MULTIPLE MYELOMA CENTER *for* NURSES

Connecting and Empowering Nurses Through Education and Resources

Multiple Myeloma FAQs

Celgene

2 Introduction

The **Multiple Myeloma Center for Nurses FAQs** provide answers to your 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

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 that secrete all or part of a monoclonal antibody.[1] Abnormal accumulation of these monoclonal plasma cells in the bone marrow causes the primary characteristics of multiple myeloma[2]:

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?

More than 90% of patients present with increased (≥10%) clonal bone marrow plasma cells and circulating monoclonal proteins in serum and/or urine as measured by immunofixation (or immunofixation plus serum free light chain assay). Other presenting characteristics include anemia; lytic bone lesions and pathologic fractures resulting in symptoms of bone pain; fatigue; weakness; renal insufficiency; hypercalcemia; weight loss; and paresthesias.[3,4]

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.[5] The median patient age at diagnosis is 69 years.[6] Men, and patients with African heritage, are at greater risk than women and whites.[6] Other risk factors include exposure to radiation and environmental toxins, such as pesticides, herbicides, and petroleum products.[5] Multiple myeloma may develop in individuals without these risk factors.[5]

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

Monoclonal gammopathy of undetermined significance (MGUS) is a condition that may precede multiple myeloma.[7] Patients with MGUS have monoclonal protein present without evidence of end organ damage (CRAB criteria [**C**alcium elevation, **R**enal dysfunction, **A**nemia, **B**one disease]).[8] The rate of progression from MGUS to multiple myeloma is 0.5% to 1% per year.[8]

Smoldering multiple myeloma (SMM) is the stage of the disease with no symptoms and no related organ or tissue impairment with one or more of the following criteria present[8]:

- Higher level of serum monoclonal protein than MGUS (≥30 g/L)
- Urinary monoclonal protein ≥500 mg per 24 hours
- Bone marrow monoclonal plasma cells 10% to 60%

Patients with higher risk features in SMM have a 40% risk of progression to active myeloma.[8] Transition from MGUS or SMM to multiple myeloma is characterized by increases in the number of multiple myeloma cells, angiogenesis, and osteolytic lesions.[7]

Active multiple myeloma is defined by the presence of clonal bone marrow cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma along with the presence of CRAB features or biomarkers of malignancy.[8]

In 2014, the International Myeloma Working Group made the following updates to the diagnostic criteria of multiple myeloma[8]:

- 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

A single pathological or molecular feature cannot be used to differentiate patients with SMM with only clonal premalignant plasma cells versus patients with clonal malignant cells.[8] Inclusion of biomarkers in the updated disease definition accounts for those patients with SMM who are at high risk of developing CRAB features.[8]

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NAME	DEFINITION[8,9]
Non-IgM Monoclonal Gammopathy of Undetermined Significance (MGUS)	• Serum monoclonal protein present <30 g/L • Absence of end organ damage (CRAB features) • Clonal bone marrow plasma cells <10%
Smoldering Multiple Myeloma (SMM)	Both criteria must be met: • Serum monoclonal protein ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10%-60% • Absence of myeloma defining events (CRAB features) or amyloidosis

Multiple Myeloma	• Clonal bone marrow cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and one or more of the following:
	• One or more CRAB features and/or indicators of organ damage* or
	• One or more biomarkers of malignancy:
	  • Clonal bone marrow plasma cell percentage ≥60%
	  • Involved:uninvolved serum free light chain ratio ≥100
	  • >1 focal lesions on MRI studies

***Organ damage classified as CRAB** or any other significant clinical problem linked to myeloma progression such as recurrent infections or neuropathy unrelated to treatment
C – calcium elevation (>11 mg/dL)
R – renal dysfunction (creatinine >2 mg/dL or creatinine clearance <40 mL/min)
A – anemia (hemoglobin <10 g/dL or >2 g/dL decrease from patient's normal)
B – bone disease (lytic lesions shown on skeletal radiography, CT, or PET/CT)
One or more CRAB features or other significant problem required for diagnosis of **Multiple Myeloma**
IgM, immunoglobulin; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography.

Adapted from Durie BGM. Patient Handbook. 2015 ed. International Myeloma Foundation website: http://myeloma.org/pdfs/PHB.pdf. Accessed October 1, 2015.

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.[10] In myeloma, malignant plasma cells overproduce a specific antibody/immunoglobulin (monoclonal protein).[10] Plasma cells tend to produce light chains in greater numbers than heavy chains, which results in free light chains (FLCs) circulating in the bloodstream.[10] The quantity of FLC production is a marker of the activity of myeloma or the growth of plasma cells.[10]

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 National Comprehensive Cancer Network (NCCN) guidelines for a patient's initial diagnostic workup and for monitoring response to treatment.[11] The use of serum FLC assays may reveal responses to treatment earlier than serum protein electrophoresis (SPEP); and because of its increased sensitivity compared with immunofixation electrophoresis, serum FLC may enable earlier detection of relapse.[10]

Recently, the US Food and Drug Administration cleared the Hevylite™ test as an in vitro test of heavy and light chains in serum[12] that can be used for monitoring previously diagnosed patients with multiple myeloma.[13]

7 Section II: Diagnosis

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

According to the National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma, the initial diagnostic workup includes a history and physical as well as a complete blood count with differential and platelet counts, blood urea nitrogen (BUN), serum creatinine, serum electrolytes, serum calcium, albumin, lactate dehydrogenase (LDH), and beta-2 microglobulin.[11] Increases in BUN and creatinine signal renal impairment.[11] LDH levels help assess tumor cell burden. Beta-2 microglobulin levels reflect tumor mass and burden.[11]

A myeloma panel includes protein electrophoresis (serum [SPEP] or urine [UPEP]), immunofixation electrophoresis (serum [SIFE] or urine [UIFE]), quantitative immunoglobulin levels, serum free light chain assay, and 24-hour urine for total protein.[11] Once the myeloma or monoclonal protein assay is complete, it is important to continue using the same test to obtain accurate measures against the baseline.[11] Serum immunofixation electrophoresis is roughly 10-fold more sensitive to monoclonal protein detection than serum protein electrophoresis.[14]

A skeletal survey is recommended by the NCCN guidelines for multiple myeloma as part of the initial diagnostic workup, and magnetic resonance imaging (MRI), computed tomography (CT) scan, and positron emission tomography (PET)/CT may be useful under some circumstances.[11] In addition, the International Myeloma Foundation recommends MRIs and CT scans are used to assess bone when X-rays are negative and/or for more detailed imaging of particular areas.[9] PET/CT combined scans provide a sensitive whole-body scanning technique.[9] 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.[11]

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 fluorescent in situ hybridization and serum lactate dehydrogenase.[15]

REVISED INTERNATIONAL STAGING SYSTEM[15]

R-ISS Stage	Stage Criteria	Criterion Definitions
I	ISS stage I and	Serum β2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dL
	Standard-risk CA by iFISH and	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 β2-microglobulin ≥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 fluorescent in-situ hybridization; LDH, lactate dehydrogenase.

Adapted from Palumbo A et al. *J Clin Oncol*. 2015;33(26):2863-2869.[15]

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The Durie/Salmon PLUS staging system (2003) is also used in the classification of multiple myeloma (see table below for stage definitions).[16]

DURIE/SALMON PLUS STAGING SYSTEM (PLUS INCLUDES IMAGING)[16]	
MGUS	• Negative MRI and/or FDG PET • Low M-protein in serum and/or urine • Monoclonal bone marrow plasma cells <10% • Normal serum calcium, hemoglobin level, and serum creatinine • No bone lesions on full skeletal X-ray survey and/or other imaging • No clinical or laboratory features of amyloidosis or light-chain deposition disease
Stage IA Smoldering or Indolent	• Single plasmacytoma and/or limited disease from imaging tests can be present • M-protein in serum and/or urine • Monoclonal plasma cells in bone marrow and/or tissue • Serum creatinine <2.0 mg/dL + no EMD • Not meeting criteria for MGUS, multiple myeloma, or solitary plasmacytoma of bone or soft tissue
Stage IB Multiple Myeloma	• Mild diffuse disease • <5 focal lesions • Serum creatinine >2.0 mg/dL + EMD • ≥10% monoclonal plasma cells in bone marrow and/or plasmacytoma • M-protein in serum and/or urine • 1 or more CRAB criteria present
Stage II A/B	• Moderate diffuse disease • 5-20 focal lesions • Serum creatinine <2.0 mg/dL + no EMD • Serum creatinine >2.0 mg/dL + EMD • ≥10% monoclonal plasma cells in bone marrow and/or plasmacytoma • M-protein in serum and/or urine • 1 or more CRAB criteria present
Stage III A/B	• Severe diffuse disease • >20 focal lesions • Serum creatinine <2.0 mg/dL + no EMD • Serum creatinine >2.0 mg/dL + EMD • ≥10% monoclonal plasma cells in bone marrow and/or plasmacytoma • M-protein in serum and/or urine • 1 or more CRAB criteria present

MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; FDG PET, fluorodeoxyglucose positron emission tomography; M-protein, monoclonal protein; EMD, extramedullary disease; CRAB, Calcium elevation; Renal dysfunction; Anemia; Bone disease.

Durie BGM et al. *Hematol J.* 2003;4(6):379-398.[16]

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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).[17] An estimated 90% of patients living with multiple myeloma will develop osteolytic bone lesions.[18] Bone lesions can lead to fractures, pain, spinal cord compression, hypercalcemia, and renal dysfunction.[18]

How does multiple myeloma affect renal function?

Renal insufficiency is associated with multiple myeloma.[17] Elevated plasma cell excretion of monoclonal gammopathies causes renal failure by (1) light chain excretion; (2) immunoglobulin tissue deposition (eg, systemic amyloidosis); and (3) tubular dysfunction (Fanconi syndrome).[17] Light chain tubular damage or "myeloma kidney" is the main cause of renal failure, and the presence of myeloma casts in the distal tubes and collecting ducts is the characteristic feature of myeloma kidney.[17,19] Renal insufficiency is reversible in 20% to 60% of patients with appropriate multiple myeloma treatment.[17] Predictive factors of recovery include serum creatinine <4 mg/dL, 24-hour urine protein excretion <1 g/24 h, and serum calcium ≥11.5 mg/dL.[17,20]

How is osteopenia different from lytic lesions?

Osteopenia describes reduced bone density that does not qualify as osteoporosis.[21] Osteopenia can be detected by a bone density test.[22] Osteolytic lesions are the result of increased bone resorption without increases in bone formation.[22] Osteolytic lesions can be detected by a positron emission tomography/computed tomography (PET/CT) scan or skeletal survey.[22]

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. It is recommended that patients who are eligible for stem cell transplants should avoid alkylating agents (most notably melphalan) prior to the stem cell harvest. Refer to the National Comprehensive Cancer Network (NCCN) guidelines for preferred primary therapies for patients based on stem cell transplant eligibility.[11]

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.[23,24] Age, physical health, and performance status determine eligibility. Factors that may render a patient ineligible include age >77 years, direct bilirubin >2.0 mg/dL, serum creatinine >2.5 mg/dL unless the patient is on chronic stable dialysis, performance status of 3 or 4 on the Eastern Cooperative Oncology Group scale unless it is due to bone pain, or a New York Heart Association Functional Status Class III (cardiac disease causing marked limitations in physical activity) or Class IV (cardiac disease causing an inability to perform physical activity without discomfort).[24,25] These criteria are considered guidelines, and patients and healthcare providers should work together to determine the optimal course of action.[24]

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.[11,26]

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Treatment Considerations/ Response Criteria

RESPONSE CRITERIA[26,a]	
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[a]
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[a]
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^{-5})
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[a]
PR–partial response	• ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg/24 h • 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 • 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% • In addition, if present at baseline, ≥50% reduction in size of soft tissue plasmacytomas is required[a,b]
Minimal response for relapsed refractory myeloma only	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50% to 89% • In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
PD–progressive disease[a]	Increase of 25% from lowest response value in any of the following: • 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; • Urine M component (absolute increase must be ≥200 mg/24 h) and/or; • Only in patients without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • 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%) • Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder

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RESPONSE CRITERIA (cont)	
SD—stable disease	Not meeting criteria for CR, VGPR, PR or PD[b]

FLC, free light chain; M-protein, monoclonal protein.

[a]Two consecutive assessments are needed.

[b]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.[27]

Clinicians may also look for minimal residual disease (MRD), a term used to describe disease detected only by laboratory techniques more sensitive than morphology (eg, flow cytometry or polymerase chain reaction).[28] Presence or absence of MRD may provide prognostic value toward patient outcomes.[29]

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IMWG UNIFORM RESPONSE CRITERIA: DISEASE PROGRESSION AND RELAPSE (2006)

RELAPSE SUBCATEGORY	RELAPSE CRITERIA[27]
Progressive disease[a] 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)	Progressive Disease: requires any one or more of the following: Increase of ≥25% from baseline in • Serum M-component and/or (the absolute increase must be ≥0.5 g/dL)[b] • Urine M-component and/or (the absolute increase must be ≥200 mg/24 h) • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL • Bone marrow plasma cell percentage: the absolute % must be ≥10%[c] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[b] 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 1. Development of new soft tissue plasmacytomas or bone lesions 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 3. Hypercalcemia (>11.5 mg/dL) [2.65 mmol/L] 4. Decrease in hemoglobin of ≥2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 µmol/Lor more]
Relapse from CR[a] (to be used only if the end point studied is DFS)[d]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow[c] • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

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

[a]All relapse categories require 2 consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
[c]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

When do patients receive anticoagulation prophylaxis and/or infection prophylaxis?

The International Myeloma Foundation Nurse Leadership Board recommends that the prevention and prophylaxis of thrombotic events be based on institutional practices, drug therapies and combinations, and factors specific to individual patients (eg, concomitant illnesses, medical history, cost of therapy, insurance, patient abilities, adherence, allergies, and sensitivities).[30]

Pneumococcal and influenza vaccinations can be considered if appropriate (as per National Comprehensive Cancer Network [NCCN] guidelines).[11] *Pneumocystis carinii* pneumonia, herpes, and antifungal prophylaxis is recommended if a high-dose dexamethasone regimen is used. Herpes zoster prophylaxis should be considered for individuals based on their therapeutic regimen.[11]

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

16 Section IV: Supportive Care

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.[9] 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.[9]

EFFECTS OF INCREASED MYELOMA CELLS IN BONE MARROW **CRAB** CRITERIA[9]	CAUSE	IMPACT ON PATIENT
C – Increase in blood **calcium**	Release in calcium from damaged bone into bloodstream.	• Mental confusion • Dehydration • Constipation • Fatigue • Weakness • Renal or kidney damage (R)
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.	• Sluggish circulation • Fatigue • Mental confusion
A – **Anemia**	Decrease in number and activity of red blood cell-producing cells in the bone marrow.	• Fatigue • Weakness
B – **Bone** Damage • Thinning (osteoporosis) or • Areas of more **severe damage (called lytic lesions), fracture, or collapse of a vertebra**	The myeloma cells activate osteoclast cells, which destroy bone, and block osteoblast cells, which normally repair damaged bone.	• Bone pain • Bone swelling • Fracture or collapse of a bone • Nerve or spinal cord damage
Additional types of organ dysfunction	Local or systemic effects of myeloma, other than CRAB features.	• Neuropathy • Recurrent infections • Bleeding problems • Other individual problems
Abnormal immune function	The myeloma cells reduce the number and activity of normal plasma cells capable of producing antibodies against infection.	• Susceptibility to infection • Delayed recovery from infection

Adapted from Durie BGM. Patient Handbook. 2015 ed. International Myeloma Foundation website: http://myeloma.org/pdfs/PHB.pdf. Accessed October 1, 2015.

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.[31] The International Myeloma Foundation Nurse Leadership Board recommends that serum glucose readings >200 mg/dL be monitored and possibly treated with oral antiglycemic agents. For glucose readings >300 mg/dL, insulin therapy may be indicated. Patients with hyperglycemia should be referred to a primary care provider or endocrinologist as needed.[31]

When does hypercalcemia become an oncologic emergency?

Hypercalcemia, or too much calcium in the blood, results in tumor-induced bone resorption in patients with multiple myeloma.[32,33] Hypercalcemia should be diagnosed based on the concentration of ionized calcium rather than serum calcium levels.[33] 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.[17,33,34] Hypercalcemia can induce renal impairment as a result of interstitial nephritis.[17] Hypercalcemia, defined as corrected serum calcium >11.5 mg/dL, is considered an oncologic emergency.[22]

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

The National Comprehensive Cancer Network (NCCN) guidelines recommend bisphosphonates as adjunctive therapy for all patients receiving primary myeloma therapy and for patients with smoldering or stage I disease in the context of a clinical trial.[11] The American Society of Clinical Oncology (ASCO) recommends use of oral or intravenous bisphosphonates in patients with lytic disease apparent on plain radiographs or imaging studies and for patients with osteopenia based on normal plain radiograph or bone mineral density measurements.[35,36] The International Myeloma Working Group (IMWG) concurs and adds magnetic resonance imaging (MRI), computed tomography (CT), and CT/positron emission tomography (PET) as other valid imaging methodologies to reveal myeloma-related bone disease.[35,37]

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ASCO recommends that bisphosphonates be administered monthly for 2 years.[35,36] 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.[36] IMWG suggests discontinuation after 1 year if complete response, very good partial response, and no active bone disease. Healthcare providers may continue at their own discretion if active bone disease is present.[35,37]

Patients taking bisphosphonates should be advised to have dental examinations and should avoid invasive dental procedures. Patients should also be informed of the importance of good dental hygiene and routine dental care.[38]

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.[35] 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.[39] In addition to decreasing bone resorption, bisphosphonates promote an increase in calcium balance and mineral content within the bone.[39]

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

A complete skeletal survey is the standard method for visualizing bone changes in patients with multiple myeloma. However, it can only detect lytic disease when 30% or more of the trabecular bone has been destroyed.[22] The National Comprehensive Cancer Network (NCCN) guidelines recommend a skeletal survey should be ordered at diagnosis and annually, or for symptoms, or as clinically indicated, in patients with active or smoldering multiple myeloma, or after response to primary therapy.[11,22] Limitations of the skeletal survey have prompted use of computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT to supplement data from the skeletal survey.[11,22]

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

Bone densitometry is recommended by the National Comprehensive Cancer Network (NCCN) guidelines as potentially useful under some circumstances as part of the initial diagnostic workup.[11,22] 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.[22]

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 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma offers guidance on follow-up visits for patients.[11]

What lifestyle changes should patients with multiple myeloma consider?

As much as possible, patients should reduce or eliminate stress in any job, family, or social situations. They should avoid contact with school-age children, avoid crowds as much as possible, and wash hands frequently because their immune system is compromised.[9] Alcohol consumption can exacerbate the side effects of multiple myeloma therapies, and alcohol misuse needs to be monitored. For patients who smoke, tobacco use should be curtailed because tobacco smoke increases the risk of pulmonary infections.[40] Patients should check with their physicians to clarify the amount of physical activity that is feasible; but usually, some form of planned walking or swimming and/or flexibility or strengthening activity can be undertaken by patients.[9]

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[40]:

- 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 ≥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

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.[41] Other disease symptoms and treatment side effects that negatively impact patients include pain, fatigue, appetite loss, reduced physical functioning, increased risk for depression, emotional distress, and sexual dysfunction.[42-44]

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 provided as an additional resource for obtaining information. Inclusion on this list does not indicate endorsement by Celgene Corporation 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.themmrf.org
- National Comprehensive Cancer Network Guidelines for Patients: http://www.nccn.org/patients/guidelines/myeloma/#2

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.[40]

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