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, decreased weight, and cataract. Selinexor is available in tablet form [6; 75; 119].

## STEM CELL TRANSPLANTATION

With the changing paradigm in treatment modalities to prolong survival and maintain patients in remission, peripheral blood stem cell (PBSC) transplantation has come to the forefront as an option in first-line treatment. The purpose of a PBSC transplant (which may also be referred to as a hematopoietic cell transplant) is to replace stem cells destroyed by chemotherapy and/or radiation. In PBSC transplants, reinfused stem cells migrate to the bone marrow, providing a new foundation for all blood cells. As noted, patients younger than 70 years of age with symptomatic disease are potentially eligible, as are chronologically older patients with favorable factors. Patient age older than 70 years is not an absolute contraindication to stem cell transplant. Factors to consider and discuss with the patient include the patient's fitness, genetic risk factors, family and work considerations, and personal preference [20]. Comorbidities, baseline performance status, and the potential to tolerate and respond to chemotherapy, immunomodulators, and/or glucocorticoids are integral to the eligibility screening process [1; 6; 68; 82; 90; 120].

When PBSC transplant is elected as the plan of care, the clinician will outline what the patient should expect in regards to the procedures. This will include discussion of the potential options for induction and will allow time for any of the patient's questions and concerns to be addressed. Transplants are only conducted at specific centers, and patients' insurance providers may dictate the location. The question of possible maintenance therapy being required following the transplant will also be included in this initial discussion.

Preparing for a PBSC transplant is not a process that occurs overnight. Planning and education are essential first steps. When any patient is confronted with a cancer diagnosis and is required to make major decisions regarding life-sustaining treatments, a discussion of healthcare benefits is necessary. If the preliminary groundwork has not been set in motion to apply for disability benefits, or if a family medical leave of absence (FMLA) is required, a case manager or social worker can assist the patient and family in going through the correct channels to obtain these.

Necessary information for patient education includes a description of the transplant procedure and possible relocation plans, as there may be a need to be away from home in close proximity to the transplant center for a minimum of two to three weeks. Encouraging patients and caregivers to read reliable sources of information or to speak to someone who has undergone a transplant is a positive approach. A great deal of information is available to those with Internet access, and information packages are available from the various myeloma foundations (***Resources***). The interaction with others who have successfully completed the procedure and have seen benefits may provide encouragement. Families and patients provide a support system to each other, and for many this is the beginning of long-term friendships.

## AN OVERVIEW OF PBSC TRANSPLANTS

The older method of transplanting bone marrow for hematologic malignancies was painful and laborious, requiring an inpatient hospital stay and the use of general anesthesia. An average of 50 to 100 sites in the pelvic bone were aspirated in order to obtain sufficient marrow for the transplant. This method is no longer necessary due to the increased ability to harvest, freeze, and store cells from peripheral blood. The peripheral cells are obtained either from the patient or, less frequently, a well-matched donor or a mismatched donor. There are several advantages with the newer process of collecting peripheral cells. Donors now have a quicker recovery time, discomfort rather than pain is experienced, and a greater number of cells can be harvested.

Several types of PBSC transplants are available. The more common and much preferred method for patients with MM is the autologous transplant. This method is usually recommended for eligible patients younger than 70 years of age with newly diagnosed MM, but, as stated, select older patients may be eligible [74]. With autologous transplants, the patient's own cells are harvested and reinfused at the optimum time in an attempt to achieve as complete a remission as possible. Sufficient cells are obtained to allow for tandem transplants if deemed necessary. Tandem transplantation is an option for patients whose response to the first autologous transplant is less than complete. However, the added benefit of tandem transplantation versus a single autologous transplant is unclear [121]. The NCCN Panel recommends collecting enough hematopoietic stem cells for at least one PBSC in all eligible patients, and for two transplants in younger patients if tandem or repeat transplant is being considered [52]. Patients given the option of an autologous transplant may choose to go through the induction process and harvest their own stem cells but continue on with maintenance therapy. Their decision, obviously after an in-depth discussion with their oncologist, is to wait until they reach a plateau, when they no longer

respond to the chemotherapy or immunomodulator, and then undergo the necessary transplant [1; 2; 22; 82; 122]. Repeat autologous transplantation (following a single autologous transplant) is an option, either on or off clinical trial, depending on the time interval between the preceding autologous transplant and documented progression [52].


The National Collaborating Centre for Cancer recommends considering using frailty and performance status measures that include comorbidities to assess the suitability of people with myeloma for first autologous stem cell transplant.

(https://www.nice.org.uk/guidance/ng35. Last accessed March 14, 2024.)

**Level of Evidence**: Expert Opinion/Consensus Statement

Donated cells from a cancer-free family member whose HLA typing matches that of the patient as closely as possible is termed allogeneic. Matched related donors are usually siblings of the patient/recipient and are generally the preferred donor for an allogeneic transplantation. Patients undergoing HLA-matched sibling allogeneic transplantation have the best five-year survival rate of all treated patients [123]. An allogeneic transplant is proposed for patients younger than 55 years of age who have already failed conventional therapies. Allogeneic transplantation is rarely recommended as a primary strategy because the risks are too great. It should preferentially be done in the context of a clinical trial when possible [20; 52]. The ability to transplant unadulterated clean cells and produce graft versus myeloma response is compelling; realistically, however, the mortality rates are dismal (15% to 40%) [20]. Allogeneic transplants are seldom performed on patients with MM. However, for patients younger than 55 years of age with a good performance status but who have failed conventional therapies, this may be a final option in an attempt to achieve some degree of remission [123]. The likelihood of a patient having an identical twin, allowing for a syngeneic stem cell transplant, is rare but is a possibility. Outcomes of syngeneic transplants are good, and the procedure should be considered if it is an option.

One of the goals of an allogeneic transplant is to produce a graft versus myeloma reaction. When the engrafted cells recognize malignant plasma cells as foreign, the engrafted cells mount an attack. Another positive is that the transplanted cells are free of any malignancy. Conversely, the potential for graft versus host disease, defined as acute if it occurs within the first 100 days and chronic after this time frame, brings a whole new disease entity with its own set of challenges [124]. With graft versus host disease, the transplanted cells attack the patient's healthy cells; the patient's skin, eyes, liver, and GI tract can all be adversely affected. For the patient who develops chronic graft versus host disease, this entails a lifetime of antirejection medication. Patients may also require periodic hospitalizations to treat ulcerated skin lesions. Pain control and weight loss become an issue when mucositis or severe esophagitis prevent the patient from consuming adequate calories or taking in sufficient fluids. Use of an unrelated matched donor is a transplant option in which cells are harvested from a donor with as close a match as possible. Recipients of unrelated donor grafts are at higher risk of graft versus host disease, and this option is very rarely used [123; 124].

The National Marrow Donor Program (NMDP) was established in 1986 as a repository for genetic typing information in an effort to match unrelated donors and recipients. More than 41 million donors worldwide are registered with the program [125]. Patients who are truly matched appear to have the best outcomes. Advances in DNA-based tissue typing have increased the accuracy and specificity of HLA typing, allowing for more precise donor/recipient matches. The NMDP has developed donor matching guidelines based on clinical research into the effect of HLA matching on transplant outcomes [126].

Another transplant option is the use of umbilical cord blood. In 2011, the FDA approved the first umbilical cord blood product for use in stem cell transplantation. Compared with stem cells from adult marrow and blood, high numbers of stem cells with superior proliferative capacity are present in umbilical cord blood at the time of delivery. These cells can be processed and cryopreserved in cord blood banks, making them readily available. This procedure carries a lower risk of transmission of bloodborne infections and graft versus host disease compared to procedures using peripheral blood or bone marrow [123].

Reduced-intensity (sometimes called mini- or nonmyeloablative) transplant is also an option. This method allows the patient to receive a reduction in the dose of chemotherapy (as opposed to the high dose normally administered) prior to the transplant, minimizing chemotherapy-induced toxicities and producing a less compromised response. Again, the goal is to create a graft versus myeloma effect [123; 127]. Occasionally, patients may have tandem autologous transplants followed by a miniallogeneic transplant two to four months later [82]. There appears to be little advantage with minitransplant, as relapse occurs more rapidly, and the risk of serious outcomes is higher than for a single transplant; some studies show immunosuppressive results as opposed to a reduced tumor burden [1; 2; 22; 82; 122; 123; 127]. Other studies are more encouraging. A report of 52 high-risk patients who underwent nonmyeloablative transplants described a 17% mortality rate, with approximately 30% progression-free survival at 18 months [128]. A phase II trial of autologous transplantation followed by a nonmyeloablative transplant demonstrated this approach to be feasible, with low treatment-related mortality. Further studies are needed to evaluate relative efficacy, but at this time, mini-allogeneic transplant should not be routinely considered [129].

Some transplant centers are performing autologous transplants followed by reduced-intensity allogeneic transplantation. This technique combines the tumor-reducing benefits of autologous transplants with the reduced-intensity of allogeneic transplantation and has resulted in lower transplant-related mortality in patients with MM [130].

## EVALUATION AND DIAGNOSTICS

When evaluating patients prior to PBSC transplant, their overall general condition should be evaluated on a continuum. Even if a patient is symptomatic and a PBSC transplant poses a viable option to achieve remission, it would be an exercise in futility if multiple comorbidities prohibit the patient from undertaking such a procedure. It is interesting to note that renal impairment will not necessarily preclude the patient from a transplant, and this will be discussed later [131].

Much of the preliminary diagnostic testing necessary prior to the transplant procedure is completed when the patient is initially diagnosed. Additional studies, if they have not already been obtained, include [1; 82; 122; 123]:

- A complete dental exam
- EKG, echocardiogram
- Pulmonary function test
- Liver function tests
- A neurologic exam (to detect primary neurologic disorders)
- Performance status (e.g., Karnofsky performance scoring system)
- Infectious disease screening (e.g., cytomegalovirus; HIV antibody; herpes and varicella zoster; Epstein-Barr virus; toxoplasmosis titer; serology for syphilis; hepatitis screening)
- ABO and Rh factor blood typing
- HLA typing
- For women: follicle stimulating hormone, luteinizing hormone, estradiol hormone, human chorionic gonadotropin levels

- For men: total and free testosterone levels
- Chemotherapy/radiation history
- Transfusion history

## PBSC TRANSPLANT PROCEDURE

### Induction

With preliminary testing completed, the first phase of the transplant procedure is induction, with the goal of reducing the number of plasma cells and M protein levels. Depending on the stage of the disease and taking into account any prior treatments administered, the following chemotherapy, immunomodulators, and/or glucocorticoids may be ordered [20]:

- Glucocorticoids (e.g., dexamethasone and prednisone)
- Immunomodulators
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
- Proteasome inhibitors
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- Alkylating agents (e.g., melphalan, cyclophosphamide)
- Other cytotoxic drugs (e.g., vincristine, doxorubicin, and liposomal doxorubicin)
- Monoclonal antibodies
  - Daratumumab
  - Elotuzumab
- Histone-deacetylase inhibitors

The most successful, induction therapy options for transplant-eligible patients include [20]:

- Bortezomib/lenalidomide/dexamethasone (preferred regimen)
- Bortezomib/cyclophosphamide/dexamethasone (preferred regimen)
- Bortezomib/thalidomide/dexamethasone
- Bortezomib/doxorubicin/dexamethasone

The current consensus is that three-drug regimens that include bortezomib are considered standard treatment in the absence of a clinical trial [52]. Three-drug regimens have shown improved efficacy compared with two-drug combinations [132]. Combination therapies have been shown to produce rapid and high response rates [52]. A review of 40 studies of various induction therapy regimens found varying levels of safety and efficacy among two- and three-drug regimens and emphasized the importance of individualized treatment approaches for transplant-eligible patients with MM [133].

Total body irradiation was once a component of the preparative regimen for transplant, but these regimens have been abandoned [52]. Newer, potentially less toxic radiation techniques that deliver total marrow irradiation while reducing toxicities to nontarget organs are undergoing evaluation in clinical trials [52].

The NCCN recommends that response to the induction be assessed after each cycle [52]. Assessment of induction treatment response includes scans, bone marrow biopsy, and blood work. If there is a 50% reduction in plasma cells, the patient is eligible to proceed with the transplant. If there is a less than 50% response, consideration will be given to whether to continue with the current induction or switch and/or alter the therapy. As an example, if a patient is receiving thalidomide plus dexamethasone, the oncologist may add bortezomib in an attempt to produce a more favorable response. Induction therapy with bortezomib/dexamethasone combination has been found to significantly improve response rates in patients undergoing autologous transplantation [134; 135; 136]. A systematic review found improved overall survival rates in trials of bortezomib versus no bortezomib with the same and with different background therapy [137].

Patients preparing for an autotransplant should not receive melphalan prior to harvesting their own stem cells, as melphalan is an alkylating agent. The damage to stem cells in the marrow can manifest in the future (usually in several years) as leukemia [22; 52; 131].

During the induction phase, which can take up to several months, the patient's day-to-day routine will include anticoagulant prophylaxis (especially for patients who are prescribed thalidomide or lenalidomide) and antibiotic prophylaxis [73]. The most common antibiotic prophylaxis is sulfamethoxazole and trimethoprim (Septra DS) 800 mg two or three times a week [52]. Steroid therapy is also continued, and blood glucose levels will be monitored for adverse effects. It is also important to monitor for opportunistic infections, such as herpes zoster, as patients will be at a heightened risk while immunocompromised. Patients should be instructed on when to report signs or symptoms of infection, including redness, swelling, or any drainage from the catheter site. Fever (a temperature of 100.4° Fahrenheit or greater), chills, sore throat, productive cough, or the inability to eat or drink sufficient fluids to maintain hydration should be reported promptly [82].

**Stem Cell Mobilization**

Only 1% of marrow cells are stem cells, and an even smaller percentage exist in the peripheral blood. Stem cells require mobilization to enable sufficient cells for collection. Colony growth stimulating factors is prescribed and given on a daily basis, boosting the number of WBCs and mobilizing them by approximately 18-fold [138]. Patients or care providers will be instructed regarding administration of the subcutaneous injection. Alternatively, patients may receive the injections at an outpatient clinic or infusion center. Most patients and caregivers, however, are able to inject the medication.

Chemotherapy mobilization (chemomobilization) is also used to increase the number of stem cells and has the ability to increase the number of cells by as much as 60-fold [138]. Chemotherapy is often used simultaneously with growth factors. The decision to use chemomobilization will depend on the success of the induction and the reduction of tumor burden. Although cyclophosphamide is an alkylating agent, it is commonly used with granulocyte macrophage colony-stimulating factor (GM-CSF) as a mobilizing agent [75; 82]. Clinical trials comparing granulocyte colony-stimulating factor (G-CSF) with GM-CSF have shown better mobilization with G-CSF in fewer apheresis (collection) sessions. Common side effects of G-CSF include bone pain, malaise, headache, chills, and fever [123].

Plerixafor, an inhibitor of chemokine receptor 4 (CXCR4), was approved by the FDA in 2008 for peripheral stem cell mobilization [75; 123]. Results of some clinical trials indicate that use of plerixafor in addition to G-CSF could lead to an increased mobilization and release of stem cells, thereby facilitating effective apheresis. The aim of one systematic review was to evaluate the efficacy and safety of additional plerixafor to G-CSF for stem cell mobilization in patients with MM [139]. Two trials evaluated 600 patients with MM or non-Hodgkin lymphoma. In both studies, the experimental group received G-CSF plus plerixafor. The control group received G-CSF plus placebo. With regard to successful stem cell collection, the analysis showed an advantage for participants randomized to the plerixafor group. There was insufficient evidence to determine whether additional plerixafor affects survival or adverse events [139]. A literature review also showed that the addition of plerixafor to G-CSF is well tolerated and resulted in a greater proportion of patients reaching optimal cell collections with fewer number of apheresis [140].

In 2023, the FDA approved motixafortide in combination with filgrastim for peripheral stem cell mobilization [141; 142]. The approval is based on results from the GENESIS trial. The GENESIS trial enrolled 122 people with multiple myeloma, ranging from 18 to 78 years of age. Trial participants with MM were randomly assigned to receive G-CSF plus motixafortide or G-CSF plus a placebo for stem cell mobilization. Motixafortide plus G-CSF enabled 92.5% of patients to successfully meet the primary endpoint (3–5 x $10^6$ CD34+ cells/kg) [123; 141; 142].

**Stem Cell Collection**

Apheresis, or stem cell collection, is performed as an outpatient procedure for both the patient (autologous transplant) and the donor (allogeneic transplant). A blood sample is obtained prior to harvesting in order to count the number of cells. If the count is determined to be inadequate, additional daily doses of the colony-stimulating factor will be given. The actual stem cell collection takes place over several days, with a two to four hour procedure time. The blood is removed in a manner similar to donating blood, except the white cells are centrifuged, separated, and bagged, and the remaining blood is returned to the donor. During cell collection, the donor may experience some dizziness or tingling in their face, hands, or feet, but the extreme symptoms of chills, tremors, or cramps are unlikely. The number of cells required for PBSC transplant equates to 2 million CD34+/kg. Sufficient cells are harvested to allow for two transplants [82; 123; 142].

**Storage of Stem Cells**

Stem cells have reportedly been stored for as long as 10 years. Dimethyl sulfoxide is used to prepare the cells for freezing; stem cells are stored in liquid nitrogen and remain frozen until required for the transplant [123].

**Undergoing the PBSC Transplant**

Prior to an autologous transplant, after admission to the transplant unit, the patient will receive high-dose chemotherapy. Melphalan is the standard conditioning agent and is used in the vast majority of centers [6; 143]. The dosing is 200 mg/$m^2$ IV alone two days prior to transplantation, or 140 mg/$m^2$ IV two days prior to transplantation in combination with busulfan 9.6 mg/kg IV [6; 75]. A reduced dose may be necessary if the patient is elderly [75; 122].

The bags containing the stem cells are thawed in warm water baths; reportedly, a smell similar to garlic is often detected as the cells thaw [122]. Patients are infused with the stem cells in a similar manner to a blood transfusion. Each bag is infused over a period of one to four hours with close observation for any signs and symptoms of reaction. Patients' urine may be pink tinged for a short period of time after the procedure.

In the 10 to 14 days following the procedure, the staff at the transplant center will monitor the patient very closely. This is termed the engraftment phase, during which time the cells begin to appear in sufficient numbers in the circulation. Engraftment can occur as early as 10 days after the transplant, but is more likely to take place after 15 to 20 days. Daily blood cell counts will monitor the absolute neutrophil count (ANC). For three consecutive days, the ANC must be 500 or more to signify that engraftment has occurred [122].

Having received the high-dose chemotherapy just prior to the transplant, the patient's nadir will be supported with antibiotic therapy, blood, and platelet transfusions as warranted per the transplant protocol. GM-CSF will be continued. Mucositis, which can often be severe, causing pain and an inability to eat, is an expected side effect and should be treated appropriately.

The amount of time until the patient can be transitioned from the transplant center to pre-arranged accommodation within close proximity will depend on the patient's recovery time and the results of the daily lab work. Every patient is individual; many patients recover sufficiently to be discharged to home within three to four weeks of the transplant [82; 122].

### Maintenance Therapy

Having undergone the PBSC transplant, patients may be placed on maintenance therapy with immunomodulators and/or prednisone. One study has shown that bortezomib increases progression-free and overall survival, and it is particularly beneficial for patients with 17p deletions [144]. Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in two independent randomized phase III studies [52]. In one study, 231 patients were randomized to maintenance therapy with lenalidomide versus 229 patients randomized to placebo after autologous transplantation. Maintenance therapy was initiated at day 100 following transplantation. At a median follow-up of 34 months, 37% of the patients who received lenalidomide versus 58% who received placebo had disease progression or died. The median time to progression in the lenalidomide group was 46 months versus 27 months in the placebo group. Second primary cancers occurred in 18 patients who received lenalidomide (8%) and in 6 patients who received placebo (3%) [145]. In the second study, 614 patients younger than 65 years of age were randomly assigned to maintenance treatment with either lenalidomide (10 mg/day for the first 3 months) or placebo until relapse [146]. The primary end point was progression-free survival. Lenalidomide maintenance therapy improved median progression-free survival (41 months vs. 23 months with placebo). With a median follow-up period of 45 months, more than 70% of patients in both groups were alive at 4 years. The incidence of second primary cancers was 3.1 per 100 patient-years in the lenalidomide group versus 1.2 per 100 patient-years in the placebo group. Median event-free survival (with events that included second primary cancers) was significantly improved with lenalidomide 175]. Routine follow-up appointments are scheduled to monitor the patient's progress and remission and to identify any indication of a relapse.

## MEASURING RESPONSE TO THE TRANSPLANT

Response to therapy is categorized as [52; 91; 120; 147]:

- Complete response (CR): No M spike in serum or urine; no detectable soft tissue plasmacytomas; marrow contains 5% or less of plasma cells
- Very good partial response (VGPR): 90% or greater reduction in M protein
- Partial response (PR): 50% to 90% reduction in M protein

The period of time the remission can be sustained has proven to be of greater significance than the degree of response achieved [91; 120; 147]. In general, patients who have undergone transplant and modern therapy, including regimens with thalidomide, lenalidomide, and bortezomib, have a five-year survival rate greater than 70%; older, transplant-ineligible patients have a five-year survival rate of approximately 50% [51]. The survival of patients with specific cytogenetic abnormalities (i.e., those with high-risk disease) remains poor in spite of aggressive therapy incorporating almost every available drug and treatment modality (median survival: two to three years).

There is a large degree of individuality attached to PBSC transplants, which results in a number of questions. What is the best induction plan? How soon, if ever, after the first autologous transplant should a tandem transplant be carried out? Which maintenance therapy offers the best possibility for sustaining remission? There is no simple answer to these questions. A number of available regimens can produce a durable response (e.g., a remission that lasts two or more years) and improved overall survival. As stated, the choice of treatment(s) should be individualized for each patient after careful dis-

cussion with the patient's physician [6]. Multiple studies and ongoing clinical trials worldwide are inconclusive as to the best regimens to offer various patients. Bortezomib/lenalidomide/dexamethasone may prove to be the standard regimen. All patients are monitored closely for any relapse in their disease, as evidenced by rising protein levels in urine or serum, an increase in plasma cell counts, and rising LDH.

## COMPLICATIONS ASSOCIATED WITH MULTIPLE MYELOMA

The side effects from treatments or complications from the MM disease process can precipitate a need for additional treatment, often in an acute setting. Effectively treating these complications can improve patients' quality of life and improve responses to treatment.

### HYPERCALCEMIA

The most common oncologic emergency, hypercalcemia, occurs in greater than 10% of patients with MM [4; 6; 148]. Calcium maintains teeth and bones and is an essential factor for clotting and intracellular metabolism. Calcium exists in three forms: 45% is bound to protein, 45% is freely ionized, and the remaining 10% is associated with phosphate, sulfate, or citrate [1; 4]. Patients with MM are at risk for hypercalcemia due to pathologic bone destruction and the subsequent release of calcium into the circulation. This is an added assault to the kidneys, which may already be impaired; the kidneys can compensate for only a limited time in trying to excrete extra calcium. The normal range of serum calcium is 9–11 mg/dL.

Extracellular calcium exerts its effects on smooth or involuntary muscle in the GI tract, cardiac muscle, voluntary skeletal muscle, and the nervous tissue. This can then result in the clinical presentation of weakness, lethargy, constipation, altered mental status, and electrocardiogram changes. Extracellular levels of calcium are precisely regulated within very narrow margins, influenced mainly by the parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, and to a lesser extent, calcitonin. These hormones are released in response to circulating ionized calcium. Maintaining extracellular calcium levels depends upon two factors: the renal threshold, regulated by the PTH, and the rate calcium is absorbed from the intestine, controlled by 1,25-dihydroxyvitamin D. On a daily basis and under normal physiologic circumstances, the kidneys filter 10 g of calcium, although only 150–200 mg is actually secreted, as the tubules resorb 98% of the filtered calcium [1; 4; 18; 41; 66; 149].

Orchestrating the calcium balance requires the PTH to bind to and activate other hormones within the proximal tubules of the kidneys, resulting in cyclic adenosine monophosphate (cAMP), a mediator within plasma membranes that promotes hormonal action. Under the influence of PTH, cAMP produces nephrogenous cAMP (NcAMP). PTH regulates calcium absorption through NcAMP; this is active resorption. PTH stimulates 1-alpha-hydroxylase, converts 1,25-dihydroxyvitamin D (basic circulating vitamin D), and influences:

- Calcium absorption through the intestine
- Mobilization of bone calcium in response to decreased levels of circulating calcium
- Distal tubule resorption in the ascending loop of Henle, where approximately 40% of calcium is reabsorbed

Within the proximal tubule, but not under the influence of PTH, water and sodium are resorbed on a parallel with calcium. This is passive resorption; about 60% of filtered calcium is resorbed here. In other words, calcium resorption is dependent on sodium resorption. This is the rationale for normal saline being administered in the treatment of hypercalcemia [1; 66].

Several factors contribute to the development of hypercalcemia, including [1; 4; 149]:

- Dehydration caused by nausea and vomiting
- Anorexia or poor nutrition
- Immobility

- Increased osteoclast activity releasing calcium into circulation
- Excessive intake of vitamin A and D supplements
- Excessive oral calcium supplements
- Metabolic activity from prostaglandins, osteoclastic activating factors
- Inappropriate use of diuretics (thiazide- and potassium-sparing diuretics act on distal tubules, contributing to dehydration and elevated calcium)
- Polyuria caused by dysfunction of anti-diuretic hormones
- Lithium use

**Clinical Presentation**

Despite the vigilance of caregivers and patients following instructions to drink plenty of fluids and remain as mobile as safety permits, the onset of hypercalcemia may be insidious, with early subtle changes in mentation and increases in urine output going unnoticed. Increasing drowsiness may be attributed to the introduction of new pain medications, with the patient's attention focused in this direction. Consideration should be paid to any new additions to the treatment regimen, previous cancer treatment, drug disease-state interactions, and comorbid pathologies, as these could potentially account for changes seen in the patient [149].

Presenting signs and symptoms of hypercalcemia result from an increase in the values of the serum calcium. Hypercalcemia is defined as serum calcium levels greater than 10.4 mg/dL or ionized serum calcium greater than 5.2 mg/dL [149]. In mild hypercalcemia, patients are often asymptomatic. If present, symptoms may include constipation, anorexia, nausea, vomiting, and polyuria [149]. When serum calcium levels are greater than 12 mg/dL, lethargy advances to confusion, lability, delirium, psychosis, and stupor; polyuria slows; and oliguria develops [149]. Changes in cognition may vary depending on previous baseline mentation and accompanying comorbidities. Cardiac contractility is adversely affected, with changes observed on EKG. If hypercalcemia is not effectively treated and reversed, continued rising levels may progress to coma and death [1; 41; 66; 149]. In many cases, early detection will result in positive outcomes, as it is reasonable to expect mild hypercalcemia to be corrected in a timely manner.

The ultimate goal in the treatment of hypercalcemia is to address the underlying disease. Being chronic and multifactorial, MM poses a challenge, as there is no "quick fix." Hypercalcemia may be a reflection of worsening disease; patients may require more frequent hospitalizations with shorter times between admissions. Any mild hypercalcemia may be treated by the administration of IV fluids in the office, or daily fluids may be prescribed in the outpatient clinic for two to three consecutive days. Taking into consideration the skills of the caregiver and the home situation, an inpatient hospital stay may be averted if adequate fluids can be administered as an outpatient and the elevated calcium corrected [1; 27; 66; 149].

**Diagnosis**

Hypercalcemia is primarily diagnosed based on several laboratory tests. In patients without hypercalcemia, serum calcium and protein bound calcium are in balance. Any abnormality in albumin (usually low in the elderly or debilitated patient) will not accurately reflect ionized calcium. The laboratory will run corrected calcium. The formula for corrected calcium is as follows: measured serum calcium + (4 - measured serum albumin [g/dL]) x 0.8. The number 4 is selected as it lies in mid-range for normal albumin [149].

Urinalysis monitoring will indicate decreased sodium phosphorous, sodium, and potassium. Electrolytes, including BUN, creatinine, and magnesium, should also be analyzed [41; 149].

**Presenting Signs and Symptoms**

***Neurologic Changes***

The neurons within the central nervous system are depressed by elevated levels of calcium. A higher level of calcium will correspond to a more exaggerated clinical picture. Patients present with lethargy, changes in mental status, and an inability to concentrate, with inappropriate conversations or behavior. Hyporeflexia, decreased muscle tone, and profound weakness will be manifested as the calcium level continues to rise. A calcium level greater than 12 mg/dL can cause emotional lability, confusion, delirium, psychosis, stupor, and coma. Hypercalcemia greater than 18 mg/dL may cause shock, renal failure, and death [149]. It is important to note that even when hypercalcemia has been corrected, older patients may require a longer recovery time to return to their baseline behavior.

***Gastrointestinal Signs and Symptoms***

Calcium exerts its effect upon smooth or involuntary muscle in the intestinal tract. When motility slows, gastric emptying is delayed, which results in nausea and vomiting. Anorexia and constipation also become part of these GI symptoms [149].

***Cardiovascular Signs and Symptoms***

Hypercalcemia affects the contractility of the heart muscle and electrical impulses. Varying levels of elevated calcium affect the heart differently; moderate hypercalcemia causes bradycardia, with a shortened QT interval and possible hypertension. Calcium levels greater than 16 mg/dL produce a prolonged QT wave; levels greater than 18 mg/dL have the potential to cause asystole. If patients are taking digoxin, there is the possibility of digoxin toxicity occurring [1; 149].

***Renal Manifestations***

As a protective mechanism, the kidneys can increase their excretion of calcium fivefold, but this can only be sustained for a very limited time. Elevated calcium affects the efficacy of antidiuretic hormones within the collecting tubules, resulting in polyuria. With the decreased ability to concentrate urine, dehydration occurs. Nausea and vomiting, coupled with depleted fluid intake, add to volume depletion, which in turn decreases the glomerular filtration rate (GFR). With a lowered GFR, sodium and water in the proximal tubule are resorbed, in an effort to retain water. Renal failure will follow. Levels of calcium bound to protein decrease when acidosis occurs, resulting in an increased level in the serum [1; 149].

**Treatment**

The underlying problems of dehydration, the excessive release of calcium due to bone destruction, and renal insufficiency should be corrected as expediently as possible. Obviously, if the elevated calcium is the result of excessive intake of calcium supplements or vitamin D, these should be discontinued immediately. If the patient is receiving total parenteral nutrition (TPN) with calcium in the formula, the nutritional support team will make adjustments as necessary. Any thiazide diuretics should be discontinued, as these inhibit calcium excretion.

Hydration should be initiated with IV normal saline at a rate of 200–300 mL per hour to inhibit resorption of calcium in the tubules. Corticosteroids will also be administered, initially by IV then orally when the patient is able to tolerate it. Corticosteroids decrease calcium absorption from the intestine and increase urinary calcium excretion. Calcitonin may also be helpful, as it inhibits bone resorption. The action is rapid but short lived. As noted, bisphosphonates are a common treatment for cancer-related hypercalcemia [149]. Diuretics such as furosemide may be ordered but only after the fluid volume has been sufficiently replaced. Laxatives may be administered to correct constipation, and antiemetics are helpful for patients experiencing nausea. In extreme cases, patients may require plasmapheresis or dialysis [1; 90; 149].

**Care of the Patient with Hypercalcemia**

For patients who experience confusion or disorientation as a result of hypercalcemia, safety is an issue. Healthcare providers should reorient the patient frequently to his or her surroundings and leave a call bell within reach. If it is feasible, a family member should stay with the patient until the confusion subsides.

Profound weakness heightens the risk for falls, which in turn may result in fractures. The use of transfer devices with a referral to physical therapy should be made, if appropriate. The patient should be mobilized as early and as frequently as possible to maintain calcium in the bones. Mobilization helps to reduce the risk of DVT and pneumonia.

Nurses should monitor medications; self-administration of supplements or antacids is prohibited. In addition, cardiac monitoring will be necessary if significant EKG changes are observed. Patients prone to congestive heart failure or with compromised cardiac status should also be assessed for fluid overload. Strict intake and output are stressed for all patients. Ideal urine output is 100–150 mL per hour. A Foley catheter may be placed for accurate output.

Laboratory values should be monitored for decreased potassium and magnesium. Skin breakdown related to bed rest and incontinence is a risk, and patients' skin should be regularly assessed. Encourage oral care to protect mucous membranes and alleviate dry mouth [1].

For patients whose hypercalcemia and probable coexisting renal failure are reflective of end-stage disease, this may be an appropriate time to re-examine goals and decide how aggressive the plan of care should be. Consultation with a palliative care specialist or initiating comfort measures may be deemed appropriate at this time.

## SPINAL CORD COMPRESSION

Education and stressing the significance of reporting early signs and symptoms of any changes in pain patterns (e.g., sudden severe pain, increased localized or radiating pain), weakness, or sensory loss is important for all patients with MM, as spinal cord compression (SCC) is a possible complication of the disease [150].

In the absence of disease, one of the functions of the 26 flexible vertebrae of the spinal column is to encase and protect the spinal cord. The spinal cord begins at the foramen magnum and terminates at the first lumbar vertebra. The nerve root endings from the second lumbar vertebra down into the sacral area are not encased within this bony structure and terminate in the cauda equina. In MM, osteolytic lesions within the vertebra destroy the bone. As a result, the vertebral bodies collapse and fracture, compressing the spinal cord. Any pressure or damage to the thecal sac impinges the nerves of the cord. This nerve impingement can result in minor damage in autonomic, sensory, or motor function. SCC may result in an oncologic emergency due to the potential not only for minor nerve damage but also for more serious and possibly longer term complications resulting in permanent damage and paralysis. Medical treatment, radiation, and/or surgical intervention should be promptly instituted to halt this process and ensure a positive outcome. Spinal cord compression remains the second most frequently occurring neurologic complication associated with malignancies [1; 27; 40; 66; 151; 152].

### Presenting Signs and Symptoms

As many as 70% of patients diagnosed with MM present with back pain due to lytic lesions of the spine upon initial diagnosis, and lytic lesions in bone never repair. Despite standardized treatment with bisphosphonates and encouraging patients to remain as mobile as possible, vertebral bodies fracture and SCC follows. The early onset of SCC may initially go undetected, but the usual pathologic sequence of this disease is [19; 27; 66; 151; 152; 153]:

1. Pain
2. Motor weakness: Stiffness, heaviness in limbs
3. Motor loss: Lack of coordination and ataxic gait; paralysis with the continuation of motor loss
4. Sensory loss: Numbness, paresthesia, inability to sense temperature variations, loss of sensation of deep pressure, inability to sense vibration
5. Autonomic loss: Early signs of bowel and bladder dysfunction, impotence, loss of sphincter tone (a later sign, equates with poorer prognosis)

The presenting symptoms may vary depending on the level of nerve damage. Injury to the cauda equina creates bilateral sensory loss and pain in the perineal area, thighs, and lateral leg area [19; 27; 66; 151; 152].

**Physical Assessment**

The definitive diagnosis of SCC is made by CT and/or MRI of the spine [1; 47; 152]. However, the patient's signs and symptoms are often the first indications. Upon examination, the patient may complain of back pain localized to the affected vertebral body. The constant pain does not subside when the patient lies down; in fact, the reverse is usually true, and the pain is less severe when the patient is standing [151; 152]. This pain differs from that associated with a herniated disc, which is relieved by a change in position. Added pressure from abdominal organs may also increase pain when the patient is lying supine [151]. Radicular pain caused by nerve compression is exacerbated by coughing, sneezing, or bowel movements. Patients may be able to trace a path of radiating pain as it travels along the dermatome of the affected nerve root [151]. With involvement in the thoracic region, patients report a tight band sensation around their chest or abdominal area.

Compression of the cord may also cause hyperactivity in deep tendon reflexes. Normal brisk reflexes are decreased with nerve root compression. Straight leg raises or neck flexion increase the pain. When patients' legs are straightened and raised and the foot dorsiflexed, resulting pain radiating from the back down the leg is confirmation of nerve root compression. A positive Babinski sign confirms motor involvement. Sensory involvement is assessed by the ability or inability to determine the sense of touch, vibration, position, and temperature variations [1; 66; 151; 152].

Patients may report symptoms of increasing weakness in their legs, which creates difficulty in walking or climbing stairs [152]. Despite the use of a walker and additional assistance, the ataxia will progressively worsen. Sensory loss can occur over varying periods of time, from hours to days and even months, depending on the disease progression. Patients may report numbness or tingling in their toes. The reported loss of sensation gradually progresses up the legs from the toes, with a feeling similar to that of pulling up stockings or socks. Trying to accurately describe symptoms that could be the progression of pre-existing neuropathies or a new disease entity presents a challenge to the patient and caregiver.

With autonomic involvement, which always coexists with other symptoms, patients may not feel the urge to void and may report incontinence or retention. Patients may report dribbling of urine; it is highly probable that this is incontinence with overflow. Little attention may have been paid to constipation, as it is often a problem patients are accustomed to dealing with on a day-to-day basis as an expected side effect from the prescribed opioids [1; 27; 66; 151; 152]. Referrals to a radiation oncologist, neurologist, and orthopedist may be required.

**Treatment**

The goals of SCC treatment are to manage the pain, stabilize the spine, and halt the underlying disease process to prevent irreversible neurologic damage. Restoring patients to their previous level of functioning (or an improved level, if possible) is the ultimate goal. Approaches to treatment include a combination of [1; 152; 154]:

- Pain management
- Bed rest (until it is determined safe to mobilize the patient)
- Bowel and bladder regimen
- Back brace to be worn when patient is out of bed
- Support hose and sequential compression device
- Anticoagulant prophylaxis
- Physical therapy
- Vertebroplasty or balloon kyphoplasty

In addition, glucocorticoids are prescribed to ameliorate symptoms. Typically, this consists of a loading dose of dexamethasone 16 mg followed by a short course of oral dosing at 16 mg daily while treatment is being planned [75; 155]. The loading dose may be given prior to imaging to reduce swelling and increase circulation to the spine. Dexamethasone should be reduced and gradually stopped in patients who do not proceed to surgery or radiotherapy and should be discontinued if neurologic function deteriorates at any time [155]. Bisphosphonates should not be used to treat spinal pain in patients with vertebral involvement from tumor types other than myeloma, breast cancer, or prostate cancer, or with the intention of preventing SCC, except as part of a randomized controlled trial [155].

Radiation may also be part of the treatment of SCC. The number of treatments ordered will depend upon its appropriateness with other modalities that have been ordered in the plan of care. Chemotherapy may be used as an adjuvant therapy with radiation therapy or surgery. The choice of chemotherapeutic agent will depend upon the primary tumor type and patient history [152].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Because plasma cell tumors are very radiosensitive even to a low-to-moderate dose of radiation, the American College of Radiology notes that the most commonly offered treatment for spinal cord compression associated with multiple myeloma is emergent external beam radiation therapy following initiation of steroid therapy.

(https://acsearch.acr.org/docs/3091670/Narrative. Last accessed March 14, 2024.)

**Level of Evidence**: Expert Opinion/Consensus Statement

### Care of the Patient with SCC

Bed rest will be ordered initially until imaging is completed and it is determined that the patient can be safely mobile without negatively affecting outcomes. Patients maintained on bed rest require assistance to turn and reposition in order to maintain skin integrity. For patients permitted to sit for meals or to be assisted to the bedside commode or to the bathroom, falls are a major issue. Call bells should be within easy reach. Transfer belts and walkers should be used for ambulation, with clear uncluttered pathways to the bathroom. Good fitting shoes or, at the very least, non-skid slipper socks should be worn. When patients can safely be mobilized, activity should be encouraged as much as possible. The mechanical stress of weight bearing will help maintain calcium in the bones. It is also a good opportunity to reiterate the role of mobility in decreasing the risk of developing a DVT.

Pain assessment and pain management are paramount. Prior to any procedure requiring the patient to lie in a supine position or remain still for any length of time, pain medication or anxiolytics should be administered. Some patients may require a patient-controlled analgesia (PCA) pump. Weaning from a PCA to a sustained-release analgesic with breakthrough pain medication should take place after the steroids and radiation therapy have succeeded in decreasing the pain. Uncontrolled pain also prevents deep breathing and increases the risk of patients developing pneumonia. Patients should be encouraged to use their incentive spirometer and to cough and deep breathe as part of their daily routine.

In many cases, radiation therapy is administered to halt the myeloma activity. Radiation departments will often provide patient education materials, and the radiation oncologist will outline the treatment plan. The severity of the cord compression will dictate how many treatments will be necessary. Patients may question why their pain seems to have increased after the first few radiation treatments when the goal was to eliminate the pain. Patients should be reassured this is temporary and the initial inflammation will subside [152]. If a patient is planning to undergo a PBSC transplant in the future and the radiated field includes the pelvic area, the number of radiation treatments may be limited. Patients should be aware that their initial appointment will take longer than subsequent treatments. Radiation treatments are usually planned Monday through Friday; the weekend break between treatments allows time for radiated tissues to heal [75; 90].

Bowel management can be a challenge when constipation results from opioids, immobility, and reluctance to bear down due to back pain. Fluids should be encouraged; adding prune juice to the patient's diet along with foods high in fiber provides a natural stimulation of the bowel. The majority of patients with MM are older and not accustomed to drinking as much water as is required. Reiterating in very simple terms the importance of keeping kidneys flushed and supplying patients with water bottles may be a simple solution. Laxatives and stool softeners should be administered routinely. An enema or suppository may be necessary if the patient has not had a bowel movement in several days. Teaching patients to intervene if they have gone longer than three days without a bowel movement prevents the development of obstipation.

If a patient exhibits signs and symptoms of urinary retention upon admission, a bladder scan to check for retained urine is an appropriate initial intervention. Depending on the volume of residual in the bladder, an in-and-out catheter may be ordered or an indwelling Foley catheter placed, if necessary. The patient will then be assessed for the optimum time to remove the catheter and begin a regular toileting schedule.

Blood glucose monitoring is performed in conjunction with steroid therapy [152]. Reassurance should be given to patients who have misunderstandings about the test or believe that they have developed diabetes. Understanding that the hyperglycemia will subside with the tapering and discontinuation of the steroids will alleviate their fears.

Case management should be consulted to assist with discharge planning for any equipment required at home, such as a walker, wheelchair, or three-in-one commode. Physical therapy may be continued at home or patients may continue rehabilitation in a skilled facility, if deemed appropriate [1; 27; 152]. Hospice referral and palliative care are appropriate for patients who have failed to respond to chemotherapy and conventional radiation therapy and who are not candidates for surgery. Goals of palliative care include the prevention of further injury, pain control, the restoration and maintenance of bowel/bladder function, and the provision of emotional support for both patient and caregiver(s) [152].

**Pain Management**

Pain is demoralizing and incapacitating and can create a multitude of problems if not adequately addressed and corrected. Percutaneous vertebroplasty (PV) and balloon kyphoplasty (BKP) are two options available to patients to address the pain associated with SCC [6; 52; 155]. The goal with either procedure is to stabilize the spine, restore height to the vertebral column, and eliminate the pain [154]. Pain relief has reportedly been sustained over long postoperative periods in patients with MM [154]. The International Myeloma Working Group recommends that patients with significant pain at a fracture site be offered either a PV or a BKP procedure and that the procedure should be performed within four to eight weeks unless there are medical contraindications [154]. Early intervention has been demonstrated to improve clinical outcome and quality of life [156; 157].

***Vertebroplasty***

Vertebroplasty is performed either in the outpatient setting or during an inpatient hospitalization, if warranted. Anesthesia in the form of moderate sedation with local anesthesia or general anesthesia is administered [154]. Preprocedure standards for both vertebroplasty and balloon kyphoplasty require:

- An informed consent
- Patient will be NPO
- A current PT/INR
- Anticoagulants be discontinued at least 12 hours preprocedure

Either an interventional radiologist or orthopedist will perform the vertebroplasty. To undergo the vertebroplasty, the patient will be required to lie in the prone position; care is required in positioning the patient to prevent rib fractures due to boney disease. Under fluoroscopy, the vertebral body is injected with radiopaque acrylic bone cement. One to three vertebrae may be injected at any one time [154].

During the procedure, there is a potential for cement to leak from the site and migrate to the lungs, with the possibility of minor to more serious side effects occurring [154; 158]. However, according to the literature, few adverse events (e.g., pulmonary embolism) have been reported.

### *Balloon Kyphoplasty*

Balloon kyphoplasty requires a more involved procedure than vertebroplasty. It is performed by an orthopedic surgeon using general anesthesia for the sedation; this may require an overnight stay in the hospital. Two small incisions are made in the skin, which allows a pathway to be tunneled into the vertebra and the positioning of a balloon on both sides of the vertebra. The height of the vertebra is restored with the use of a bone tamp, and the cement-filled balloon is then positioned in place. After the space in the vertebra is filled with cement, the balloon can be removed. One of the advantages of the balloon kyphoplasty is a reduced risk of cement leakage. There is, however, the risk that some of the bone marrow may be displaced into the lungs. Again, according to the literature, the risks associated with this procedure appear to be minimal [154; 159].

With completion of either vertebroplasty or balloon kyphoplasty, patients are required to remain flat in bed for at least one hour, allowing time for the cement to harden. In addition to routine postoperative vital signs, the operative site should be monitored for any bleeding or swelling; generally, no more than a small bandage covers the site.

If the procedure is successful, patients report that back pain is minimal if not completely resolved [154].

## RENAL FAILURE

Renal failure plays a significant role in the progression of MM. In approximately one-fifth of patients with advancing disease, renal impairment with a serum creatinine level of >1.5 mg/dL is detected upon initial diagnosis of the malignancy. Poorer prognosis correlates with increased renal impairment [10]. The correlation between tumor burden, amount of damage to the kidneys, and the response to treatment predicts prognosis and outcome [73; 87]. Renal failure and insufficiency are seen in 25% of patients with MM and rank high in the causes of death in patients with MM; they are second only to sepsis [73; 87]. Most cases of renal disease in patients with MM are chronic and caused by excessive light chains in the urine. These excessive light chains initiate a pathologic process, and with other contributing factors, such as dehydration and hypercalcemia, renal failure occurs [160; 161]. Renal impairment may slowly develop over many months before the diagnosis is made.

Renal failure may be one of the presenting symptoms of MM, but it can manifest at any time during the disease trajectory. There is a high probability that patients admitted to an oncology unit will have a diagnosis of myeloma kidney as the cause of their renal failure [18; 19; 21; 28; 131; 162]. Causes of renal failure in patients with MM include [18; 73; 131; 162]:

- Myeloma kidney or myeloma cast nephropathy
- Renal tubular dysfunction
- Primary amyloidosis (AL)
- Light chain deposition disease (LCDD)

In AL, enzymes convert light chains into fibrils, which are deposited in the kidneys. Heavy proteinuria is detected with dipstick, and hypoalbuminemia and edema are present due to glomerular damage. Lambda light chains predominate in AL.

Patients with LCDD usually present with nephrotic syndrome. With this disease, light chains are deposited in the kidneys, heart, liver, skin, and nervous tissue. Kappa light chains predominate in LCDD [18; 131; 162; 163].

It is unusual to find more than one pathologic process developing with renal failure. For example, patients with myeloma kidney are unlikely to develop nephropathy from LCDD as well.

### Pathophysiology

In normal renal function, approximately 50 mg of free light chains, comprised of kappa or lambda chains, are excreted on a daily basis [18]. These light chains are filtered and reabsorbed in the proximal tubule within the nephrons. In patients with MM, a reverse of this process happens; light chains build up when they are not catabolized by lysosomal enzymes and are unable to be resorbed by the proximal tubular cells. Resisting the actions of the enzymes or proteases, the chains are not degraded. Damage from the light chains causes atrophy of the cells within the proximal tubule. Leaving the damaged proximal tubules, the light chains progress to the distal tubule and collecting duct in the nephron. Here, further damage results when light chains precipitate with Tamm-Horsfall mucoprotein (THMP) on the ascending wall of the loop of Henle. The chains and THMP precipitate, forming hyaline casts [163]. Aggregation of casts causes obstruction within the tubules and prevents the flow of urine. THMP is implicated in sodium homeostasis, blood pressure regulation, and a defense molecule against infections in the urinary system. Investigations have focused on the immunomodulatory effects of THMP on immune cells and on THMP as a disease biomarker of acute and chronic kidney diseases [164]. Evidence also indicates that the mucoprotein has an affinity for and binds to *Escherichia coli* [165].

With damage to the tubules, dehydration subsequently follows. This is compounded even further by underlying hypercalcemia. With nausea and/or an inability to drink adequate fluids, the cycle continues. This perpetuates an even further reduction of the flow of urine through the impaired kidneys created by the casts blocking the tubules [27; 28; 131].

### Presenting Signs and Symptoms

There may be few physical signs and symptoms exhibited with early renal impairment. When present, they may include:

- Changes in mentation (e.g., confusion, lethargy that can progress to a coma if renal failure is not reversed)
- Oliguria
- Dry mouth
- Nausea and vomiting
- Anorexia
- Fatigue
- Serum creatinine >1.5 mg/dL
- Elevated BUN
- Edema
- Anemia
- In end-stage renal failure, CHF may be present

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Department of Veterans Affairs guideline panel suggests that periodic evaluation for chronic kidney disease be considered in patients with multiple myeloma.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPGFinal5082142020.pdf. Last accessed March 14, 2024.)

**Level of Evidence:** Expert Opinion/Consensus Statement

### Factors Contributing to Renal Failure

Several factors may contribute to the development of renal failure in patients with MM, including [18; 131]:

- Light chain proteinuria
- Dehydration
- Hypercalcemia
- Pyelonephritis
- Diuretic use
- NSAID use
- Hyperviscosity
- Sepsis (due to compromised immunity post chemotherapy)
- Nephrotoxic medications, including radiocontrast dyes

**Diagnosis**

Determining the cause of renal failure is of paramount importance in effectively managing the symptoms and preventing additional complications. Assessment of patients should begin with a complete history and physical examination. Additional laboratory and imaging tests may include:

- CBC, including manual differential
- CMP, including measurements of potassium, magnesium, BUN, creatinine, and phosphorus
- SPEP
- Free light chain assay
- 24-hour urine
- Urine osmolality
- Serum osmolality
- LDH (will be elevated with increasing tumor burden)
- EKG (if hyperkalemia present)
- IFE (to detect light chains in urine)
- CT scan of kidneys
- Renal ultrasound

Several referrals may be necessary to effectively address renal failure. The first referral is often to a nephrologist. A referral to interventional radiology may be necessary for placement of a dialysis catheter for plasmapheresis or renal dialysis.

**Treatment**

The initial treatment approach for renal failure in patients with MM is treatment of the underlying malignancy. VAD is effective when rapid reduction in the M protein is a priority. Cyclophosphamide or melphalan and prednisone at a reduced dose may be the preferred choice for older patients. The efficacy of bortezomib in relapsed and refractory MM has been discussed. Studies have also shown that bortezomib-based regimens may be effective in patients with MM who present with renal failure [166; 167; 168; 169; 170]. If angiotensin-converting enzyme (ACE) inhibitors and diuretics are being taken, they should be discontinued immediately. Diet modification is often also necessary.

Intravenous fluids may be necessary to maintain volume homeostasis. Urine alkalinization should be monitored, and if necessary, IV sodium bicarbonate infusion may be administered.

As with many complications, glucocorticoids are often administered. If anemia is present, erythropoietin or blood transfusion may be ordered [52]. Allopurinol may be included in the medication regimen to prevent hypercalciuria from chemotherapy [75]. If hypercalciuria is present, it may be reduced by the use of IV bisphosphonates [52; 75]. Hyperkalemia may be corrected with either oral or rectal sodium polystyrene sulfonate. In severe cases, plasmapheresis or renal dialysis may be required.

If the patient has a central venous access device, astute care is pivotal in preventing line sepsis; conversely, if the central venous access device is deemed to be the source of infection, blood cultures and the initiation of IV antibiotics with subsequent line removal will be ordered [28; 131].

***Plasmapheresis***

If standard treatment is not sufficient to reverse the renal failure, plasmapheresis, or more drastically renal dialysis, may be offered to patients in an attempt to prolong survival [52]. In order to carry out the plasma exchange, a catheter will be placed in interventional radiology after an informed consent has been obtained. A current PT/INR with CBC is required. For patients taking lenalidomide, thrombocytopenia may be an issue. Platelets should be available for administration just prior to this procedure if the platelet count is low. If a patient's mentation does not allow him or her to sign an informed consent, a healthcare proxy or legally designated decision maker will be requested to do so. After the vascular catheter is in place, transfer of the patient to a unit equipped to perform the plasma exchange will be necessary. Most institutions have policies requiring nurses to complete training and/or receive certification in order to flush implanted catheters for plasma exchange and/or renal dialysis [28; 52].

### Care of the Patient with Renal Failure

Nursing care of patients with MM and renal compromise is relatively involved. Of course, patient safety should be strenuously maintained. Several factors should be continuously monitored to ensure that interventions are effective and that the condition is not worsening. Strict and accurate intake and output measures should be recorded. The patient should also be weighed daily; typically, the dry weight (before patient eats breakfast) is measured. A Foley catheter may be inserted to measure hourly urine output.

Vital signs should be closely monitored. Blood pressure will decrease in cases of hypovolemia, and a fever may indicate sepsis, which may not be reflected with neutropenia. Laboratory results should also be regularly assessed. Bleeding precautions for thrombocytopenia and compromised host precautions for neutropenia should be initiated. In many cases, continuous EKG monitoring for hyperkalemia is necessary.

Skin turgor should be evaluated for signs of dehydration or fluid overload. Fluid overload is a particular concern if the patient is rigorously rehydrated. Oral fluid intake should be encouraged when nausea is controlled and the patient is no longer at risk for aspiration. Administration of antiemetics may be indicated. Amino glycosides should be held for 48 hours after the patient has received contrast for CT scans [27; 28; 72; 90]. The oncologist may write an order requesting the pharmacy to adjust medication doses according to renal function.

## CONCLUSION

It has been well over 150 years since the first documentation of MM demanded the attention of the medical arena. In that time, the disease has remained incurable, but it has thankfully become more treatable, with longer survival times than ever before. The tireless and dedicated research to find a cure or to categorize MM as a chronic disease continues. It has been projected that the median survival time for patients with MM will reach 8 to 10 years within the next decade, which is a source of hope to patients and caregivers [21].

## RESOURCES

**International Myeloma Foundation**
https://www.myeloma.org

**Multiple Myeloma Research Foundation (MMRF)**
https://themmrf.org

**NMDP**
https://bethematch.org

**Implicit Bias in Health Care**

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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