



Multiple Myeloma  
Center for Nurses

# Multiple Myeloma FAQs



Content is consistent with the Oncology Nursing Society Standards and Guidelines. The Oncology Nursing Society Seal of Approval does not constitute medical advice and does not imply product endorsement by ONS. Healthcare providers should exercise their own independent medical judgment. Website content or other resources referenced in these materials have not been reviewed for the Oncology Nursing Society Seal of Approval.

# 2 Introduction

The **Multiple Myeloma Center for Nurses FAQs** provide answers to some of the most common questions about caring for people with multiple myeloma, from disease information to survivorship.

FAQs are organized by the following topics:

**Section I: Overview of Multiple Myeloma**

**Section II: Diagnosis**

**Section III: Treatment Considerations/Response Criteria**

**Section IV: Supportive Care**

**Section V: Lifestyle Issues**

# 3 Section I: Overview of Multiple Myeloma

### What is the pathogenesis of multiple myeloma?

Multiple myeloma is a systemic malignancy of plasma cells that typically involves multiple sites within the bone marrow and secretes all or part of a monoclonal antibody.<sup>1</sup> The malignant plasma cells, or myeloma cells, accumulate in the bone marrow.<sup>2</sup> Abnormal accumulation of these monoclonal plasma cells in the bone marrow causes the primary characteristics of multiple myeloma<sup>2</sup>:

1. Interference with primary bone marrow function leading to anemia and/or low white blood cell or platelet counts
2. Bone destruction surrounding the bone marrow cavity
3. Production of monoclonal proteins that are released into the blood and/or urine
4. Reduced immune function indicated by decreased levels of normal immunoglobulins and increased susceptibility to infection

### What are presenting clinical signs and symptoms and laboratory values seen in a patient with multiple myeloma?

The Revised International Myeloma Working Group (IMWG) defines myeloma as: clonal bone marrow plasma cells  $\geq 10\%$  or biopsy-proven bony or extramedullary plasmacytoma<sup>a</sup> and any 1 or more of the following myeloma-defining events (also known as CRAB features)<sup>3</sup>:

- Hypercalcemia: serum calcium  $>0.25$  mmol/L ( $>1$  mg/dL) higher than the upper limit of normal or  $>2.75$  mmol/L ( $>11$  mg/dL)
- Renal insufficiency: creatinine clearance  $<40$  mL/min<sup>b</sup> or serum creatinine  $>177$   $\mu$ mol/L ( $>2$  mg/dL)
- Anemia: hemoglobin value of  $>2$  g/dL below the lower limit of normal or a hemoglobin value  $<10$  g/dL
- Bone lesions:  $\geq 1$  osteolytic lesion on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)-CT.<sup>c</sup>

Or one or more of the following biomarkers of malignancy:

- 60% plasmacytosis BM plasma cell infiltration  $\geq 60\%$
- Light chains I/u  $>100$  involved and uninvolved serum FLC (not urine FLC) ratio  $\geq 100$  (with involved FLC  $>10$  mg/dL)
- MRI  $\geq 1$  focal lesion  $>5$ mm.

<sup>a</sup> Clonality should be established by showing  $\kappa/\lambda$  light chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should be estimated preferably from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.<sup>3</sup>

<sup>b</sup> Measured or estimated by validated equations.<sup>3</sup>

<sup>c</sup> If bone marrow has  $<10\%$  clonal plasma cells,  $>1$  bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.<sup>3</sup>

Continued on next page

# Multiple Myeloma FAQs

## Overview of Multiple Myeloma

### 4

Anemia is the most common hematologic complication present in patients with MM. Approximately 35% of patients have a hemoglobin <9 g/dL and ~10% of patients have a hemoglobin <8 g/dL.<sup>4</sup>

Approximately 70% of patients with MM have lytic bone lesions with or without osteoporosis, while an additional 20% have severe osteopenia with no lytic lesions.<sup>4</sup>

A 2003 study showed that bone pain is present at diagnosis in 58% of patients: mild in 29%, moderate in 20%, and severe (Grade 3 or 4) in 9%.<sup>5</sup>

Hypercalcemia is observed in 15%-20% of patients with MM at the time of diagnosis.<sup>4</sup>

Infectious complications remain a major cause of morbidity and mortality in patients with MM.<sup>4</sup>

Bacterial infection is the presenting feature in 15% of patients with MM.<sup>4</sup>

Between 20% and 25% of patients with MM have a serum creatinine equal to or higher than 2 mg/dL at the time of diagnosis.<sup>4</sup>

An estimated 19% of patients with MM present with severe fatigue.<sup>6</sup>

### What are the risk factors associated with multiple myeloma?

The most significant risk factor for multiple myeloma is age: 96% of cases are diagnosed in people older than 45 years, and more than 63% are diagnosed in people older than 65 years. Thus, it is thought that susceptibility to myeloma may increase with the aging process.<sup>7</sup> The median patient age at diagnosis is 69 years according to SEER data from 2017.<sup>8</sup> One 2017 study that used data from the SEER database with data linkage to Medicare claims analyzed median age at diagnosis in 5338 people with multiple myeloma, and showed that the median age for African Americans and Hispanics was 74, and the median age for white and Asian patients was 76.<sup>9</sup> Men, and patients with African heritage, are at greater risk than women and whites.<sup>8</sup> Other risk factors include exposure to radiation and environmental toxins, such as pesticides, herbicides, and petroleum products.<sup>7</sup> Multiple myeloma may develop in individuals without these risk factors.<sup>7</sup>

# Multiple Myeloma FAQs

## Overview of Multiple Myeloma

5

### What is the difference between MGUS, smoldering, and active myeloma?

Monoclonal gammopathy of undetermined significance (MGUS) is a condition that may precede multiple myeloma.<sup>10</sup> Patients with MGUS have monoclonal protein present without evidence of end organ damage (CRAB criteria [Calcium elevation, Renal dysfunction, Anemia, Bone disease]).<sup>3</sup> Symptoms also include serum monoclonal protein <30 g/L and clonal marrow plasma cells <10%.<sup>3</sup> The rate of progression from MGUS to multiple myeloma is 0.5% to 1% per year.<sup>3,10</sup>

Smoldering multiple myeloma (SMM) is the stage of the disease with no symptoms and no related organ or tissue impairment with both of the following criteria present<sup>3</sup>:

- Higher level of serum monoclonal protein than MGUS ( $\geq 30$  g/L) or urinary monoclonal protein  $\geq 500$  mg per 24 hours, and/or bone marrow monoclonal plasma cells 10% to 60%
- Absence of myeloma-defining events or amyloidosis

However, this high-risk cohort does not represent the majority of patients with SMM.<sup>3</sup>

Patients with higher risk features in SMM have a 40% risk of progression to active myeloma.<sup>3</sup> Transition from MGUS to multiple myeloma is characterized by increases in the number of multiple myeloma cells, angiogenesis, and osteolytic lesions.<sup>10</sup>

Active multiple myeloma is defined by the presence of clonal bone marrow cells  $\geq 10\%$  or biopsy-proven bony or extramedullary plasmacytoma along with the presence of CRAB features or biomarkers of malignancy.<sup>3</sup>

In 2014, the International Myeloma Working Group made the following updates to the diagnostic criteria of multiple myeloma<sup>3</sup>:

- Added biomarkers of malignancy to the disease definition in addition to the existing criteria of end organ damage (CRAB features)
- Updated laboratory and radiographic results for the criteria of CRAB features
- Revised histological and monoclonal protein requirements for diagnosis

No single pathological or molecular feature can be used to differentiate patients with SMM with only clonal premalignant plasma cells versus patients with clonal malignant cells.<sup>3</sup> There is a need for a group of biomarkers that could identify patients with SMM who are at risk of developing CRAB features of symptomatic MM.<sup>3</sup>

Continued on next page

# Multiple Myeloma FAQs

## Overview of Multiple Myeloma

6

NAME	DEFINITION <sup>2,3</sup>
Monoclonal Gammopathy of Undetermined Significance (MGUS) <sup>2</sup>	<ul style="list-style-type: none"> <li>• Serum monoclonal protein present &lt;30 g/L</li> <li>• Absence of end organ damage (CRAB features)*</li> <li>• Clonal bone marrow plasma cells &lt;10%</li> </ul>
Smoldering Multiple Myeloma (SMM) <sup>3</sup>	<ul style="list-style-type: none"> <li>• Serum monoclonal protein ≥3 g/dL</li> <li><i>Or</i></li> <li>• Bence-Jones protein ≥500 mg/24 h</li> <li><i>And/Or</i></li> <li>• Clonal bone marrow plasma cells 10%–59%</li> <li><i>And</i></li> <li>• Absence of myeloma-defining events or amyloidosis<sup>3</sup> <ul style="list-style-type: none"> <li>— If skeletal survey negative, assess for bone disease with whole-body MRI, FDG PET/CT, or low-dose CT scan</li> </ul> </li> </ul>
Multiple Myeloma <sup>3</sup>	<p>Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma</p> <p><i>And</i></p> <p>Any one or more of the following myeloma-defining events:</p> <ul style="list-style-type: none"> <li>• Calcium &gt;0.25 mmol/L (&gt;1 mg/dL) higher than the upper limit of normal or &gt;2.75 mmol/L (&gt;11 mg/dL)</li> <li>• Renal insufficiency (creatinine &gt;2 mg/dL) (&gt;177 μmol/L) or creatinine clearance &lt;40 mL/min</li> <li>• Anemia (hemoglobin &lt;10 g/dL or hemoglobin &gt;2 g/dL below the lower limit of normal)</li> <li>• One or more osteolytic bone lesions on skeletal radiography, CT, or FDG PET/CT</li> <li>• Clonal bone marrow plasma cells ≥60%</li> <li>• Involved: uninvolved serum FLC ratio ≥100 and involved FLC concentration 10 mg/dL or higher</li> <li>• &gt;1 focal lesion on MRI studies ≥5 mm<sup>3</sup></li> </ul>
<p><b>*Organ damage classified as CRAB</b> or any other significant clinical problem linked to myeloma progression such as recurrent infections or neuropathy unrelated to treatment</p> <p><b>C</b> – Calcium elevation &gt;0.25 mmol/L (&gt;1 mg/dL) higher than the upper limit of normal or &gt;2.75 mmol/L (&gt;11 mg/dL)</p> <p><b>R</b> – Renal insufficiency (creatinine &gt;2 mg/dL) (&gt;177 μmol/L) or creatinine clearance &lt;40 mL/min</p> <p><b>A</b> – Anemia (hemoglobin &lt;10 g/dL or hemoglobin &gt;2 g/dL below the lower limit of normal)</p> <p><b>B</b> – Bone disease (one or more osteolytic bone lesions on skeletal radiography, CT, or FDG PET/CT)</p> <p><b>One or more CRAB features</b> or other significant problem required for diagnosis of Symptomatic Myeloma</p> <p><b>SLiM biomarkers of malignancy</b></p> <p><b>S</b> – Clonal bone marrow plasma cells ≥60%</p> <p><b>Li</b> – Abnormal serum FLC ratio ≥100 (involved kappa) or ≤0.01 (involved lambda)</p> <p><b>M</b> – &gt;1 focal lesion on MRI studies ≥5 mm<sup>3</sup></p>	

Concise review of the disease and treatment options: multiple myeloma cancer of the bone marrow. 2018 ed. International Myeloma Foundation. Accessed May 29, 2019.<sup>2</sup> Rajkumar SV, et al. *Lancet Oncol.* 2014;15(12):e538-e548.

# Multiple Myeloma FAQs

## Overview of Multiple Myeloma

7

### **What is a free light chain?**

### **What is its significance in monitoring patients with multiple myeloma?**

Normal plasma cells produce immunoglobulins or antibodies which are made up of light chains and heavy chains.<sup>11</sup> In myeloma, malignant plasma cells overproduce a specific antibody/immunoglobulin (monoclonal protein also known as M-protein).<sup>11</sup> Plasma cells tend to produce light chains in greater numbers than heavy chains, which results in free light chains (FLCs) circulating in the bloodstream.<sup>11</sup> "The quantity of FLC production is a marker of the activity of myeloma or the growth of plasma cells."<sup>11</sup>

Urine-based and plasma-based tests that detect and evaluate monoclonal protein levels, including the serum FLC assay, are part of a panel of tests recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for a patient's initial diagnostic workup and for monitoring response to treatment.<sup>12</sup> Monitoring the individual's FLC levels and the kappa/lambda ratio during treatment is useful to see if treatment is working.<sup>11</sup> Monitoring FLC can be beneficial. During a relapse, small amounts of myeloma cells produce measurable amounts of light chains, in most cases. These light chains may increase before the heavy chains and intact immunoglobulins can be detected by SPEP or immunofixation tests.<sup>11</sup>

# 8 Section II: Diagnosis

### What tests are recommended for the initial diagnostic workup of multiple myeloma?

According to the NCCN Guidelines<sup>®</sup> for Multiple Myeloma, the initial diagnostic workup includes a history and physical exam, complete blood count with differential and platelet counts, a peripheral blood smear, serum blood urea nitrogen (BUN)/creatinine, electrolytes, liver function tests, albumin, calcium, serum uric acid, serum lactate dehydrogenase (LDH), and beta-2 microglobulin, among other tests.<sup>12</sup> Increases in BUN and creatinine signal renal impairment.<sup>12</sup> LDH and beta-2 microglobulin levels help indicate tumor cell characteristics.<sup>12</sup>

A myeloma panel includes protein electrophoresis (serum [SPEP]), immunofixation electrophoresis (serum [SIFE]), quantitative immunoglobulin levels, serum free light chain assay, and 24-hour urine for total protein, as well as the other tests mentioned previously.<sup>12</sup> Serum immunofixation electrophoresis is roughly 10-fold more sensitive to monoclonal protein detection than serum protein electrophoresis.<sup>13</sup>

A whole-body low-dose computed tomography (CT) scan or a whole-body fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan is recommended by NCCN Guidelines for Multiple Myeloma as part of the initial diagnostic workup.<sup>12</sup> A whole-body magnetic resonance imaging (MRI) may be useful to distinguish active from smoldering multiple myeloma if the whole-body low-dose CT is negative.<sup>12</sup> If FDG PET/CT has been performed on the patient, there is no need for a skeletal survey.<sup>12</sup> Unilateral bone marrow aspirate and biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry, cytogenetics, and fluorescence in situ hybridization (FISH) are also recommended.<sup>12</sup>

# Multiple Myeloma FAQs

## Diagnosis

9

### How is multiple myeloma staged? What tests are required for staging?

In 2015, the International Myeloma Working Group updated the staging system for multiple myeloma to include former International Staging System criteria. The staging system now includes chromosomal abnormalities as detected by interphase fluorescence in situ hybridization and serum lactate dehydrogenase.<sup>14</sup>

REVISED INTERNATIONAL STAGING SYSTEM <sup>14</sup>		
R-ISS Stage	Stage Criteria	Criterion Definitions
I	ISS stage I and Standard-risk CA by iFISH and	Serum $\beta$ 2-microglobulin <3.5 mg/L, serum albumin $\geq$ 3.5 g/dL
	Normal LDH	No high-risk CA
	Normal LDH	Serum LDH <upper limit of normal
II	Not R-ISS stage I or III	
III	ISS stage III and either	Serum $\beta$ 2-microglobulin $\geq$ 5.5 mg/L
	High-risk CA by iFISH or	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
	High LDH	Serum LDH >upper limit of normal

R-ISS, revised International Staging System; ISS, International Staging System; CA, chromosomal abnormalities; iFISH, interphase fluorescence in situ hybridization; LDH, lactate dehydrogenase.

Adapted from Palumbo A et al. *J Clin Oncol.* 2015;33(26):2863-2869.<sup>14</sup>

Continued on next page

## Multiple Myeloma FAQs

### Diagnosis

#### **How does multiple myeloma affect the skeletal system?**

Multiple myeloma causes an imbalance resulting in increased osteoclast activation (bone damage) and inhibition of osteoblast formation (bone building).<sup>15</sup> An estimated 90% of patients living with multiple myeloma will develop osteolytic bone lesions.<sup>16</sup> Bone lesions can lead to fractures, pain, spinal cord compression, hypercalcemia, and renal dysfunction.<sup>16</sup>

#### **How does multiple myeloma affect renal function?**

In patients with MM, renal insufficiency is often present at diagnosis and can occur throughout the disease.<sup>17</sup> Immunoglobulin light chain proteins combine with proteins secreted by the kidneys and cause cast formation. This combination results in "myeloma kidney" (also called "cast nephropathy").<sup>17</sup> The casts may obstruct and rupture the tubular epithelium, resulting in tubulointerstitial damage. The result is increased serum creatinine levels, electrolyte imbalance, and decreased GFR.<sup>17</sup>

#### **How is osteopenia different from lytic lesions?**

Osteopenia describes reduced bone density that does not qualify as osteoporosis.<sup>18</sup> Osteopenia can be detected by a bone density test.<sup>19</sup> Osteolytic lesions are the result of increased bone resorption without increases in bone formation.<sup>19</sup> Osteolytic lesions can be detected by a positron emission tomography/computed tomography (PET/CT) scan or skeletal survey.<sup>19</sup>

# 11 Section III: Treatment Considerations/ Response Criteria

### What are treatment considerations for multiple myeloma?

Prior to beginning therapy, a patient diagnosed with multiple myeloma will be evaluated for stem cell transplant eligibility. This eligibility will determine initial treatment regimens.<sup>12</sup> It is recommended that patients who are eligible for stem cell transplants should avoid nitrosoureas and alkylating agents (most notably melphalan) prior to the stem cell harvest.<sup>12</sup> Refer to the NCCN Guidelines for preferred primary therapies for patients based on stem cell transplant eligibility.<sup>12</sup>

The preferred therapy regimens for patients eligible for transplant are:<sup>12</sup>

- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone<sup>a</sup>

The preferred treatment regimens for patients not eligible for transplant are:<sup>12</sup>

- Bortezomib/lenalidomide/dexamethasone<sup>b</sup>
- Daratumumab<sup>c</sup>/lenalidomide/dexamethasone
- Lenalidomide/low-dose dexamethasone<sup>d</sup>
- Bortezomib/cyclophosphamide/dexamethasone<sup>a</sup>

### How do immunotherapies such as CAR T cell therapy work?

Immunotherapy works by enhancing or suppressing the body's immune response.<sup>20</sup> Some examples of types of immunotherapy include immunomodulatory agents, monoclonal antibodies, antibody-drug conjugates, and CAR T cell therapy.<sup>21,22</sup>

Specifically, CAR T cell therapy works by recognizing and directing an immune response against targeted cells displaying a specific antigen. CAR T cells are generally engineered from a patient's own T cells.<sup>23</sup>

<sup>a</sup> Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

<sup>b</sup> This is the only regimen shown to have overall survival benefit.

<sup>c</sup> Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.

<sup>d</sup> Continuously until progression.

Continued on next page

## Multiple Myeloma FAQs

### Treatment Considerations/ Response Criteria

#### **Which patients with multiple myeloma are candidates for transplant?**

Although stem cell transplant is standard practice in the treatment of multiple myeloma, not all patients are eligible.<sup>24</sup> Age, physical health, and performance status determine eligibility. However, it should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant.<sup>12</sup> Patients and healthcare providers should work together to determine the optimal course of action.<sup>24</sup>

#### **Are the considerations for patient selection for CAR T cell therapy the same as for stem cell transplant?**

Patient selection considerations for CAR T cell therapy may differ from stem cell transplant. Patients may be eligible for CAR T cell therapy whether or not they have received a prior stem cell transplant. Some clinical trials have included transplant-ineligible patients.<sup>25</sup>

#### **How is response to therapy and disease status monitored?**

A widely used response criteria is the International Myeloma Working Group Uniform Response Criteria. Response categories require 2 consecutive assessments before new therapy is implemented. All categories of response require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required for fulfillment of the response criteria. Response categories include complete response, stringent complete response, immunophenotypic complete response, molecular complete response, very good partial response, partial response, minimal response for relapsed refractory myeloma only, stable disease, and progressive disease.<sup>26</sup>

Continued on next page

# Multiple Myeloma FAQs

## Treatment Considerations/ Response Criteria

13

RESPONSE CRITERIA <sup>26,a</sup>	
CR–complete response	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required <sup>a</sup>
sCR–stringent complete response	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry <sup>a</sup>
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with >4 colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10 <sup>-5</sup> )
VGPR–very good partial response	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-component plus urine M-component <100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, >90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required <sup>a</sup>
PR–partial response	<ul style="list-style-type: none"> <li>• ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to &lt;200 mg/24 h</li> <li>• If serum and urine M-protein are not measurable, ≥50% decrease in difference between involved and uninvolved FLC levels is required in place of M-protein criteria</li> <li>• If serum and urine M-protein and serum FLC are not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30%</li> <li>• In addition, if present at baseline, ≥50% reduction in size of soft tissue plasmacytomas is required<sup>a,b</sup></li> </ul>
Minimal response for relapsed refractory myeloma only	<ul style="list-style-type: none"> <li>• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50% to 89%</li> <li>• In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required</li> <li>• No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)</li> </ul>
PD–progressive disease <sup>a</sup>	<p>Increase of 25% from lowest response value in any of the following:</p> <ul style="list-style-type: none"> <li>• Serum M component with absolute increase ≥0.5 g/dL; serum M component increases ≥1 g/dL are sufficient to define relapse if starting M component is ≥5 g/dL and/or;</li> <li>• Urine M component (absolute increase must be ≥200 mg/24 h) and/or;</li> <li>• Only in patients without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase must be &gt;10 mg/dL);</li> <li>• Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥10%)</li> <li>• Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas</li> <li>• Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder</li> </ul>

Continued on next page

# Multiple Myeloma FAQs

## Treatment Considerations/ Response Criteria

14

RESPONSE CRITERIA (CONT)	
SD—stable disease	Not meeting criteria for CR, VGPR, PR or PD <sup>b</sup>

FLC, free light chain; M-protein, monoclonal protein.  
<sup>a</sup>Two consecutive assessments are needed.  
<sup>b</sup>No known evidence of progressive or new bone lesions if radiographic studies were performed.  
For definitions of measurable disease, refer to Table 4 in Durie BGM et al. *Leukemia*. 2006;20:1467-1473.<sup>29</sup>

Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved. Palumbo A et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*. 2014;32(6):587-600.<sup>26</sup>

Even if a patient achieves sCR, myeloma cells remain. The minimal residual population of myeloma plasma cells (minimal residual disease, MRD) results in a relapse.<sup>27</sup> Clinicians may test for MRD using techniques such as next-generation sequencing, whole body MRI/PET/CT, or multicolor flow cytometry, among other tests.<sup>27</sup> Each has advantages and sensitivities with which MRD can be detected.<sup>27</sup> Presence or absence of MRD may provide prognostic value toward patient outcomes in patients receiving ASCT.<sup>28</sup>

# Multiple Myeloma FAQs

## Treatment Considerations/ Response Criteria

15

IMWG UNIFORM RESPONSE CRITERIA: DISEASE PROGRESSION AND RELAPSE (2006)	
RELAPSE SUBCATEGORY	RELAPSE CRITERIA <sup>29</sup>
<p>Progressive disease<sup>a</sup> To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)</p>	<p>Progressive disease: requires any one or more of the following: Increase of <math>\geq 25\%</math> from baseline in</p> <ul style="list-style-type: none"> <li>• Serum M-component and/or (the absolute increase must be <math>\geq 0.5</math> g/dL)<sup>b</sup></li> <li>• Urine M-component and/or (the absolute increase must be <math>\geq 200</math> mg/24 h)</li> <li>• Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be <math>&gt;10</math> mg/dL</li> <li>• Bone marrow plasma cell percentage: the absolute % must be <math>\geq 10\%</math><sup>c</sup></li> <li>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas</li> <li>• Development of hypercalcemia (corrected serum calcium <math>&gt;11.5</math> mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder</li> </ul>
<p>Clinical relapse<sup>a</sup></p>	<p>Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).<sup>b</sup> It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice</p> <ol style="list-style-type: none"> <li>1. Development of new soft tissue plasmacytomas or bone lesions</li> <li>2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion</li> <li>3. Hypercalcemia (<math>&gt;11.5</math> mg/dL) [2.65 mmol/L]</li> <li>4. Decrease in hemoglobin of <math>\geq 2</math> g/dL [1.25 mmol/L]</li> <li>5. Rise in serum creatinine by 2 mg/dL or more [177 <math>\mu</math>mol/L or more]</li> </ol>
<p>Relapse from CR<sup>a</sup> (to be used only if the end point studied is DFS)<sup>d</sup></p>	<p>Any one or more of the following:</p> <ul style="list-style-type: none"> <li>• Reappearance of serum or urine M-protein by immunofixation or electrophoresis</li> <li>• Development of <math>\geq 5\%</math> plasma cells in the bone marrow<sup>c</sup></li> <li>• Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)</li> </ul>

CR, complete response; DFS, disease-free survival.

<sup>a</sup>All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.

<sup>b</sup>For progressive disease, serum M-component increases of  $\geq 1$  gm/dL are sufficient to define relapse if starting M-component is  $\geq 5$  g/dL.

<sup>c</sup>Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

<sup>d</sup>For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Reprinted by permission from Macmillan Publishers Ltd: *Leukemia* (Durie BGM, Harousseau J-L, Miguel JS, et al, on behalf of the International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20:1467-1473.<sup>29</sup>), © 2006.

# 16 | Section IV: Supportive Care

### **What are the recommendations for anticoagulation prophylaxis and/or infection prophylaxis?**

The International Myeloma Foundation Nurse Leadership Board recognizes that prevention of venous thromboembolism (VTE) is essential for patients with multiple myeloma who are at risk for thrombosis.<sup>30</sup>

A heightened awareness of VTE prevention has occurred and many standards of care for VTE prevention have been implemented.<sup>30</sup> In patients at risk, suggestions include anti-coagulation therapy.<sup>30</sup>

Pneumococcal vaccinations should be considered if appropriate (as per NCCN Guidelines).<sup>12</sup> Pneumocystis jiroveci pneumonia (PJP), herpes zoster, and antifungal prophylaxis is recommended if a high-dose dexamethasone regimen is used. Herpes zoster prophylaxis is recommended in all patients treated with proteasome inhibitors, daratumumab, isatuximab-irfc, or elotuzumab.<sup>12</sup>

It is important to carefully evaluate individual patients and to read and understand prescribing information for all drugs before starting a treatment regimen.

# Multiple Myeloma FAQs

## Supportive Care

17

### What complications do nurses need to watch for in patients with multiple myeloma?

Multiple myeloma impacts many body systems. The CRAB features generally specify symptoms that lead to complications in multiple myeloma: Calcium elevation; Renal dysfunction; Anemia; Bone disease.<sup>31</sup> The table below shows how each of these criteria can impact the patient. Other complications of multiple myeloma that impact the patient include organ dysfunction and abnormal immune function. These complications also translate into a variety of symptoms for the patient.<sup>31</sup>

EFFECTS OF INCREASED MYELOMA CELLS IN BONE MARROW CRAB CRITERIA <sup>31</sup>	CAUSE	IMPACT ON PATIENT
C – Increase in blood calcium	Release in calcium from damaged bone into bloodstream.	<ul style="list-style-type: none"> <li>• Dehydration</li> <li>• Constipation</li> <li>• Fatigue</li> <li>• Weakness</li> <li>• Renal or kidney damage</li> </ul>
R – Renal problems – kidney damage	Abnormal monoclonal proteins produced by the myeloma cells are released into the bloodstream and can pass into the urine and produce kidney damage. High blood calcium, infections, and other factors can also cause or increase the severity of kidney damage.	<ul style="list-style-type: none"> <li>• Sluggish circulation</li> <li>• Fatigue</li> <li>• Mental confusion</li> </ul>
A – Anemia	Decrease in number and activity of red blood cell-producing cells in the bone marrow.	<ul style="list-style-type: none"> <li>• Fatigue</li> <li>• Weakness</li> </ul>
B – Bone Damage <ul style="list-style-type: none"> <li>• Thinning (osteoporosis) or</li> <li>• Areas of more severe damage (called lytic lesions), fracture, or collapse of a vertebra</li> </ul>	The myeloma cells activate osteoclast cells, which destroy bone, and block osteoblast cells, which normally repair damaged bone.	<ul style="list-style-type: none"> <li>• Bone pain</li> <li>• Bone swelling</li> <li>• Fracture or collapse of a bone</li> <li>• Nerve or spinal cord damage</li> </ul>
Additional types of organ dysfunction	Local or systemic effects of myeloma, other than CRAB features.	<ul style="list-style-type: none"> <li>• Neuropathy</li> <li>• Recurrent infections</li> <li>• Bleeding problems</li> <li>• Other individual problems</li> </ul>
Abnormal immune function	The myeloma cells reduce the number and activity of normal plasma cells capable of producing antibodies against infection.	<ul style="list-style-type: none"> <li>• Susceptibility to infection</li> <li>• Delayed recovery from infection</li> </ul>

Adapted from Durie BGM. Patient Handbook. 2018 ed. International Myeloma Foundation website: <https://www.myeloma.org/sites/default/files/resource/patient-handbook.pdf>. Accessed June 5, 2019.  
 © International Myeloma Foundation (IMF), Patient Handbook 2018, www.myeloma.org. 800-452-CURE.<sup>31</sup>

# Multiple Myeloma FAQs

## Supportive Care

18

### Why does hyperglycemia occur in patients with multiple myeloma?

Patients with multiple myeloma can develop hyperglycemia as a result of taking therapy regimens that include steroids.<sup>32</sup> Patients should be monitored for signs of raised glucose levels.<sup>32</sup> Patients and caregivers should be educated on the signs and symptoms of hypo- and hyperglycemia.<sup>32</sup> For those at risk for diabetes, increased surveillance is recommended.<sup>32</sup>

### When does hypercalcemia become an oncologic emergency?

Hypercalcemia, or too much calcium in the blood, often results in tumor-induced bone resorption in patients with multiple myeloma.<sup>33,34</sup> Hypercalcemia should be diagnosed based on the concentration of ionized calcium rather than serum calcium levels.<sup>34</sup> In concentrations of 12 to 16 mg/dL, hypercalcemia can cause dry mouth, nausea, vomiting, anorexia, constipation, polydipsia (excessive thirst), polyuria (excessive urination), fatigue, depression, dehydration, confusion, and coma.<sup>4,34</sup> Hypercalcemia can induce renal impairment as a result of interstitial nephritis.<sup>4</sup> Hypercalcemia, defined as corrected serum calcium >11.5 mg/dL, is considered an oncologic emergency.<sup>19</sup>

### When should bisphosphonate therapy be initiated and what is the recommended length of therapy?

The NCCN Guidelines for Multiple Myeloma recommend bisphosphonates or denosumab for all patients receiving myeloma therapy for symptomatic disease regardless of documented bone disease.<sup>12</sup> In patients with renal disease, National Comprehensive Cancer Network® (NCCN®) Multiple Myeloma Panel members prefer denosumab.<sup>12</sup> A baseline dental exam and monitoring for osteonecrosis of the jaw is also recommended by NCCN Guidelines for all patients receiving a bone-modifying agent.<sup>12</sup> The Guidelines also recommend monitoring for renal dysfunction with use of bisphosphonate therapy.<sup>12</sup>

The American Society of Clinical Oncology (ASCO) recommends that bisphosphonates be administered monthly for up to 2 years.<sup>35</sup> Intravenous bisphosphonates are also recommended for patients with pain as a result of osteolytic disease and as adjunctive treatment for patients receiving radiation therapy, analgesics, or surgical intervention to stabilize fractures or impending fractures.<sup>35</sup> IMWG also concurs for a duration of 2 years. However, IMWG suggests discontinuation after 1 year if complete response, very good partial response, and no active bone disease.<sup>36</sup>

Patients taking bisphosphonates should be advised to have dental examinations and should avoid invasive dental procedures.<sup>35</sup> Patients should also be informed of the importance of good dental hygiene and routine dental care.<sup>35</sup> Osteonecrosis of the jaw is an uncommon, but potentially serious, side effect.

Continued on next page

## Multiple Myeloma FAQs

### Supportive Care

#### **What is the mechanism of action of bisphosphonates?**

Bisphosphonates are recommended for patients with multiple myeloma with or without detectable osteolytic bone lesions who are receiving antimyeloma therapy and in patients with osteoporosis or osteopenia as a result of multiple myeloma.<sup>35</sup> Bisphosphonates inhibit osteoclastic bone resorption in 4 ways: inhibiting osteoclastic recruitment and maturation, preventing the development of monocytes into osteoclasts, inducing osteoclastic cell death, and interrupting osteoclast attachment to bone.<sup>37</sup> In addition to decreasing bone resorption, bisphosphonates promote an increase in calcium balance and mineral content within the bone.<sup>37</sup>

#### **What are the recommendations for performing skeletal surveys and other imaging studies?**

As part of the initial diagnostic workup, NCCN recommends whole-body low-dose CT or FDG PET/CT for patients suspected to have multiple myeloma or solitary plasmacytoma. A skeletal survey is acceptable in some circumstances, but has been shown to be less sensitive than whole-body low-dose CT or FDG PET/CT in detecting osteolytic lesions. If a negative result is obtained for the whole-body low-dose CT or FDG PET/CT, whole-body MRI without contrast may be considered to discern smoldering myeloma from multiple myeloma.<sup>12</sup>

#### **Which patients should have bone density testing? When? How often?**

The International Myeloma Foundation Nurse Leadership Board recommends bone density tests if the patient shows risk factors for osteoporosis outside of new-onset pain or fracture.<sup>19</sup>

# 20 Section V: Lifestyle Issues

### How often should patients with multiple myeloma be seen for follow-up by their oncologist and primary care provider?

The frequency of follow-up visits to an oncologist or primary care provider after primary therapy will vary based on many patient- and disease-specific factors. The NCCN Guidelines for Multiple Myeloma offer guidance on follow-up visits for patients.<sup>12</sup>

### What are some lifestyle changes for patients with multiple myeloma to consider?

Patients may consider the following suggestions: 1) reduce stress from jobs, family, or social situations<sup>31</sup>; 2) limit contacts with school-aged children and crowds, and consider increasing hand washing; 3) reduce alcohol consumption, as it may exacerbate side effects of multiple myeloma therapies; 4) reduce tobacco use because tobacco smoke increases risk of pulmonary infections<sup>38</sup>; 5) consult with their physicians about the level of physical activity in which they can engage—typically, some form of planned walking, swimming, and/or flexibility or strengthening activity can be undertaken by patients.<sup>31</sup>

### Are there any precautions or special screening recommendations for continued care?

Screening and precautionary recommendations from the International Myeloma Foundation Nurse Leadership Board include the following<sup>38</sup>:

- Routine screening for breast, cervical, prostate, colorectal, and skin cancers
- Routine screening for opportunistic infections because multiple myeloma may increase the risk of infection
- Multiple myeloma treatments may increase the risk of hypertension or hypotension, and blood pressure changes need to be monitored routinely. Steroid treatment may lead to hyperglycemia requiring therapeutic interventions
- Patients receiving exogenous erythropoietin therapy need to be evaluated for the adequacy of their iron stores
- Regular hearing and vision tests because multiple myeloma treatments may negatively impact both hearing and vision
- Routine vaccinations, including the annual influenza vaccine, tetanus booster every 10 years, and pneumococcal vaccine every 5 years in patients aged  $\geq 65$ . Varicella vaccine is contraindicated for patients with multiple myeloma who have a compromised immune system
- Oral hygiene is important to mitigate the risk of osteonecrosis of the jaw, for which patients with multiple myeloma have an increased risk

# Multiple Myeloma FAQs

## Lifestyle Issues

21

### How is overall health impacted in patients with multiple myeloma?

Spontaneous fractures, spinal cord compression, osteolytic lesions, recurrent infections, renal failure, anemia, mood disorders accompanied by reduced physical functioning, and side effects of different types of treatments negatively impact the well-being of patients with multiple myeloma.<sup>39</sup> Other disease symptoms and treatment side effects that negatively impact patients include pain, neuropathy, fatigue, gastrointestinal symptoms, reduced physical functioning, increased risk for depression, emotional distress, and sexual dysfunction.<sup>40</sup>

### What online resources are available for patients with multiple myeloma and their caregivers?

The following websites contain information that patients and caregivers may find useful.

This list of independent organizations is not a comprehensive list and is provided as an additional resource for obtaining information. Inclusion on this list does not indicate endorsement by Bristol Myers Squibb of an organization or its communications.

- American Cancer Society: <http://www.cancer.org/cancer/multiplemyeloma/>
- Cancer Financial Assistance Coalition: <http://www.cancerfac.org/>
- International Myeloma Foundation: <http://www.myeloma.org/Main.action>
- Leukemia and Lymphoma Society: <http://www.lls.org>
- Multiple Myeloma Research Foundation: <http://www.themmr.org>
- NCCN Guidelines for Patients: <http://www.nccn.org>
- Be the Match: <https://bethematch.org>

### What are some general guidelines for health maintenance for patients with multiple myeloma?

The International Myeloma Foundation Nurse Leadership Board developed a set of recommendations for screening and disease prevention for this population. These recommendations include screening for malignancies, cardiovascular screening, routine hearing and vision tests, regular influenza vaccines, and frequent screening for cognitive or emotional decline.<sup>38</sup>

## References:

1. National Cancer Institute. Plasma cell neoplasms (including multiple myeloma) treatment (PDQ®). <https://www.cancer.gov/types/myeloma/hp/myeloma-treatment-pdq>. Accessed October 27, 2020.
2. Durie BGM. Concise review of the disease and treatment options: multiple myeloma cancer of the bone marrow. 2018 ed. International Myeloma Foundation website. <https://www.myeloma.org/sites/default/files/resource/ConciseReview.pdf>. Accessed October 27, 2020.
3. Rajkumar SV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.
4. Bladé J, Rosinol R. Complications of multiple myeloma. *Hematol Oncol Clin North Am*. 2007;21(6):1231-1246.
5. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78(1):21-33.
6. Coleman EC, Goodwin JA, Coon SK, et al. Fatigue, sleep, pain, mood and performance status in patients with multiple myeloma. *Cancer Nurs*. 2011;34(3):219-227.
7. Multiple Myeloma Research Foundation. Understanding multiple myeloma: what is multiple myeloma? <https://themmr.org/multiple-myeloma/what-is-multiple-myeloma/>. Accessed October 27, 2020.
8. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, [https://seer.cancer.gov/csr/1975\\_2017/](https://seer.cancer.gov/csr/1975_2017/), based on November 2019 SEER data submission, posted to the SEER web site, April 2020. Available at: <https://seer.cancer.gov/statfacts/html/mulmy.html>. Accessed October 27, 2020.
9. Ailawadhi S, Frank RD, Advani P, et al. Racial disparity in utilization of therapeutic modalities among multiple myeloma patients: a SEER-medicare analysis. *Cancer Med*. 2017;6(12):2876-2885.
10. Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. *Nat Rev Cancer*. 2002;2(3):175-187.
11. International Myeloma Foundation. Understanding Freelite® and Hevylite® Tests. [https://www.myeloma.org/sites/default/files/resource/u-freelite\\_hevylite.pdf](https://www.myeloma.org/sites/default/files/resource/u-freelite_hevylite.pdf). Accessed October 27, 2020.
12. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed October 27, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
13. Jenner E. Serum free light chains in clinical laboratory diagnostics. *Clinica Chimica Acta*. 2014;427:15-20.
14. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: a report from the International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-2869.
15. American Cancer Society. What is multiple myeloma? Available at: <https://www.cancer.org/cancer/multiple-myeloma/about/what-is-multiple-myeloma.html>. Accessed October 27, 2020.
16. Bilotti E, Faiman BM, Richards TA, et al; International Myeloma Foundation Nurse Leadership Board. Survivorship care guidelines for patients living with multiple myeloma: consensus statements of the International Myeloma Foundation Nurse Leadership Board. *Clin J Oncol Nurs*. 2011;15(4 suppl):5-8.
17. Faiman B, Doss D, Colson K, et al and the International Myeloma Foundation Nurse Leadership Board. Renal, GI, and peripheral nerves. Evidence-based recommendations for the management of symptoms and care for patients with multiple myeloma. *Clin J Oncol Nurs*. 2017;21(5)(suppl):19-36.
18. MedlinePlus. Bone density. U.S. National Library of Medicine website. Available at: <https://medlineplus.gov/bonedensity.html>. Accessed October 27, 2020.
19. Miceli TS, Colson K, Faiman BM, Miller K, Tariman JD; International Myeloma Foundation Nurse Leadership Board. Maintaining bone health in patients with multiple myeloma: survivorship care plan of the International Myeloma Foundation Nurse Leadership Board. *Clin J Oncol Nurs*. 2011;15(4 suppl):9-23.
20. National Cancer Institute. Immunotherapy to Treat Cancer. Available at: <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy>. Accessed: December 21, 2020.

21. American Cancer Society. How Immunotherapy Is Used to Treat Cancer. Available at: <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/what-is-immunotherapy.html>. Accessed: December 21, 2020.
22. Myeloma Crowd. Antibody Drug Conjugates As Immunotherapy In Myeloma. Available at: <https://www.myelomacrowd.org/antibody-drug-conjugates-as-immunotherapy-in-myeloma/>. Accessed December 21, 2020.
23. Maus MV, Levine BL. Chimeric antigen receptor T-cell therapy for the community oncologist. *Oncologist*. 2016;21:608-617.
24. Rajkumar SV. Patient education: multiple myeloma treatment (beyond the basics). 2020. UpToDate, Inc. website. <http://www.uptodate.com/contents/multiple-myeloma-treatment-beyond-the-basics>. Accessed October 27, 2020.
25. Chavez JC, Bachmeier C, Kharfan-Dabaja MA. CAR T-cell therapy for B-cell lymphomas: clinical trial results of available products. *Ther Adv Hematol*. 2019;10:1-20.
26. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*. 2014;32(6):587-600.
27. Galtseva IV, Davydova YO, Kapranov HM, et al. Minimal residual disease in multiple myeloma. Benefits of flow cytometry. *Int J Lab Hem*. 2018;40:12-20.
28. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the medical research council myeloma IX study. *J Clin Oncol*. 2013;31(20):2540-2547.
29. Durie BGM, Harousseau J-L, Miguel JS, et al; International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20:1467-1473.
30. Noonan K, Rome S, Faiman B et al. Heart and lung complications. Assessment and prevention of venous thromboembolism and cardiovascular disease in patients with multiple myeloma. *Clin J Nurs Oncol*. 2017;21(5):37-46.
31. Durie BGM. Patient handbook. 2018 ed. International Myeloma Foundation website. <https://imf-d8-prod.s3.us-west-1.amazonaws.com/2020-06/patient-handbook.pdf>. Accessed October 27, 2020.
32. King T, Faiman B. Steroid-associated side effects: a symptom management update on multiple myeloma treatment. *Clin J Nurs Oncol*. 2017;21(12):240-249.
33. MedlinePlus. Hypercalcemia. U.S. National Library of Medicine website. <https://medlineplus.gov/ency/article/000365.htm>. Accessed October 27, 2020.
34. Ludwig H, Zojer N. Supportive care in multiple myeloma. *Best Pract Res Clin Haematol*. 2007;20(4):817-835.
35. Anderson K, Ismaila, N, and Kyle RA. Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology clinical practice guideline update summary. *J Clin Pract*. 2018;14(4):266-269.
36. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol*. 2013;31(18):2347-2357.
37. Terpos E, Rahemtulla A. Bisphosphonate treatment for multiple myeloma. *Drugs of Today*. 2004;40(1):29-40.
38. Bilotti E, Gleason CL, McNeill A; International Myeloma Foundation Nurse Leadership Board. Routine health maintenance in patients living with multiple myeloma: survivorship care plan of the International Myeloma Foundation Nurse Leadership Board. *Clin J Oncol Nurs*. 2011;15(4 suppl):25-40.
39. Cömert M, Güneş AE, Şahin F, Saydam G. Quality of life and supportive care in multiple myeloma. *Turk J Hematol*. 2013;30(3):234-246.
40. Catamero D, Noonan K, Richards T, et al. Distress, fatigue, and sexuality: understanding and treating concerns and symptoms in patients with multiple myeloma. *Clin J Oncol Nurs*. 2017;21(5 suppl):7-18.