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Multiple Myeloma, Version 3.2017

Clinical Practice Guidelines in Oncology

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Overview

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. MM accounts for approximately 1.8% of all cancers and slightly >15% of hematologic malignancies in the United States.[1] Myeloma is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.[2] In 2016, the American Cancer Society estimated that 30,330 new cancer cases occurred in the United States, with an estimat-

Abstract

Multiple myeloma (MM) is caused by the neoplastic proliferation of plasma cells. These neoplastic plasma cells proliferate and produce monoclonal immunoglobulin in the bone marrow causing skeletal damage, a hallmark of multiple myeloma. Other MM-related complications include hypercalcemia, renal insufficiency, anemia, and infections. The NCCN Multiple Myeloma Panel members have developed guidelines for the management of patients with various plasma cell dyscrasias, including solitary plasmacytoma, smoldering myeloma, multiple myeloma, systemic light chain amyloidosis, and Waldenström's macroglobulinemia. The recommendations specific to the diagnosis and treatment of patients with newly diagnosed MM are discussed in this article.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Multiple Myeloma Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Multiple Myeloma Panel members can be found on page 269. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

ed 12,650 deaths.[1] Over the past decade, statistics show that the rates for new myeloma cases have been increasing an average of 0.8% each year.[2] However, statistics also reveal that death rates have been declining an average of 0.8% each year over the period of 2004 through 2013 due to the availability of newer and more effective treatment options.[2]

MM is typically sensitive to a variety of cytotoxic drugs, both as initial treatment and as treatment for relapsed disease. Unfortunately, responses are typically durable, and MM is not considered curable with current approaches. However, treatment of MM has been rapidly evolving due to the introduction of new classes of drugs, such as immunomodulatory drugs (IMiDs), proteasome inhibitors, monoclonal antibodies, and histone deacetylase inhibitors.[3–5] Additionally, there is increasing understanding of its tumor biology, creating the rationale for new combinations of therapies and new drug development.[6,7] Studies of the associated cytogenetic abnormalities indicate that MM is a heterogeneous disease, suggesting that risk-adapted approaches and individualizing treatment will further help refine patient management.

These NCCN Guidelines discuss the diagnosis and treatment of newly diagnosed MM; the full version of NCCN Guidelines for MM and other plasma cell dyscrasias are available at NCCN.org. The NCCN Guidelines are updated annually or sometimes more often, if new high-quality clinical data become available. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient to provide optimal care.

Text cont. on page 246.

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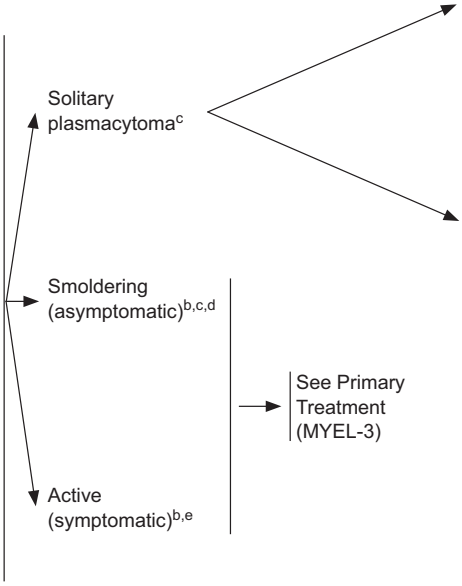
INITIAL DIAGNOSTIC WORKUP

- History and physical exam
- CBC, differential, platelet count
- Serum BUN/creatinine, electrolytes, albumin, and calcium
- Serum LDH and beta-2 microglobulin
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Metaphase cytogenetics on bone marrow
- Plasma cell FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 amplification]

Useful Under Some Circumstances

- Whole body low-dose CT scan
- Whole body MRI or whole body PET/CT scan[a]
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Bone densitometry
- Plasma cell proliferation
- Staining of marrow and fat pad for amyloid
- Serum viscosity
- HLA typing

CLINICAL PRESENTATION



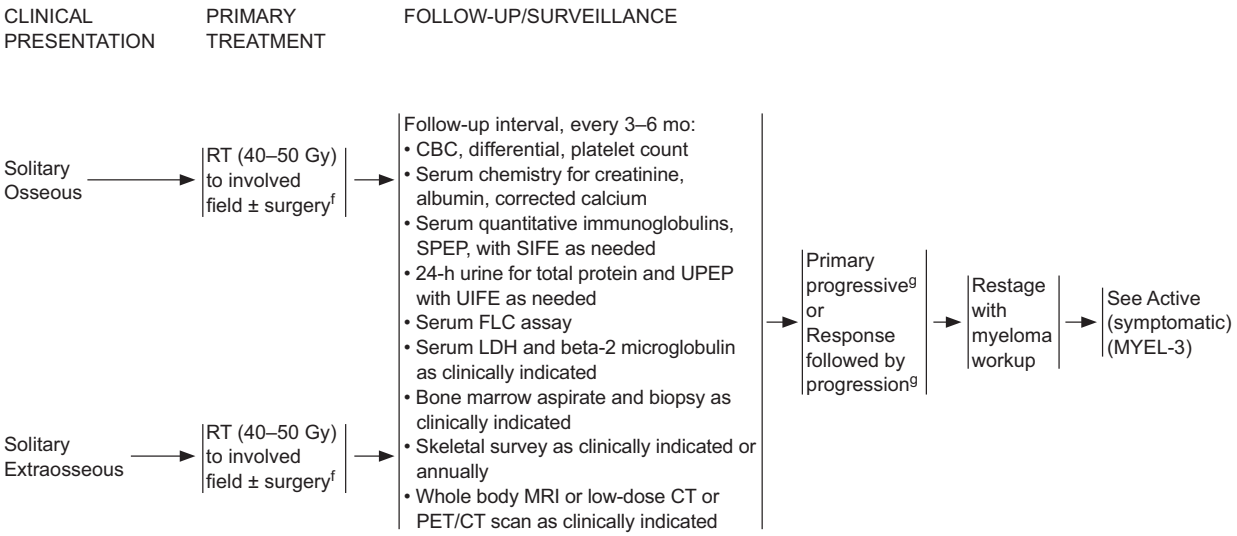
[a]Additional testing (whole body MRI or whole body PET/CT scan) is recommended to discern active from smoldering myeloma, if skeletal survey is negative. Recommendations for MRI are with contrast

[b]See Smoldering Myeloma (Asymptomatic) (MYEL-A).

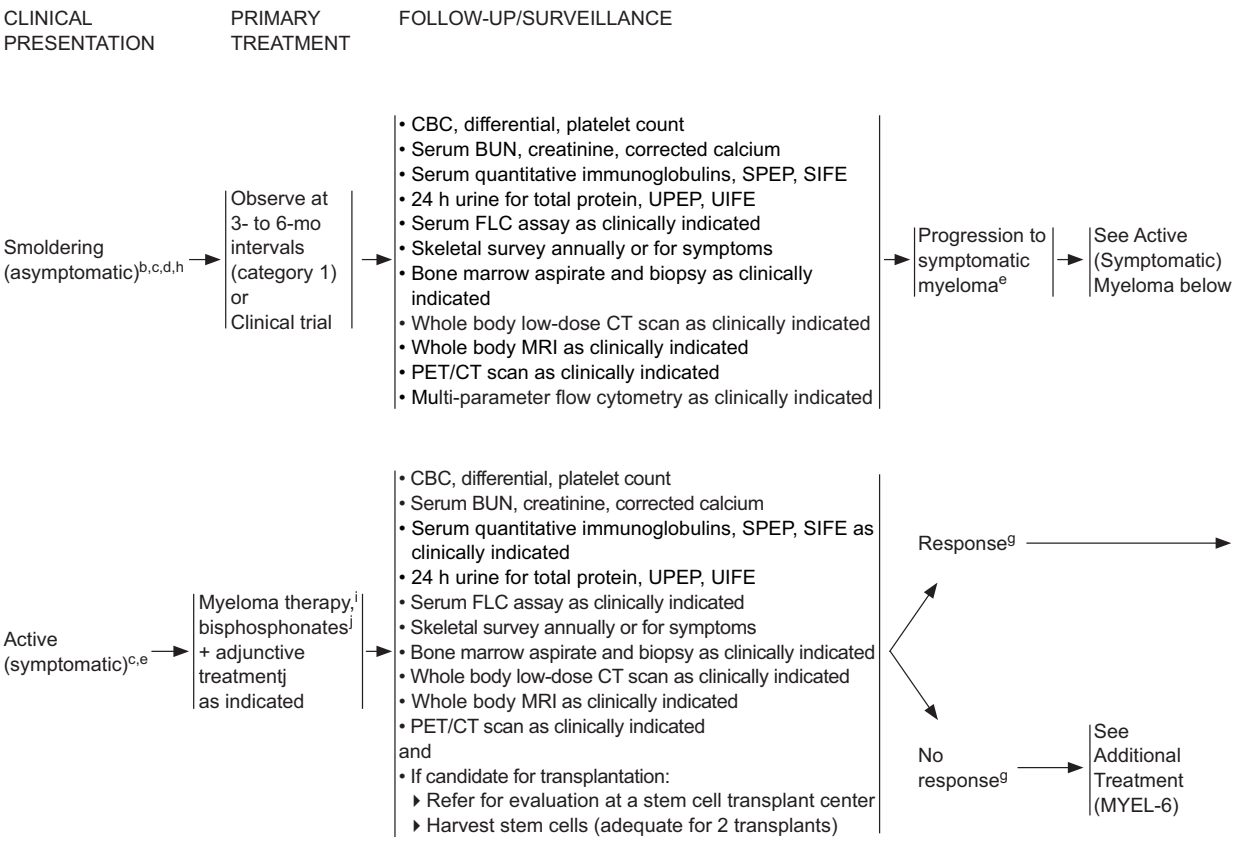
[c]See Staging Systems for Multiple Myeloma (MYEL-B).

[d]Includes Durie-Salmon Stage I Myeloma.

[e]See Active (Symptomatic) Myeloma (MYEL-A).



[f]Consider surgery if structurally unstable or if there are neurological compression issues.
[g]See Response Criteria for Multiple Myeloma (MYEL-C).



[b]See Smoldering Myeloma (Asymptomatic) (MYEL-A).

[c]See Staging Systems for Multiple Myeloma (MYEL-B).

[d]Includes Durie-Salmon Stage I Myeloma.

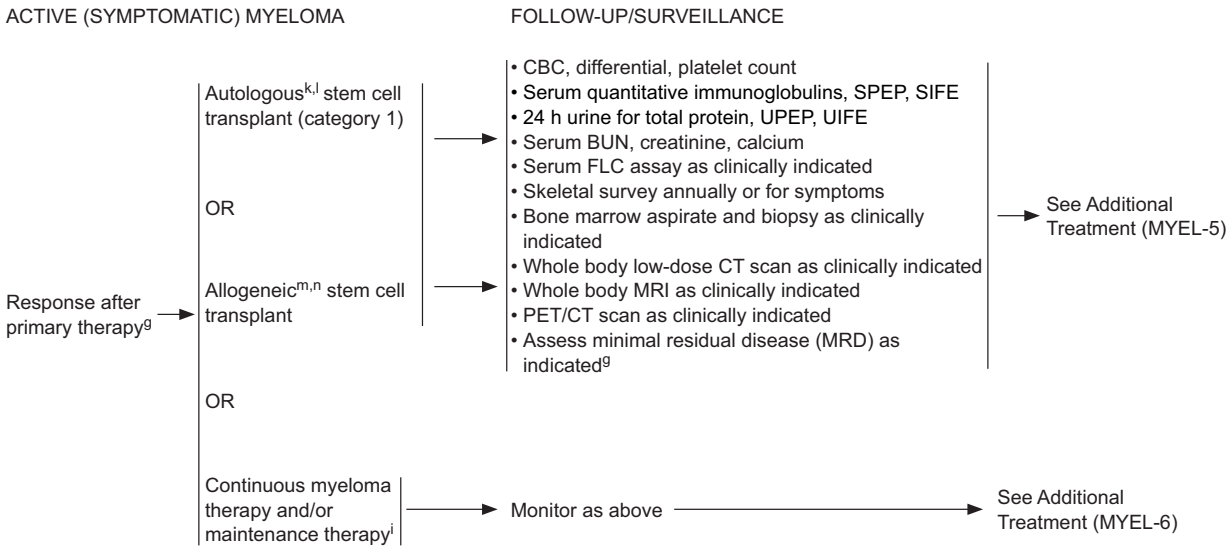
[e]See Active (Symptomatic) Myeloma (MYEL-A).

[g]See Response Criteria for Multiple Myeloma (MYEL-C).

[h]A relatively small randomized prospective study has shown benefit of early treatment with lenalidomide and dexamethasone for a subset of patients with smoldering myeloma with certain high-risk features predictive for early clinical progression (Mateos MV, Hernandez M, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-447). However, the high-risk criteria specified in the study are not in common use. Alternative criteria are under investigation (Dispienzeri A, Kyle R, Katzmann J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood 2008;111:785-789). The NCCN panel strongly recommends enrolling eligible smoldering myeloma patients with high-risk criteria in clinical trials.

[i]See Myeloma Therapy (MYEL-D).

[j]See Adjunctive Treatment (MYEL-E).



[g]See Response Criteria for Multiple Myeloma (MYEL-C).

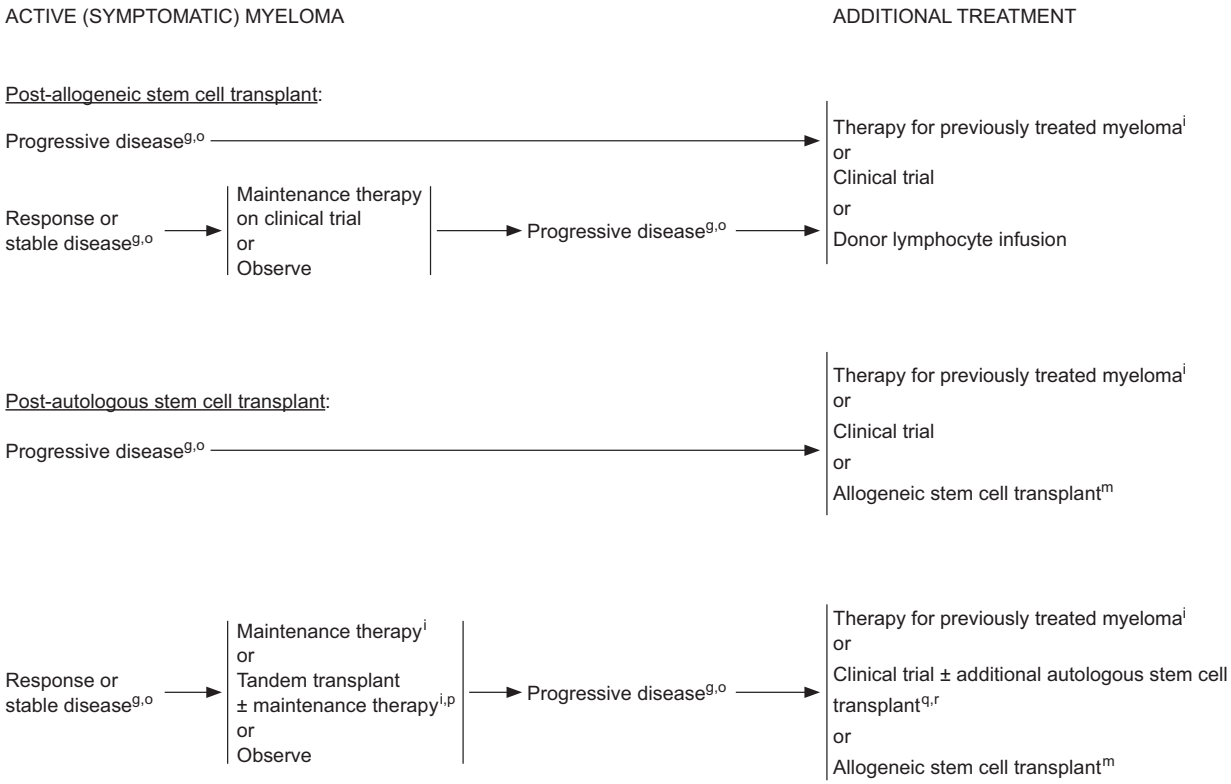
[i]See Myeloma Therapy (MYEL-D).

[k]Autologous transplantation: Category 1 evidence supports proceeding straight after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant. (See Discussion section).

[l]Renal dysfunction and advanced age are not contraindications to transplant.

[m]Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative, preferably in a clinical trial. Current data do not support miniallografting alone.

[n]A prospective trial by Bruno et al found improved survival for patients receiving an autologous transplant followed by non-myeloablative allograft compared to patients who received tandem autologous grafts. In contrast, the IFM trial (99-03) and the BMT-CTN 0102 trial reported no overall survival or progression-free survival with autologous transplant followed by mini-allograft in high-risk myeloma patients. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007;356:1110-1120.
Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006;107:3474-3480.
Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol 2011;12:1195-1203.
Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. J Clin Oncol 2011;29:3016-3022.



[g]See Response Criteria of Multiple Myeloma (MYEL-C).

[i]See Myeloma Therapy (MYEL-D).

[m]Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.

[o]Response to treatment as determined by the follow-up tests listed on MYEL-4.

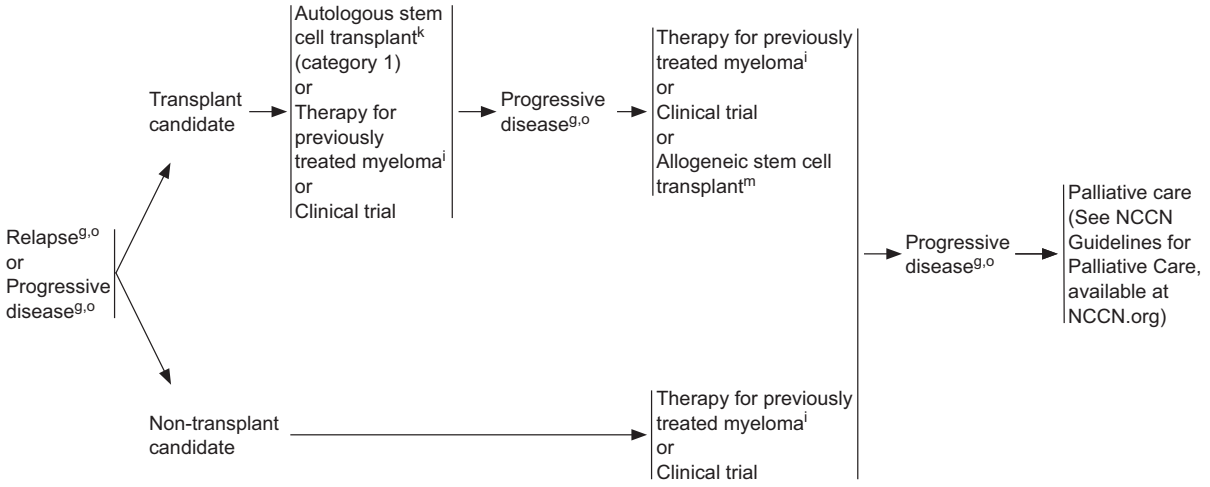
[p]There is evidence from a randomized, phase III trial showing that maintenance therapy after tandem transplant significantly reduced the risk of disease progression (HR, 0.47). Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 2014;371:895-905.

[q]Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression.

[r]Retrospective studies suggest a 2–3 y minimum length of remission for consideration of a second autologous stem cell transplant for salvage therapy (category 2B).

ACTIVE (SYMPTOMATIC) MYELOMA

ADDITIONAL TREATMENT
(FOR PATIENTS TREATED WITH OR WITHOUT A PRIOR TRANSPLANT)



[g]See Response Criteria for Multiple Myeloma (MYEL-C).

[i]See Myeloma Therapy (MYEL-D).

[k]Autologous transplantation: Category 1 evidence supports proceeding straight after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival although progression-free survival can be prolonged by an early transplant. (See Discussion section)

[m]Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.

[o]Response to treatment as determined by the follow-up tests listed on MYEL-4.

DEFINITION OF MULTIPLE MYELOMA (SMOLDERING AND ACTIVE)

Smoldering (Asymptomatic) Myeloma[1,2]

- Serum monoclonal protein
  - IgG or IgA ≥3 g/dL;

Or

- Bence-Jones protein ≥500 mg/24 h

And/Or

- Clonal bone marrow plasma cells 10%–60%

And

- Absence of myeloma-defining events or amyloidosis
  - If skeletal survey negative, assess for bone disease with whole body MRI or PET/CT

Active (Symptomatic) Myeloma[2,3]

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

And

Any one or more of the following myeloma-defining events:

- 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 >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min
- Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)
- One or more osteolytic bone lesions on skeletal radiography, CT, or PET/CT
- Clonal bone marrow plasma cells ≥60%
- Abnormal serum FLC ratio ≥100 (involved kappa) or ≤0.01 (involved lambda)
- >1 focal lesions on MRI studies ≥5 mm

[1]The understanding of smoldering (asymptomatic) myeloma is evolving rapidly. Some studies have shown that patients with certain characteristics, including IgG levels of >3 g/dL, IgA of >2 g/dL, or urinary Bence Jones protein of >1 g/24 h (Mateos MV, Hernandez M, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-447) or abnormal free light chain ratios (Dispienzeri A, Kyle R, Katzmann J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood 2008;111:785-789) have an increased risk of progression to active (symptomatic) myeloma. It is also increasingly recognized that the classical definition of smoldering myeloma using certain tests such as plain x-rays is outdated. Efforts to modify these criteria and reclassify some patients previously classified as "asymptomatic" to having "active disease" are underway.

[2]Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538-548.

[3]Other examples of active disease include: repeated infections, amyloidosis, or hyperviscosity.

MYEL-A

STAGING SYSTEMS FOR MULTIPLE MYELOMA[1]

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta-2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by iFISH[2] and Serum LDH ≤ the upper limit of normal
II	Not ISS stage I or III	Not R-ISS stage I or III
III	Serum beta-2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by iFISH[2] or Serum LDH > the upper limit of normal

Return to Clinical Presentation (MYEL-1)

[1]Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 2015;33:2863-2869.

[2]Standard-risk: No high-risk chromosomal abnormality. High-risk: presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).

RESPONSE CRITERIA FOR MULTIPLE MYELOMA
(Revised based on the new criteria by International Myeloma Working Group [IMWG])

IMWG criteria for response assessment including criteria for minimal residual disease (MRD)	
Response Category	Response Criteria
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)[†]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[‡] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10^5 nucleated cells[§] or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue[¶]
Standard IMWG response criteria[‖]	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)[††]
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)[§§] of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in SPD[§§] of soft tissue plasmacytomas is also required

(Table continues on the next page)

RESPONSE CRITERIA FOR MULTIPLE MYELOMA
(Revised based on the new criteria by International Myeloma Working Group [IMWG])

Response Category	Response Criteria
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease[¶¶,||||]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD[§§] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[§§] of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia) (see above)
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

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(Footnotes on next page)

*All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

†Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡Bone marrow MFC should follow NGF guidelines. The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilised mixture of antibodies, which reduces errors, time, and costs. Five million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10 plasma cells. Paiva B, Gutierrez NC, Rosinol L, et al, for the GEM (Grupo Españolde MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood 2012; 119: 687–91.

§DNA sequencing assay on bone marrow aspirate should use a validated assay.

¶Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma Criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax = 2.5 within osteolytic CT areas >1 cm in size, or SUVmax = 1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS. Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma.Clin Cancer Res 2015; 21: 4384–90.

‖Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response. Durie BG, Harousseau JL, Miguel JS, et al, for the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467–73.

**All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated serum FLC assay.

††Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

¶¶Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

‖‖In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

MYEL-C
3 OF 3

MYELOMA THERAPY[1-4]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

Primary Therapy for Transplant Candidates (assess for response after 2 cycles)	
Preferred Regimens:	Other Regimens:
• Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide[5]/dexamethasone (category 1)	• Bortezomib/dexamethasone (category 1)[6] • Bortezomib/thalidomide/dexamethasone (category 1) • Carfilzomib[9,10]/lenalidomide[5]/dexamethasone • Ixazomib/lenalidomide[5]/dexamethasone • Lenalidomide[5]/dexamethasone (category 1)[6]
Primary Therapy for Non-Transplant Candidates (assess for response after 2 cycles)	
Preferred Regimens	Other Regimens
• Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[6,7]	• Bortezomib/dexamethasone[6] • Carfilzomib[10]/lenalidomide/dexamethasone (category 2B) • Ixazomib/lenalidomide/dexamethasone
Maintenance Therapy	
• Bortezomib • Lenalidomide[8] (category 1)	

[1]Selected, but not inclusive of all regimens.

[2]Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.

[3]Subcutaneous bortezomib is the preferred method of administration for patients with pre-existing or high-risk peripheral neuropathy.

[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.

[5]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.

[6]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

[7]Continuously until progression. Facon T, Dimopoulos MA, Dispenzieri A, et al. Continuous lenalidomide and low-dose dexamethasone demonstrates a significant PFS and OS advantage in transplant ineligible NDMM patients. The FIRST: MM-020/IFM0701 [oral]. Oral presentation presented at the 55th Annual Meeting of the American Society of Hematology (ASH) 2013; December 7-10; New Orleans, Louisiana.

[8]There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

[9]Optimal dosing in this regimen has not been defined.

[10]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

MYELOMA THERAPY[1-4,11]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplants.

Therapy for Previously Treated Multiple Myeloma	
Preferred Regimens:	Other Regimens:
• Repeat primary induction therapy (if relapse at >6 mo) • Bortezomib/dexamethasone (category 1)[6] • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Carfilzomib[10]/dexamethasone (category 1)[6] • Carfilzomib[10]/lenalidomide/dexamethasone (category 1)[12] • Daratumumab[13,14] • Daratumumab[14]/bortezomib/dexamethasone (category 1) • Daratumumab[14]/lenalidomide/dexamethasone (category 1) • Elotuzumab[15]/lenalidomide/dexamethasone (category 1)[12] • Ixazomib[16]/lenalidomide/dexamethasone (category 1)[12] • Lenalidomide/dexamethasone[17] (category 1)[6] • Pomalidomide[18]/dexamethasone[17] (category 1)[6] • Pomalidomide[18]/bortezomib/dexamethasone • Pomalidomide[18]/carfilzomib[10]/dexamethasone	• Bendamustine • Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1)[6] • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[19] • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)[19] • Elotuzumab/bortezomib/dexamethasone • High-dose cyclophosphamide • Ixazomib[16]/dexamethasone[6] • Panobinostat[20]/bortezomib/dexamethasone (category 1) • Panobinostat[20]/carfilzomib[6,10] • Pomalidomide[18]/cyclophosphamide/dexamethasone

[1]Selected, but not inclusive of all regimens.

[2]Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.

[3]Subcutaneous bortezomib is the preferred method of administration for patients with pre-existing or high-risk peripheral neuropathy.

[4]Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.

[6]Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, elderly or frail patients may be treated with doublet regimens.

[11]Consideration for appropriate regimen is based on the context of clinical relapse.

[10]Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

[12]Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.

[13]Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.

[14]May interfere with serological testing and cause false-positive indirect Coombs test.

[15]Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.

[16]Indicated for the treatment of patients who have received at least one prior therapy.

[17]Consider single-agent lenalidomide or pomalidomide for steroid-intolerant individuals.

[18]Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.

[19]Generally reserved for the treatment of aggressive multiple myeloma.

[20]Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.

MYEL-D
2 OF 2

ADJUNCTIVE TREATMENT

Bone Disease
- Bisphosphonates (pamidronate and zoledronic acid)[1]
  - All patients receiving primary myeloma therapy should be given bisphosphonates (category 1)
    - A dental exam is recommended before starting bisphosphonate therapy
  - Use of bisphosphonates in smoldering or stage I disease preferably in the context of a clinical trial. These patients should have skeletal survey annually and if symptomatic
  - Monitor for renal dysfunction with use of bisphosphonates
  - Monitor for osteonecrosis of the jaw
- RT
  - Low-dose RT (10–30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or for impending cord compression
  - Limited involved fields should be used to limit the impact of irradiation on stem-cell harvest or impact on potential future treatments
- Orthopedic consultation should be sought for impending or actual long-bone fractures or bony compression of spinal cord or vertebral column instability
- Consider vertebroplasty or kyphoplasty for symptomatic vertebral compression fractures

Hypercalcemia
- Hydration/furosemide, bisphosphonates (zoledronic acid preferred), steroids, and/or calcitonin

Hyperviscosity
- Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity

Anemia
- See NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia (available at NCCN.org)
- Consider erythropoietin for anemic patients

Infection
- See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (available at NCCN.org)
- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection
- Consider pneumococcal polysaccharide vaccine and influenza vaccine
- *Pneumocystis jiroveci pneumonia* (PJP), herpes, and antifungal prophylaxis if high-dose dexamethasone regimen
- Herpes zoster prophylaxis for patients treated with proteasome inhibitors

Renal Dysfunction
- Maintain hydration to avoid renal failure
- Avoid use of NSAIDs
- Avoid IV contrast
- Plasmapheresis (category 2B)
- Not a contraindication to transplant
- Monitor for renal dysfunction with chronic use of bisphosphonates

Coagulation/Thrombosis
- Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
- See NCCN Guidelines for Venous Thromboembolic Disease (available at NCCN.org)

[1]Both pamidronate and zoledronic acid have shown equivalence in terms of reducing risk of skeletal-related events in randomized trials. In a recent MRC IX trial, in addition to benefits for bone health, zoledronic acid reduced mortality by 16% versus clodronic acid and extended median overall survival by 5.5 months. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomized controlled trial. Lancet 2010;376:1989-1999.

MYEL-E

Cont. from page 231.

Initial Diagnostic Workup

Initial diagnostic workup in all patients should include a history and physical examination and the following baseline blood studies and biological assessments to differentiate symptomatic and asymptomatic MM: a CBC with differential and platelet counts, blood urea nitrogen (BUN), serum creatinine and serum electrolytes, serum calcium, albumin, lactate dehydrogenase (LDH), and beta-2 microglobulin. Increased BUN and creatinine levels indicate decreased kidney function, whereas LDH and beta-2 microglobulin levels reflect tumor cell burden.

The monoclonal protein (M-protein) components in serum and urine are evaluated by the urine and serum analyses. Urine analysis as a part of the initial diagnostic workup includes evaluating 24-hour urine for total protein, urine protein electrophoresis, and urine immunofixation electrophoresis.

Serum analysis includes quantitative immunoglobulin levels (IgG, IgA, and IgM), serum protein electrophoresis, and serum immunofixation electrophoresis to obtain more specific information about the type of M-protein present. Assessing changes and proportions of various proteins, particularly the M-protein, helps track disease progression and response to treatment. Use of serum free light chain (FLC) assay along with serum protein electrophoresis and serum immunofixation electrophoresis yields high sensitivity while screening for MM and related plasma cell disorders.[8] Therefore, this assay is now included as part of the initial diagnostic workup in the NCCN Guidelines for MM. The serum FLC assay also has prognostic value in plasma cell disorders, including monoclonal gammopathy of undetermined significance, smoldering myeloma, active myeloma, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.[8,9] The serum FLC assay also allows for quantitative monitoring of patients with light chain amyloidosis and oligosecretory myeloma. In addition to all of the aforementioned, the FLC ratio is required for documenting stringent complete response (CR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.[10] The FLC assay cannot replace the 24-hour urine protein electrophoresis for monitoring patients with measurable urinary M-proteins.

Most patients have serum M-protein with or without associated urinary M-protein. In the *Mayo Clinic* review of 1,027 patients newly diagnosed with MM, 20% had secretory urinary M-proteins; however, 3% had neither serum nor urine M-protein and therefore had nonsecretory myeloma.[11] The serum FLC assay is useful to monitor disease response and progression in a proportion of patients with nonsecretory myeloma. After the myeloma or M-protein is quantified, it is important to use the same test for serial studies to ensure accurate relative quantification.

To evaluate bone marrow plasma cell infiltration, bone marrow aspiration and biopsy is recommended to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells. To evaluate lytic bone lesions, full skeleton radiographic survey or whole-body, low-dose CT is recommended.

Although MM may be morphologically similar, several subtypes of the disease have been identified at the genetic and molecular level. Bone marrow studies at initial diagnosis should include chromosome analysis by metaphase cytogenetics and fluorescence in situ hybridization (FISH) should be performed with the plasma cells obtained from the bone marrow aspiration. Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications.

Deletion of 17p13 (the locus for the tumor-suppressor gene, p53) leads to loss of heterozygosity of *TP53* and is considered a high-risk feature in MM.[12–14] Other high-risk chromosomal aberrations in MM are characterized by structural changes that include specific rearrangements involving the *IGH* gene (encoding immunoglobulin heavy chain) located at 14q32. Several subgroups of patients are identified on the basis of 14q32 translocations. The 3 main translocations are t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23). Several studies have confirmed that patients with t(4;14) and t(14;16) have a poor prognosis, although t(11;14) is believed to impart no increased risk.[15–17] Del13q is a common abnormality observed on FISH studies, but is a negative prognostic factor only when observed on metaphase cytogenetics.

Abnormalities of chromosome 1 are also among the frequent chromosomal alterations in MM[18]; the short arm is most often associated with deletions and the long arm with amplifications.[19] Gains/amplification of 1q21 increases the risk of MM progression and incidence of the amplification is higher in relapsed than in patients with newly diagnosed disease.[18,20]

Stratification of patients into various risk groups based on chromosomal markers is being utilized by some centers for prognostic counseling, selection, and sequencing of therapy approaches.[21,22] According to the NCCN Multiple Myeloma Panel members, the FISH panel for prognostic estimation of plasma cells should include, at the minimum, probes for t(4;14), t(14;16), 17p13 deletions, and chromosome 1 amplification. The utility of this information is to determine biological subtype and for prognostic recommendations.

In addition to cytogenetic markers of prognosis, it is postulated that biological factors or gene expression signatures may be capable of discerning prognosis and helping rational therapeutic decisions.[23,24] Further understanding of the molecular subtypes of MM is emerging from the application of high-throughput genomic tools such as gene expression profiling (GEP).[25] With the currently available novel treatment approaches, a majority of patients with MM can now anticipate long-term disease control. However, patients with cytogenetically and molecularly defined high-risk disease do not receive the same benefit from certain approaches as low-risk patients and need alternative therapies. GEP is a powerful and fast tool with the potential to provide additional prognostic value to further refine risk stratification, help therapeutic decisions, and inform novel drug design and development. Several groups have identified and developed 15-gene, 70-gene, and 92-gene models based on GEP signatures of MM cells.[26–28] Studies show that patients in the high-risk group based on the 15-gene,[26] 70-gene,[27] or 92-gene[28] models had shorter survival compared with the low-risk group. The NCCN panel unanimously agreed that although GEP is not currently routinely used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate disease aggressiveness and individualize treatment.

Bone marrow immunohistochemistry may be useful in some cases to confirm presence of monoclonal plasma cells and to more accurately quantify plasma cell involvement; bone marrow flow cytometry can help in certain situations.

Additional Diagnostic Tests

The NCCN panel recommends additional tests that may be useful under some circumstances, and include whole-body MRI[29] or whole-body PET/CT scan.[30] Active myeloma is positive on PET scan.[31,32] PET/CT and MRI scans are more sensitive than plain radiographs and are indicated when symptomatic areas show no abnormality on routine radiographs. FDG PET/CT results after induction therapy and stem cell transplant (SCT) help in predicting the prognosis of patients with symptomatic MM.[33,34]

A tissue biopsy may also be necessary to confirm the presence of plasmacytomas. Plasma cell proliferation assays may be helpful to identify the fraction of proliferating myeloma cell population.[35] Also, bone marrow and fat pad staining for the presence of amyloid should be considered if amyloidosis is suspected and serum viscosity should be evaluated, particularly in those with high levels of M-protein.

In selected patients with MM, allogeneic transplantation may be considered. In this approach, myeloablative or nonmyeloablative/reduced-intensity therapy is administered with an infusion of stem cells (ie, peripheral blood or bone marrow) obtained from a donor, preferably an HLA-identical sibling. In such cases, the patient will need to be HLA-typed.

Because bisphosphonate therapy is a consideration in patients with MM, a baseline bone densitometry test may be recommended.

Diagnostic Categories

Based on the results of the clinical and laboratory evaluation discussed in prior sections, patients are initially classified as either having smoldering (asymptomatic) disease or active (symptomatic) disease (for definitions of these, see page MYEL-A [page 238]).

The IMWG recently updated the disease definition of MM to include biomarkers in addition to existing requirements of CRAB features[36]; the CRAB criteria that define MM include hypercalcemia (>11.5 mg/dL), renal insufficiency (creatinine >2 mg/dL or creatinine clearance <40 mL/min), anemia (hemoglobin <10 g/dL or 2 g/dL < normal), and the presence of bone lesions. The IMWG has also clarified that presence of ≥1 osteolytic lesions seen on skeletal radiography, whole-body MRI, or whole-body PET/CT fulfills the criteria for bone disease.[36] The MM-defining biomarkers identified by the IMWG include ≥1 of the following: ≥60% clonal plasma cells in the bone marrow; involved/uninvolved FLC ratio of ≥100 with the involved

FLC being ≥100 mg/L; or MRI with ≥1 focal lesion (involving bone or bone marrow).[36]

The IMWG criteria for a diagnosis of smoldering (asymptomatic) myeloma include serum M-protein (IgG or IgA) ≥30 g/L and/or clonal bone marrow plasma cells 10% to 60% *and* absence of myeloma-defining events or amyloidosis.[36] The updated IMWG diagnostic criteria for MM allow initiation of therapy before end-organ damage on the basis of specific biomarkers, and also allow the use of sensitive imaging criteria to diagnose MM, including PET/CT and MRI.[36]

Those with active myeloma can be staged using either the Durie-Salmon staging system or the International Staging System (ISS).[37] The ISS is based on easily obtained laboratory measures (serum beta-2 microglobulin and serum albumin) and is easier to use than the Durie-Salmon staging system for patients with previously untreated MM. The ISS has been recently revised to incorporate the serum LDH and high-risk FISH abnormalities [t(4;14), t(14;16), 17p13 deletion].[38]

Response Criteria

Assessing the response to treatment is a key determinant of myeloma treatment. The IMWG response criteria were developed from the European Society for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (EBMT/IBMTR/ABMTR) response criteria,[39] with revisions and improvements to help uniform reporting.

The updated IMWG response criteria definitions[10,40,41] for CR, stringent CR, immunophenotypic CR, molecular CR, very good partial response (VGPR), partial response (PR), minimal response for relapsed/refractory myeloma, stable disease, and progressive disease (PD) are outlined on pages 240–242 (MYEL-C). The response criteria has recently been updated to include measures of minimal residual disease (MRD) assessments. It is recommended that the IMWG uniform response criteria should be used in future clinical trials.[42]

Active (Symptomatic) MM

Primary Therapy for Active (Symptomatic) MM

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and, in selected patients, primary therapy is followed by high-dose chemotherapy with autologous stem cell support. Research into various primary regimens has focused on improving the response rates and depth of response in both transplant and non-transplant candidates. The panel members have noted that it is important to assess for response to primary therapy after 1 to 2 cycles of therapy.

Stem cell toxins, such as nitrosoureas or alkylating agents, may compromise stem cell reserve, and regimens with these agents (notably melphalan) should be avoided in patients who are potential candidates for SCT. Therefore, one of the first steps in evaluating patients with advanced MM is to determine whether they are candidates for high-dose therapy and transplant, based on age and comorbidities. However, it should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant. It is also important to consider supportive care for all patients at diagnosis. For example, 80% of patients have bone disease and up to 33% have renal compromise. Proteosome inhibitor–based regimens may be of value in patients with renal failure and in those with certain adverse cytogenetic features.[43]

Bone disease, renal dysfunction, and other complications such as hypercalcemia, hyperviscosity, and coagulation/thrombosis should be treated with appropriate adjunctive measures (see "Adjunctive Treatment for MM," page 262). In all patients, careful attention to supportive care is critical to avoid early complications that may compromise therapeutic outcome.

"Myeloma Therapy" on MYEL-D, page 243 and 244, has a list of primary therapy regimens recommended by the NCCN panel for transplant and non-transplant candidates and also lists recommended drugs for maintenance therapy. The list is selective and is not inclusive of all regimens. The NCCN panel has categorized all myeloma therapy regimens as "preferred" or "other." The purpose of classifying regimens as such is to convey the sense of the panel regarding the relative efficacy and toxicity of the regimens. Factors considered by the panel include the efficacy, toxicity, and treatment schedules of the regimens.

The NCCN panel prefers 3-drug regimens over 2-drug regimens as the standard of care for primary treatment of myeloma. This is based on improved re-

sponse rates, depth of response, and rates of progression-free survival (PFS) and overall survival (OS) seen with 3-drug regimens in clinical trials. However, the panel notes that doublets could be used if a patient is elderly and/or frail and unable to tolerate a 3-drug regimen.

Regimens no longer considered the current standard of care for patients with MM, either due to concerns of toxicity and/or the availability of more effective regimens, were removed from the list of treatment options in the NCCN Guidelines. For SCT candidates, these regimens include: thalidomide/dexamethasone, dexamethasone as a single agent, and liposomal doxorubicin/vincristine/dexamethasone (DVD). For non-transplant candidates, the regimens no longer recommended include all melphalan-containing regimens, thalidomide/dexamethasone, DVD, and vincristine/doxorubicin/dexamethasone (VAD). Melphalan-based regimens can lead to significant cytopenias and may limit subsequent use of the newer drugs.

Prophylaxis with full-dose aspirin is recommended for those receiving an IMiD-based therapy. An anticoagulation agent is recommended for patients receiving an IMiD-based therapy and who are at high risk for thrombosis. Prophylactic antiviral therapy is recommended for all patients receiving proteosome inhibitor–based therapies,[44,45] because impaired lymphocyte function that results from MM and/or its treatment-related myelosuppression may lead to reactivation of herpes simplex infection or herpes zoster.[45–48]

Carfilzomib can potentially cause cardiac and pulmonary toxicities.[49] Careful assessment before initiating treatment with carfilzomib and close monitoring during treatment is recommended.[49]

Preferred Primary Therapy Regimens for Transplant Candidates: Bortezomib-based 3-drug regimens have been listed as preferred primary therapy options for patients who are SCT eligible; these regiments include bortezomib/lenalidomide/dexamethasone, bortezomib/doxorubicin/dexamethasone, and bortezomib/cyclophosphamide/dexamethasone.

The NCCN panel noted that subcutaneous administration is the preferred route for bortezomib, based on the results of the MMY-3021 trial. The trial randomized 222 patients to single-agent bortezomib administered either by the conventional intravenous route or by subcutaneous route.[50] The findings from the study demonstrate noninferior efficacy with subcutaneous versus intravenous bortezomib with regard to the primary end point (overall response rate [ORR] after 4 cycles of single-agent bortezomib); consistent results were shown with regard to secondary end points.[50] The results showed no significant differences in terms of time to progression or in one-year OS between groups.[50,51] However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy (PN). The panel recommends herpes prophylaxis in patients receiving bortezomib therapy.

The NCCN panel recommends harvesting peripheral blood early in the course of primary treatment, preferably after 3 to 4 cycles of initial therapy.

Bortezomib/Lenalidomide/Dexamethasone: Results from phase II and III studies have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is active and well-tolerated in all newly diagnosed patients with MM, transplant eligible, and transplant ineligible.[52–54]

In the first phase I/II prospective study of bortezomib/lenalidomide/dexamethasone in patients with newly diagnosed MM, the rate of PR was 100%, with 74% VGPR or better and 52% CR/near CR.[52] The benefits of bortezomib/lenalidomide/dexamethasone as primary therapy were also seen in the results of the phase II IFM2008 trial[54] and phase II EVOLUTION trial.[53] In the phase II IFM2008 trial, patients received bortezomib/lenalidomide/dexamethasone as induction therapy followed by SCT.[54] Patients subsequently received 2 cycles of bortezomib/lenalidomide/dexamethasone as consolidation cycles and 1-year lenalidomide maintenance. VGPR rate or better at the completion of induction was 58%.[54] After transplantation and consolidation therapy the rate of VGPR or better was 70% and 87%, respectively.[54] The phase II EVOLUTION trial was designed to examine the tolerability and efficacy of combining bortezomib/cyclophosphamide/lenalidomide/dexamethasone versus bortezomib/lenalidomide/dexamethasone versus bortezomib/cyclophosphamide/dexamethasone (CyBorD) in a randomized multicenter setting.[53] The ORR after primary treatment with bortezomib/lenalidomide/dexamethasone followed by maintenance with bortezomib was 85% (51% ≥VGPR; 24% CR) and corresponding 1-year

PFS was 83% in the bortezomib/lenalidomide/dexamethasone arm.[53]

This triplet was compared to lenalidomide and dexamethasone in the multicenter phase III SWOG S077 trial.[55] Patients (n=525) with previously untreated MM were randomly assigned to receive 6 months of induction therapy with either bortezomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone each followed by maintenance therapy with lenalidomide/dexamethasone until progression or unacceptable toxicity. At a median follow-up of 55 months, treatment with bortezomib/lenalidomide/dexamethasone compared with lenalidomide/dexamethasone resulted in higher rates of ORR (82% vs 72%) and CR (16% vs 8%), superior median PFS (median, 43 vs 30 months; hazard ratio [HR], 0.71; 95% CI, 0.56–0.91), and improved OS (median, 75 vs 64 months; HR, 0.71; 95% CI, 0.52–0.97). As expected, grade 3 or higher neuropathy was more frequent in the bortezomib-containing arm (24% vs 5%; *P*<.0001).[55]

The NCCN panel included the bortezomib/lenalidomide/dexamethasone regimen as a category 1 recommendation for the primary treatment of transplant-eligible patients with MM.

Bortezomib/Cyclophosphamide/Dexamethasone: Data from 3 phase II studies involving newly diagnosed patients with MM have demonstrated high response rates with CyBorD as primary treatment.[53,56,57] The trial by Reeder et al[56] conducted in the United States and Canada showed an ORR of 88%, including rates of VGPR or greater of 61% and CR/near CR of 39% with CyBorD as the primary regimen. The depth of response seen after primary treatment was maintained after transplant in those who underwent transplantation (70% rates of CR/near CR; rate of at least VGPR or better was 74%).[56] According to the long-term follow-up analysis, the 5-year PFS and OS rates were 42% (95% CI, 31–57) and 70% (95% CI, 59–82).[58]

Analysis of the German DSMM XIa study also demonstrated high responses with CyBorD as primary treatment (ORR, 84%; PR, 74%; CR, 10%). High response rates were seen in patients with unfavorable cytogenetics.[57] In updated results of the phase II EVOLUTION study, primary treatment with CyBorD demonstrated an ORR of 75% (CR, 22%; ≥VGPR, 41%) and the 1-year PFS rate was 93%.[53]

Based on data from these and other phase II studies, the NCCN panel included the combination of cyclophosphamide/bortezomib/dexamethasone as a category 2A recommendation to the list of primary treatment options available for transplant candidates.

Twice-weekly bortezomib can be associated with toxicities that may limit efficacy caused by treatment delays or discontinuation. Therefore, Reeder et al[59] modified the regimen to a once-weekly schedule. In the study, patients treated with weekly bortezomib achieved responses similar to the twice-weekly schedule (ORR, 93% vs 88%; VGPR, 60% vs 61%, respectively). In addition, they experienced fewer grade 3/4 adverse events (37%/3% vs 48%/12%). Fewer dose reductions of bortezomib/dexamethasone were required in the modified schedule and neuropathy rates were the same in both cohorts, even though the total bortezomib dose per cycle was higher in the weekly versus the twice-weekly schedule (6.0 mg/m^2 vs 5.2 mg/m^2).[59]

Bortezomib/Doxorubicin/Dexamethasone: Updated results from the HOVON-65/GMMG-HD4 group phase III trial of newly diagnosed patients with stage II/III MM demonstrated high response rates after primary therapy with bortezomib/doxorubicin/dexamethasone (PAD) versus VAD, and this superior response rate (CR + near CR, 31% vs 15%; *P*<.001) was maintained after SCT, with a significantly higher ORR.[60] No unexpected toxicities occurred, and del(13q) did not have a significant impact on response. Response rates improved with bortezomib maintenance (34% vs 49%; *P*<.001).[60] After a median follow-up of 41 months, PFS in patients treated with PAD as primary therapy followed by SCT and bortezomib maintenance was 35 versus 28 months in patients treated with VAD followed by SCT and maintenance with thalidomide. Patients treated with PAD had a significantly better PFS (HR, 0.75; 95% CI, 0.62–0.90; *P*=.002).[60] OS was also found to be improved in the PAD arm (HR, 0.77; 95% CI, 0.60–1.00; *P*=.049). In high-risk patients presenting with increased creatinine >2 mg/dL, bortezomib significantly improved PFS from a median of 13 to 30 months (HR, 0.45; 95% CI, 0.26–0.78; *P*=.004) and OS from a median of 21 to 54 months (HR, 0.33; 95% CI, 0.16–0.65; *P*<.001). A benefit in terms of increased PFS was also observed in patients with deletion of 17p13.[60] The rate of grade 2 to 4 PN was higher in those treated with the

bortezomib-containing regimen versus VAD (40% vs 18%). In addition, newly developed grade 3 to 4 PN occurred in 8% of patients during thalidomide maintenance and 5% of patients during bortezomib maintenance.[60]

Based on data from the HOVON-65/GMMG-HD4 trial and the uniform consensus among the NCCN panel members, PAD was designated a category 1 recommendation for primary therapy for transplant-eligible patients with MM.

Other Primary Therapy Regimens for Transplant Candidates: Although triple-drug regimens remain the preferred primary therapy option for patients with MM, elderly or frail patients may be treated with regimens containing 2 drugs such as bortezomib/dexamethasone or lenalidomide/dexamethasone. Other regimens listed as primary therapy options for transplant-eligible patients include carfilzomib or ixazomib in combination with lenalidomide and dexamethasone.

Bortezomib/Dexamethasone: In the IFM cooperative group trial, 482 patients eligible for transplant were randomized to 1 of the 4 primary therapy arms: VAD (n=121) alone, VAD plus consolidation therapy with dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP; n=121); bortezomib/dexamethasone (n=121); or bortezomib/dexamethasone plus consolidation with DCEP (n=119).[61] The primary end point was assessing response rate after primary therapy. Investigators evaluated the response according to modified EBMT criteria,[39] including additional categories of near CR (CR but immunofixation-positive)[62] and VGPR (serum M-protein reduction ≥90%; urine light chain <100 mg/24 hours).[10] After primary therapy, the ORR (78.5% vs 62.8%) and rates of CR/near CR (14.8% vs 6.4%) and VGPR (37.7% vs 15.1%) were significantly higher with bortezomib/dexamethasone versus VAD.[61] At a median follow-up of 32.2 months, median PFS was modestly, but not statistically significantly, prolonged compared with VAD (36.0 vs 29.7 months).[61] Use of DCEP as consolidation therapy after primary therapy did not have a significant impact on the rates of response.[61] The bortezomib/dexamethasone regimen was equally effective in patients with high-risk MM, including those with ISS stage III disease and poor-risk cytogenetic abnormalities. The incidence of severe adverse events reported was similar between the 2 groups. Hematologic toxicity and deaths related to toxicity were more frequent with VAD versus bortezomib/dexamethasone. The rates of grade 2 (20.5% vs 10.5%) and grades 3 to 4 (9.2% vs 2.5%) PN during induction through first transplantation were significantly higher with bortezomib/dexamethasone compared with VAD.[61]

The IFM conducted a phase III randomized trial comparing bortezomib/dexamethasone with a combination of reduced doses of bortezomib and thalidomide plus dexamethasone.[63] Response rates achieved in the comparison bortezomib/dexamethasone arm in this study match those described in previous trials comparing VAD with bortezomib and dexamethasone.[61]

Patients with either t(4;14) or del(17p) are known to have a short event-free survival (EFS) and OS. A study analyzed a large series of patients (aged <65 years) with newly diagnosed transplant-eligible MM and t(4;14) or del(17p) treated with bortezomib/dexamethasone versus VAD as primary therapy before treatment.[43] The analysis demonstrated that bortezomib improves the prognosis (in terms of both EFS and OS; $P<.001$ and $P<.001$, respectively) of patients with t(4;14) compared with patients treated with VAD primary therapy.[43]

Based on these data and the uniform consensus among the NCCN panel, bortezomib/dexamethasone is listed as a category 1 primary therapy option for transplant-eligible patients with MM.

Lenalidomide/Dexamethasone: Lenalidomide is a potent analogue of thalidomide. Like thalidomide, it is believed to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis and inhibition of angiogenesis and cytokine circuits, among others. Lenalidomide received approval from the FDA for the treatment of relapsed/refractory MM in combination with dexamethasone. Lenalidomide and dexamethasone have also been investigated as primary therapy. The phase III randomized controlled study, S0232, by SWOG compared dexamethasone single agent with dexamethasone plus lenalidomide for patients newly diagnosed with MM.[64] This trial was halted at interim analysis and patients on dexamethasone alone were allowed to switch to lenalidomide/dexamethasone. The SWOG data and safety monitoring committee based its recommendation to permanently close enrollment based on the preliminary results from the ECOG phase III study (E4A03).[65] At the time the SWOG trial was halted, at the end of 1 year, the lenalidomide plus dexa-

methasone arm showed improved CR rate compared with dexamethasone alone (22.1% vs 3.8%).[64]

In an open-label trial, 445 newly diagnosed patients with MM were randomly assigned to high-dose or low-dose regimens. The response was superior with high-dose dexamethasone. A total of 169 (79%) of 214 patients receiving high-dose therapy and 142 (68%) of 205 patients on low-dose therapy had CR or PR within 4 cycles.[66] However, the high response rates did not result in superior time to progression, PFS, or OS compared with low-dose dexamethasone. The trial was stopped after 1 year. Patients on high-dose therapy were allowed to cross over to the low-dose arm because the OS rate was significantly higher in that arm. At 1-year interim analysis, the OS rate was 96% in the low-dose dexamethasone group compared with 87% in the high-dose group (P=.0002); 2-year OS was 87% versus 75%, respectively.

The cause of inferior OS with high-dose dexamethasone seems to be related to increased deaths caused by toxicity. In the first 4 months, 52% of patients on the high-dose regimen compared with 35% on the low-dose regimen had grade 3 or worse toxic effects, including DVT (26% vs 12%), infections including pneumonia (16% vs 9%), and fatigue (15% vs 9%). The 3-year OS rate of patients who received 4 cycles of primary treatment with either dose followed by autologous SCT was 92%, suggesting that lenalidomide and dexamethasone is a reasonable choice for primary therapy before SCT. However, it should be noted that the choice to proceed to SCT was not randomized but based on physician and patient preference.

The incidence of DVT is low with single-agent lenalidomide or lenalidomide plus low-dose dexamethasone, but risk increases when combined with high-dose dexamethasone. According to a recent report, patients treated with lenalidomide and high-dose dexamethasone that developed a venous thromboembolismdid not experience shorter OS or time to progression.[67] Prophylactic anticoagulation is recommended in patients receiving this therapy.[44,68]

A decrease in CD34-positive cells collected after prolonged lenalidomide treatment has been reported.[69,70] Guidelines by the IMWG suggest that patients treated with lenalidomide and dexamethasone should have stem cells collected within the first 4 cycles of therapy.[71] This inability to collect stem cells may be overcome by chemomobilization.[72] There are data indicating successful stem cell harvest with the addition of plerixafor when conventional mobilization methods fail.[73,74]

Lenalidomide/dexamethasone is listed as a category 1 primary treatment option in these NCCN Guidelines. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Bortezomib/Thalidomide/Dexamethasone: Thalidomide attacks multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others. The GIMEMA Italian Multiple Myeloma Network reported results of a phase III trial investigating bortezomib, thalidomide, and dexamethasone (n=241) versus thalidomide and dexamethasone (n=239) as primary therapy, followed by tandem autologous SCT with high-dose melphalan and then consolidation therapy with the same primary regimen.[75] The addition of bortezomib to thalidomide and dexamethasone significantly improved ORR after primary treatment. After primary therapy, CR/near CR was achieved in 73 patients (31%; 95% CI, 25.0–36.8) receiving bortezomib/thalidomide/dexamethasone, and 27 patients (11%; 95% CI, 7.3–15.4) on thalidomide/dexamethasone.[75] Rates of CR/near CR and VGPR or better continued to be significantly higher in the bortezomib/thalidomide/dexamethasone (VTD) group than in the thalidomide/dexamethasone group after the first and second autologous SCT, and subsequent consolidation therapy.[75] Patients receiving the bortezomib-containing regimen experienced grade 3/4 PN.

Data from a single-institution retrospective study are similar to the interim data from the GIMEMA trial.[76] The findings of this analysis demonstrate that ORR after primary therapy with bortezomib, thalidomide, and dexamethasone was 94% of the patients (32 of 34 patients showed some response, including a VGPR rate ≥56%).[76]

The results of the randomized phase III trial by the Spanish Myeloma Group (PETHEMA/GEM) also demonstrated a significantly higher CR rate with VTD as primary therapy overall (35% vs 14%; P=.001) and in patients with high-risk cytogenetics (35% vs 0%; P=.002).[77] The CR rate continued to be significantly higher after autologous SCT (46% vs 24%) in patients treated with VTD versus thalidomide/dexamethasone as primary therapy.[77]

The phase III IFM 2013-04 trial is evaluating 4 cycles of CyBorD versus 4 cycles of VTD as induction therapy before autologous SCT in patients (N=340) with newly diagnosed MM.[78] The results reported during the 2015 ASH meeting show that patients who received VTD as induction therapy experienced higher ORR (92.3%) compared with those who received CyBorD (84%). Those who received VTD had significantly greater VGPR (*P*=.04) and PR (*P*=.02) rates.[78] The hematologic toxicity was greater in CyBorD arm however higher rates of PN were reported in the VTD arm.[78]

VTD is listed as a primary treatment option (category 1) in the NCCN Guidelines. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Carfilzomib/Lenalidomide/Dexamethasone: Carfilzomib is a second-generation proteasome inhibitor that binds highly selectively and irreversibly to the proteasome. It is administered intravenously. Preclinical studies with carfilzomib show lack of neurodegeneration in vitro[79] and less neurotoxicity in animal studies.[80] Carfilzomib has demonstrated antimyeloma activity in patients with relapsed and/or refractory MM with an acceptable tolerability profile, including limited neuropathy after prolonged treatment.[81–83]

The safety and efficacy of carfilzomib in combination with lenalidomide and dexamethasone, as primary therapy for patients with MM, were evaluated in 2 single-arm trials.

First, a multicenter phase I/II trial evaluated the combination of carfilzomib/lenalidomide/dexamethasone in patients with newly diagnosed MM.[84] In this trial, patients (n=53) received carfilzomib with lenalidomide and low-dose dexamethasone. After 4 cycles, stem cells were collected from eligible patients.[84] Of 35 patients from whom stem cells were collected, 7 proceeded to transplantation, and the remainder continued with carfilzomib/lenalidomide/dexamethasone.[84] With median follow-up of 13 months, 24-month PFS was estimated at 92%.The most common grade 3 and 4 toxicities in ≥10% of patients included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and neutropenia (17%). Peripheral neuropathy was limited to grade 1/2 (23%).[84]

The second phase II trial also evaluated the same regimen (carfilzomib in combination with lenalidomide and dexamethasone) in patients (n=45) with newly diagnosed MM. After 8 cycles of treatment, patients with stable disease received up to 24 cycles of lenalidomide, 10 mg/d on days 1 to 21[85]; 38 patients were evaluable for response and toxicity. After a median follow-up of 10 months, PFS was 83.3%. A total of 25 patients completed 8 cycles of the carfilzomib/lenalidomide/dexamethasone regimen, of which 24 continued to lenalidomide therapy and 1 patient opted to exit the study after initial therapy. The most common nonhematologic and hematologic toxicities (≥grade 3) in >10% of patients included electrolyte disturbances (18%), liver function test elevation (13%), rash/pruritus (11%), fatigue (11%), lymphopenia (63%), anemia (16%), leukopenia (13%), and thrombocytopenia (11%).[86]

Based on the above data, the NCCN panel has included the carfilzomib/lenalidomide/dexamethasone regimen as a category 2A option for primary treatment of transplant-eligible patients with MM.

Ixazomib/Lenalidomide/Dexamethasone: Ixazomib is an oral proteosome inhibitor that was approved by the FDA in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least one prior therapy.

In a phase I/II trial, Kumar et al[87] studied an all oral combination of ixazomib/lenalidomide/dexamethasone in patients with newly diagnosed MM. The results of this trial show that the regimen was well tolerated and active in the study population. Of the 64 patients in whom the response could be evaluated, 37 (58%; 95% CI, 45–70) had a VGPR or better. Grade 3 or higher adverse events related to any drug in the combination were reported in 41 (63%) patients. These included skin and subcutaneous tissue disorders (11 patients, 17%), neutropenia (8 patients, 12%), and thrombocytopenia (5 patients, 8%); drug-related PN of grade 3 or higher occurred in 4 (6%) patients.

Based on these phase II results and the fact that the combination of other proteosome inhibitors (bortezomib or carfilzomib) in combination with lenalidomide/dexamethasone have been shown to be effective as primary therapy in newly diagnosed MM,[55,84–86,88] the NCCN panel has included ixazomib/lenalidomide/dexamethasone as an option (category 2A) for the treatment of patients with newly diagnosed MM.

Preferred Primary Therapy Regimens for Non-Transplant Candidates: Many of the regimens described for transplant candidates are also options for

non-transplant candidates. As in transplant-eligible patients, 3-drug regimens are preferred by the NCCN panel. because these regimens have been shown to induce higher response rates and better depth of response in clinical trials. The 2-drug regimens are reserved for elderly and/or frail patients. The list of preferred options for non-transplant candidates includes bortezomib/cyclophosphamide/dexamethasone, bortezomib/lenalidomide/dexamethasone, and lenalidomide/low-dose dexamethasone. Melphalan-containing regimens are no longer considered the standard of care in this setting because novel agents are available and accessible to patients in the United States.

Bortezomib/Cyclophosphamide/Dexamethasone: The role of CyBorD as initial therapy for patients with MM ineligible for SCT was studied in a small phase II trial (n=20).[89] The median age of patients in this study was 76 years (range, 66–90 years). After a median of 5 cycles, the ORR was 95%, with 70% of patients achieving a VGPR or better. With respect to toxicity, 6 patients experienced nonhematologic grade 3/4 adverse events (20%), including muscle weakness, sepsis, and pneumonia. Neutropenia and thrombocytopenia were seen in 2 patients (10%).[89]

Based on these findings[89]; the results from the EVOLUTION trial[53] (described earlier)z, which included transplant-ineligible patients; and the phase II trial results described earlier,[53,56,57] the NCCN panel included CyBorD as a primary therapy option (category 2A) for non-transplant candidates.

Bortezomib/Lenalidomide/Dexamethasone: Phase II study results (discussed in the transplant setting) have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is active and well tolerated in all patients with newly diagnosed MM regardless of autologous SCT status.[90]

The randomized phase III SWOG S0777 trial (discussed in the transplant setting), comparing bortezomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone as induction therapy without an intent of immediate transplantation, reported superior results with the 3-drug regimen.[55] The NCCN panel included the bortezomib/lenalidomide/dexamethasone regimen as a category 1 option for patients with MM who are ineligible for SCT.

Lenalidomide/Low-Dose Dexamethasone: The results of the SWOG SO232 trial,[64] which included transplant-ineligible patients, and the ECOG E4A03 trial,[91] which included elderly patients with MM, demonstrate that lenalidomide in combination with low-dose dexamethasone is a well-tolerated and effective regimen for these patients. In the ECOG E4A03 trial the OS rate was significantly higher in the lenalidomide plus low-dose dexamethasone arm compared with the lenalidomide plus high-dose dexamethasone arm (also discussed in "Preferred Primary Therapy Regimens for Transplant Candidates," page 249).[66] The inferior survival outcome seen with high-dose dexamethasone was greatest in patients aged ≥65 years. At 2 years, patients who did not proceed to transplant had an OS rate of 91% with lenalidomide and low-dose dexamethasone.[66]

The international, multicenter trial (FIRST trial) evaluated efficacy and safety of lenalidomide/dexamethasone given continuously or for 72 weeks with melphalan/prednisone/thalidomide (MPT) in elderly (n=1,623) transplantation-ineligible patients with newly diagnosed MM.[92] The primary end point of this trial was PFS, and secondary end points were OS and adverse events, including the incidence of secondary malignancies. After a median of 37 months of follow-up, the risk of progression or death was reduced by 28% in patients receiving continuous lenalidomide/dexamethasone versus MPT (HR, 0.72; 95% CI, 0.61–0.85; $P<.001$).[92] Continuous lenalidomide/dexamethasone also reduced the risk of progression or death compared with 18 cycles of lenalidomide/dexamethasone (HR, 0.70; 95% CI, 0.89–1.20; $P=.70$). In the interim analysis, an OS benefit was seen in the lenalidomide/dexamethasone arm versus MPT (HR, 0.78; CI, 0.64–0.96; $P=.02$).[92]

There are several reports showing higher incidences of secondary malignancies when lenalidomide is used as a maintenance therapy posttransplantation or in a melphalan-containing regimen.[93–96] In the FIRST trial, the overall incidence of secondary malignancies, including hematologic malignancies, was lower in the continuous lenalidomide/dexamethasone arm. The overall rates of second primary cancers were 3.0% in the continuous lenalidomide/dexamethasone arm, 6.0% in the arm receiving 18 cycles of lenalidomide/dexamethasone, and 5.0% in the MPT arm.[92] In an analysis based on renal function of patients enrolled in the FIRST trial, continuous lenalidomide/low-dose dexamethasone compared with MPT reduced the risk of progression or death in patients with normal, mild,

and moderate renal impairment by 33%, 30%, and 35%, respectively.[97]

Lenalidomide/low-dose dexamethasone is considered a category 1 option by the NCCN panel for transplant-ineligible patients with MM. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Based on the results of the FIRST trial,[92] the NCCN panel recommends considering treatment with continuous lenalidomide/dexamethasone until disease progression for patients who are not eligible for transplant.

Bortezomib/Dexamethasone: A US community-based, randomized, open-label, multicenter phase IIIb, UPFRONT trial compared safety and efficacy of 3 highly active bortezomib-based regimens in previously untreated elderly patients with MM ineligible for SCT.[98] The patients with symptomatic, measurable MM were randomized (1:1:1) to one of the following regimens: bortezomib/dexamethasone (n=168); VTD (n=167); or melphalan/prednisone/bortezomib (n=167) followed by maintenance therapy with bortezomib. The primary end point was PFS; secondary end points included ORR, CR/near-CR and VGPR rates, OS, and safety. All 3 induction regimens exhibited substantial activity, with ORR of 73% (bortezomib/dexamethasone), 80% (VTD), and 69% (melphalan/prednisone/bortezomib) during the treatment period.[98] After a median follow-up of 21.8 months, no significant difference in PFS was observed between the treatment arms.[98] Response rates, including CR and VGPR or better, improved after bortezomib maintenance, with no concomitant increase in the incidence of PN.

The NCCN panel has included bortezomib/dexamethasone as a category 2A primary therapy option for patients with MM who are ineligible for transplant.

Ixazomib/Lenalidomide/Dexamethasone: A phase I/II study (discussed in the previous section for SCT-eligible candidates) evaluated the safety and efficacy of the all-oral combination of ixazomib with lenalidomide and dexamethasone in patients with newly diagnosed MM treated with combination lenalidomide and dexamethasone.[87] Both tolerability and activity of this regimen in older patients (those aged ≥65 years) was similar to that in younger patients in this study.

Based on this phase II study, the NCCN panel included ixazomib in combination with lenalidomide and dexamethasone as a primary treatment option for all patients with newly diagnosed MM, including those not eligible for SCT.

Carfilzomib/Lenalidomide/Dexamethasone: The results of a phase I/II trial demonstrated that the combination of carfilzomib/lenalidomide/dexamethasone is well-tolerated and is also effective in all patients with newly diagnosed MM.[84] An updated follow-up analysis of the subset of 23 elderly patients (age ≥65 years) showed that use of the carfilzomib/lenalidomide/low-dose dexamethasone regimen for an extended period resulted in deep and durable responses. All patients experienced at least a PR and with a median follow-up of 30.5 months. The reported PFS rate was 79.6% (95% CI: 53.5–92.0) and OS was 100%.[88]

The phase II trial by Korde et al[86] also showed that treatment with carfilzomib/lenalidomide/dexamethasone regimen results in high rates of deep remission and no MRD. The results were very similar across age groups, with the oldest patient on the trial being 88 years of age,[86] and the regimen was found to be effective in individuals with high-risk disease.[99]

Based on these phase II studies that did not exclude transplant ineligible patients, the NCCN panel has included carfilzomib/lenalidomide/dexamethasone as an option (category 2B) for the treatment of all patients with newly diagnosed MM, including those who are not eligible for SCT. Carfilzomib can potentially cause cardiac and pulmonary toxicities in elderly patients.[100]

Monitoring After Primary Myeloma Therapy of Both Transplant and Non-Transplant Candidates: Patients on treatment should be monitored for response to primary therapy and for symptoms related to disease and/or treatment. It is recommended to re-evaluate (after 1–2 cycles) with the laboratory tests, skeletal survey, and bone marrow aspiration and biopsy if indicated, to determine treatment response or whether the primary disease is progressive. Potential transplant candidates must undergo a stem cell harvest after 4 to 6 cycles of therapy, collecting enough stem cells for 2 transplants (depending on the intended number of transplants and age) in anticipation of a tandem transplant or a second transplant as subsequent therapy. Alternatively, all patients may consider continuation of primary therapy until the best response is reached. The optimal duration of primary therapy after achieving maximal response is unknown; hence, maintenance therapy (see section

on "Maintenance Therapy," page 261) or observation can be considered beyond maximal response.

Follow-up tests after primary myeloma therapy include those used for initial diagnosis: a CBC with differential and platelet counts; BUN; serum creatinine and corrected serum calcium; and quantification of M-protein and immunoglobulins. The serum FLC may be assessed as clinically indicated (especially in patients with oligosecretory or nonsecretory MM). According to the NCCN panel, response should be assessed using the IMWG criteria.[10] Other tests, such as skeletal survey, bone marrow aspiration and biopsy, MRI, and PET/CT scan, may be performed as indicated by symptoms to detect disease progression. Patients eligible for SCT should be referred for evaluation by SCT center and stem cells should be harvested.

Stem Cell Transplants

High-dose therapy with stem cell support is a critical component in the treatment plan of eligible patients newly diagnosed with MM. The types of SCT may be single autologous SCT, a tandem SCT (a planned second course of high-dose therapy and SCT within 6 months of the first course), or an allogeneic SCT. An allogeneic SCT can be performed after prior myeloablative therapy or after nonmyeloablative therapy. Nonmyeloablative therapy, also referred to as "mini transplant," has been investigated as a technique to decrease toxicity of the allotransplant while preserving the alloimmune graft-versus-myeloma effect.[101,102] It is important to note that nonmyeloablative allogeneic transplant by itself is not adequate therapy and is usually performed following maximal tumor control through adequate induction therapy or an autologous SCT. An allogeneic SCT may also follow an autologous SCT.

These NCCN Guidelines indicate that all types of SCT are appropriate in different clinical settings; these indications are discussed further in the following sections. In general, all candidates for high-dose chemotherapy must have sufficient liver, renal, pulmonary, and cardiac function. However, renal dysfunction is not an absolute contraindication to transplant. Earlier studies of autologous transplant included total body irradiation (TBI) as a component of the preparative regimen. Regimens with chemotherapy have only recently been shown to have equivalent efficacy and less toxicity than TBI. TBI regimens have now been abandoned,[103] but newer, potentially less toxic radiation techniques aimed to deliver total marrow irradiation while reducing toxicities to nontarget organs are currently undergoing evaluation in clinical trials.[104]

Autologous SCTs

Autologous SCT results in high response rates and remains the standard of care after primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous SCT is associated with statistically significant higher response rates and increased OS and EFS when compared with the response of similar patients treated with conventional therapy.[105] In 2003, results of a second trial comparing high-dose therapy with standard therapy showed an increase in the CR rate and an improvement in OS (54 months in the high-dose group vs 42 months for standard therapy).[106] The benefit was more pronounced for higher-risk patients. Barlogie et al[107] reported on the results of an American trial that randomized 510 patients to receive high-dose therapy with autologous stem cell support or standard therapy. With a median follow-up of 76 months, no differences were seen in response rates, PFS, or OS between the groups. The reasons for the discrepant results are not clear, but may be related to differences in the specific high-dose and conventional regimens between the American and French study. For example, the American study included TBI as part of the high-dose regimen; TBI has subsequently been found to be inferior to high-dose melphalan.[103]

Another trial included 190 patients 55 to 65 years of age randomized to standard or high-dose therapy.[108] This study was specifically designed to include older patients; the median age in this trial was 61 years, whereas the median age of the participants in other trials ranged from 54 to 57 years. After 120 months of follow-up, no significant difference was seen in OS, although a trend was seen toward improved EFS in the high-dose group (P=.7). Additionally, the period without symptoms, treatment, or treatment toxicity was significantly longer in the high-dose group. The study concluded that the equivalent survival suggests that the treatment choice between high-dose and conventional-dose chemotherapy should be based on personal choice in older patients. For example, an early transplant may be favored because patients can en-

joy a longer interval of symptom-free time. However, this study[109] also showed that a transplant performed at relapse has a similar OS compared with an early transplant. The choice of early versus late transplant was examined in a randomized French trial, and the results in both arms are comparable with respect to OS.[110] However, early SCT was superior in terms of quality of life, assessed as time without symptoms and side effects from therapy.[110]

It should be noted that all randomized studies of autologous SCT after primary therapy were designed and implemented before the availability of thalidomide, lenalidomide, or bortezomib. Therefore, the role of transplant may evolve in the future. The results of the PETHEMA trial strongly support the use of upfront autologous SCT for MM even in the era of novel agents.[77] The response rates were evaluated after induction therapy and after autologous SCT. Taking into consideration patients who actually underwent the autologous SCT, the CR rates increased from 35% pretransplant to 57% posttransplant in the group treated with VTD as induction therapy, and from 14% to 40%, respectively, in the group treated with thalidomide and dexamethasone as induction therapy.[77]

A recent phase III study compared high-dose melphalan followed by autologous SCT with MPR (melphalan/prednisone/lenalidomide). Patients (n=402) were randomly assigned (in a 1:1:1:1 ratio) to 1 of 4 groups: high-dose therapy and SCT followed by maintenance with lenalidomide; high-dose therapy and SCT alone; primary therapy with MPR followed by lenalidomide; and primary therapy with lenalidomide alone. The primary study end point was PFS. Secondary end points included OS, the ORR, the time to a response, and safety.[111] The comparison of the group treated with high-dose melphalan therapy followed by SCT with MPR shows that high-dose melphalan therapy followed by SCT was associated with a significant reduction in the risk of progression or death (HR, 0.44) and prolonged OS (HR for death, 0.55).[112]

Results from the IFM 2005-01 study of patients with symptomatic myeloma receiving primary therapy with bortezomib and dexamethasone versus VAD showed a marked improvement in ORR with bortezomib and dexamethasone over VAD (discussed in "Preferred Primary Therapy Regimens for Transplant Candidates," page 249).[61] Responses were evaluated after primary treatment and post-autologous SCT. After the first autologous SCT, CR/near-CR rates were 35.0% in the bortezomib plus dexamethasone arm, compared with 18.4% in the VAD arm.[61] The VGPR rates were 54.3% versus 37.2%. Median PFS was 36.0 months versus 29.7 months (P=.064) with bortezomib plus dexamethasone versus VAD after a median follow-up of 32.2 months.[61] Also, PFS was also significantly longer in the patients achieving greater than or equal to a VGPR after primary treatment than in patients achieving a less than VGPR (median, 36 vs 29.7 months). [61]

In another study, 474 patients were randomized to primary therapy with VTD (n=236) or thalidomide and dexamethasone (n=238) before double autologous SCT.[113] The 3-drug regimen yielded high response rates compared with the 2-drug regimen, with a CR rate of 19% (vs 5%) and greater than or equal to VGPR of 62% (vs 31%). After SCT, improved incremental responses were still seen with VTD compared with thalidomide plus dexamethasone. Taken together, these studies suggest that improved responses with the primary regimen result in improved outcomes after transplantation.

Studies have found that PD emerging after primary therapy does not preclude a good response to autologous SCT.[107,114,115] For example, Kumar et al[115] reported on a case series of 50 patients with primary progressive MM receiving an autologous SCT. Results were compared with those of 100 patients with responsive disease undergoing autologous SCT. The 1-year PFS from the time of transplant was 70% in the primary progressive group compared with 83% in the chemosensitive group. According to the NCCN Guidelines, for transplant-eligible patients, autologous SCT is a category 1 option after primary induction therapy and for treatment of primary progressive or refractory disease after primary treatment.

Tandem SCTs

Tandem SCT refers to a planned second course of high-dose therapy and SCT within 6 months of the first course. Planned tandem transplants have been studied in several randomized trials. The IFM94 trial reported by Attal et al[116] randomized newly diagnosed patients with MM to single or tandem autologous transplants. A total of 78% of patients assigned to the tandem transplant group received the second transplant at a median time of 2.5 months

after the first. A variety of options for therapy of relapsed disease were provided. For example, patients with disease relapse in either group underwent either no therapy, additional conventional therapy, or another SCT. EFS 7 years after diagnosis was 10% in the single transplant group compared with 20% in the double transplant group. An accompanying editorial by Stadtmauer[117] questions whether the promising results might be related to regimens used, rather than to the effect of 2 courses of high-dose therapy. For example, patients in the single transplant arm received 140 mg/m^2 of melphalan plus TBI, whereas those in the tandem arm received the same dose without TBI for the initial transplant and with TBI for the second transplant. As noted earlier, TBI has been shown to be more toxic without providing additional benefit. Based on this, the editorial suggests that the increased survival in IFM94's tandem arm may have resulted from greater cumulative exposure to melphalan (280 vs 140 mg/m^2). In a subset analysis, the patients who did not achieve a complete CR or a VGPR within 3 months after the first transplant appeared to benefit the most from a second transplant. The investigators of the IFM94 study suggested that the improvement in projected survival associated with tandem transplant is related not to improved response rates but rather to longer durations of response. Four other randomized trials have compared single versus tandem transplant.[108,118–120] None of these trials showed a significant improvement in OS. However, because the median follow-up in these trials ranged from 42 to 53 months, the lack of significant improvement is not surprising. The trial by Cavo et al[118] found that patients not in CR or near-CR after the first transplant benefited the most from a second transplant. This confirms the observations of the IFM94 trial using non–TBI-based high-dose regimens.

In both the French and Italian trials, the benefit of a second autologous SCT was seen in patients o do not performed at relapse who do not achieve a CR or VGPR (>90% reduction in M-protein level) with the first procedure. These 2 studies were not adequately powered to evaluate the equivalence of 1 versus 2 transplants in patients achieving a CR or VGPR after the first transplantation.

A review of long-term outcomes of several trials of autologous transplantation by Barlogie et al[121] found that tandem transplantations were superior to both single transplantations and standard therapies. Also, postrelapse survival was longer when EFS was sustained for at least 3.5 years after tandem transplantation. The NCCN panel recommends collecting enough stem cells for 2 transplants in all eligible patients. According to the NCCN panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT. The support for use of maintenance therapy after tandem transplant comes from the study by Palumbo et al[111] (discussed in the previous section), which addressed the role of maintenance therapy with lenalidomide after autologous transplantation. Although associated with more frequent grade 3 or 4 neutropenia and infections, maintenance therapy with lenalidomide was found to significantly reduce risk of disease progression or death (HR, 0.47) after both single and tandem transplantation compared with no maintenance.[111]

The benefit from the second transplant in patients who have CR or VGPR, and also in those who achieve less than a VGPR after the first SCT, should preferably be determined in a clinical trial. In fact, such a randomized prospective NIH- and Intergroup-supported trial is currently ongoing. The other options for this group of patients include maintenance therapy or observation.

A retrospective case-matched control analysis was performed comparing patients who underwent a second autologous SCT versus those treated with conventional chemotherapy for relapsed MM.[122] Similar to previously published smaller studies,[123–125] this retrospective analysis demonstrated that a second autologous SCT is associated with superior relapse-associated mortality compared with conventional chemotherapy (68% vs 78%), along with improved OS (32% vs 22%) at 4 years. In this analysis, factors associated with improved OS and PFS included younger age (<55 years), beta-2 microglobulin level <2.5 mg/L at diagnosis, a remission duration of >9 months, and better than a PR to their first autologous SCT. This analysis indicates that a second autologous transplant, for relapsed or progressive MM, may be an option for carefully selected patients. Some of these patients can achieve durable complete or partial remission.[125,126]

A multicenter, randomized phase III trial compared treatment with high-dose melphalan plus

second autologous SCT with cyclophosphamide in patients with relapsed MM who had received autologous SCT as primary treatment.[127] The patients included in the study were >18 years of age and needed treatment for progressive or relapsed disease at least 18 months after a previous autologous SCT. All patients first received PAD induction therapy. Then patients with adequately harvested stem cells were randomized to high-dose melphalan plus second autologous SCT (n=89) or oral cyclophosphamide (n=85). The primary end point was time to disease progression.[127] After a median follow-up of 31 months, median time to progression in patients who underwent second autologous SCT after induction therapy was 19 months versus 11 months for those treated with cyclophosphamide (HR, 0.36; 95% CI, 0.25–0.53; *P*<.0001). Grade 3/4 neutropenia (76% vs 13%) and thrombocytopenia (51% vs 5%) were higher in the group that underwent autologous SCT versus cyclophosphamide.[127]

The recently reported results of the StaMINA trial indicate that a tandem autologous SCT followed by lenalidomide maintenance has similar outcomes to a single autologous SCT followed by lenalidomide maintenance in the initial treatment of MM.[128] Other recently reported results of an intergroup, multicenter, phase III study (EMN02/HO95 MM trial) suggests that tandem autologous SCT for newly diagnosed MM appears to be superior in extending PFS compared with single autologous SCT after induction therapy with a bortezomib-based regimen.[129]

According to the NCCN panel, repeat autologous SCT for relapsed disease may be considered either on or off clinical trial depending on the interval between the preceding SCT and documented progression (category 2A). Based on the data from retrospective studies,[130–133] the NCCN panel suggests 2 to 3 years as the minimum length of remission for considering second autologous SCT for relapsed disease (category 2B).

Allogeneic SCT

Allogeneic SCT includes either myeloablative or nonmyeloablative (ie, mini transplant) transplants. Allogeneic SCT has been investigated as an alternative to autologous SCT to avoid the contamination of reinfused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population. Nonmyeloablative transplants are designed to decrease the morbidity of the high-dose chemotherapy but preserve the beneficial graft-versus-tumor effect. Therefore, the principal difference between myeloablative and nonmyeloablative transplants relates to the chemotherapy regimen used. Specific preparatory regimens have not been a focus of the NCCN Guidelines, and therefore these guidelines do not make a distinction between these approaches.

Given the small candidate pool, it is not surprising that there have been no randomized clinical trials comparing myeloablative allogeneic to autologous SCT, but multiple case series have been published describing allogeneic SCT as an initial or as therapy for relapsed/refractory MM. In a 1999 review, Kyle[134] reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured. Other reviews have also reported increased morbidity without convincing proof of improved survival.[114,135] However, there are intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.[107] The original trial had an ablative, allogeneic transplant group consisting of patients with HLA identical siblings; 36 received allografts, and due to the high 6-month mortality of 45%, the allogeneic arm was closed. With 7 years of follow-up the OS of the conventional chemotherapy, autologous, and allogeneic arms were all identical at 39%. The autologous and conventional chemotherapy arms do not demonstrate a plateau, whereas the allogenic curve was flat at 39%. This suggests that a proportion of these patients are long-term survivors. Thus, there is ongoing interest in myeloablative allogeneic SCT, particularly given the lack of a significant cure rate for single or tandem autologous SCT.

The NCCN Guidelines consider myeloablative allogeneic SCT an accepted option, preferably in a clinical trial in patients (1) whose disease responds to primary therapy; (2) with primary PD; or (3) with PD after an initial autologous SCT.

Another strategy that has been investigated is initial autologous SCT followed by a mini-al-

logeneic transplant. A prospective trial by Bruno et al[136] showed that, among patients (<65 years) with HLA-matched siblings who received an autograft-allograft regimen, the CR rate after allografting was 55% compared with 26% after double autograft in patients without HLA-matched siblings. Median OS was higher (80 vs 54 months). In the prospective PETHEMA trial in patients who did not achieve at least a near-CR with a first autologous SCT, no significant difference was seen in OS after double autologous SCT versus autologous SCT followed by mini-allogeneic transplant. However, a trend toward a longer PFS was observed in the group treated with autologous SCT followed by mini-allogeneic transplant.[137] In contrast, the IFM99-03 trial by Garban et al[138] and the BMT CTN 0102 trial[139] reported no OS or PFS advantage with autologous transplant followed by allogeneic transplant in patients with high risk.

In a prospective study of previously untreated MM, patients were selected for treatment with autologous SCT followed by reduced-intensity conditioning allogeneic SCT or autologous SCT based on the availability of an HLA-identical sibling.[140] The induction chemotherapy in this study consisted of the chemotherapy that was standard at the time (the VAD or VAD-like regimen). After 60 months, the incidence of relapse/progression was 49% in the group treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT versus 78% in the autologous SCT group. At 60 months, the OS and CR rates were 65% and 51%, respectively, for patients treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT compared with 58% and 41%, respectively, for those treated with autologous SCT. Based on these study results, patients who have an HLA-identical sibling may be considered candidates for reduced-intensity allogeneic SCT as part of their first-line treatment.

Mini-allogeneic transplants have also been investigated as therapy for relapsed/refractory disease by virtue of their graft-versus-myeloma effect. Responsive disease to prior transplantation and younger age are associated with better response and OS rates.[141–144] In a case series report, 54 patients with previously treated relapsed disease or PD were treated with an autologous SCT followed by a mini-allogeneic transplant.[142] The OS rate was 78% at a median 552 days after the mini-allogeneic transplant, with a 57% CR rate and an ORR of 83%. This study concluded that this approach reduced the acute toxicities of a myeloablative allogeneic SCT while preserving antitumor activity.

The largest case series was reported by the EBMT.[143] In this heterogeneous population of 229 patients, the 3-year OS and PFS were 41% and 21%, respectively. Adverse OS was associated with chemoresistant disease and more than 1 prior transplant, whereas improved[145] OS was associated with graft-versus-host disease, confirming the importance of a graft-versus-leukemia effect. This study concluded that mini-allogeneic transplantation is feasible, but that heavily pretreated and patients with PD are unlikely to benefit.

Patients whose disease either does not respond to or relapses after allogeneic stem cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft-versus-myeloma effect[146–153] or other myeloma therapies on or off a clinical trial.

Follow-Up After SCT

Follow-up tests after SCT are similar to those performed after primary myeloma therapy (see "Monitoring After Primary Myeloma Therapy of Both Transplant and Non-Transplant Candidates," page 255).

In addition, MRD assessment is increasingly being incorporated into posttreatment assessments. MRD has been identified as an important prognostic factor. A prospective study of patients with newly diagnosed MM evaluated MRD in bone marrow samples and showed that at a median follow-up of 57 months, MRD negativity after autologous SCT translated to significantly improved PFS and OS rates.[154] Similarly, in another study, MRD negativity after autologous SCT was predictive of favorable PFS and OS.[155]

Similar results have also been reported in the allogeneic SCT setting where the presence of MRD after allogeneic SCT has been associated with a significantly adverse PFS and OS.[145] The NCCN panel recommends assessing for MRD during follow-up as indicated.[42]

Maintenance Therapy

Lenalidomide as Maintenance Therapy After Autologous SCT

Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in 2 independent randomized phase III studies.[93,94]

In the CALGB 100104 trial, patients were randomized to maintenance therapy with lenalidomide (n=231) versus placebo (n=229) after autologous SCT.[94] 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 versus 27 months in the placebo group (*P*<.001). Second primary cancers occurred in 18 patients who received lenalidomide (8%) and in 6 patients who received placebo (3%).[94]

Data from the international, randomized, double-blind phase III IFM2005-02 trial[93] (n=614) show that patients treated with lenalidomide as consolidation therapy after an autologous SCT followed by lenalidomide as maintenance therapy had upgraded responses. Of the 614 patients enrolled in the trial, 307 were randomly assigned to lenalidomide maintenance therapy and 307 to placebo. Maintenance treatment was continued until the patient withdrew consent, the disease progressed, or unacceptable toxic effects occurred. The final analysis of the IFM2005-02 trial was performed after a median follow-up of 30 months and 264 patients had disease progression (104 in the lenalidomide group and 160 in the placebo group). The median PFS was 41 months in the lenalidomide group compared with 23 months in the placebo group (HR, 0.50; *P*<.001; median follow-up period was 30 months). The probability of surviving without progression for 3 years after randomization was 59% in those treated with lenalidomide and 35% in those who received the placebo. The benefit of lenalidomide maintenance therapy, evidenced by rate of PFS at 3 years after randomization, was higher in all patients who received lenalidomide maintenance therapy compared with those who received placebo. This benefit was observed in patients who had a VGPR at randomization (64% vs 49%; *P*=.006) and those who did not (51% vs 18%; *P*<.001). An increased incidence of second primary cancers was observed in the lenalidomide group (32 had second primary cancers in the lenalidomide group and 12 in the placebo group).[93]

In a phase II study by the IFM group, lenalidomide maintenance was shown to upgrade responses seen in 27% of patients (8 of 31 patients) after induction therapy with lenalidomide/bortezomib/dexamethasone followed by autologous transplant.[54]

The study by Palumbo et al[111] (discussed in "Autologous SCTs," page 256) showed that although maintenance therapy with lenalidomide is associated with more frequent grade 3/4 neutropenia and infections, it significantly reduced risk of disease progression or death (HR, 0.47) compared with no maintenance.[111]

A report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option after mini-allogeneic SCT.[156] However, another recently reported study has shown the feasibility of maintenance therapy with low-dose lenalidomide after allogeneic SCT in patients with high-risk MM.[157]

Lenalidomide as Maintenance Therapy After Non-Transplant Active Primary Treatment

Data from the phase III MM-015 study show that lenalidomide maintenance after primary therapy with MPR significantly reduced the risk of disease progression and also increased PFS.[158] In this study, newly diagnosed patients with MM (n=459) aged ≥65 years were randomized to receive MP followed by placebo, MPR, or MPR followed by lenalidomide until progression. Maintenance with lenalidomide significantly prolonged PFS. The PFS of patients treated with MPR followed by maintenance lenalidomide was significantly prolonged (n=152; median, 31 months) compared with the other 2 arms: MPR (n =153; median, 14 months; HR, 0.49; *P*<.001) or MP (n=154; median, 13 months; HR, 0.40; *P*<.001). Lenalidomide maintenance therapy improved PFS by 66% compared with placebo, regardless of age.[158] In the FIRST trial, use of lenalidomide indefinitely till progression was associated with a superior PFS compared with a fixed duration of 18 months.

Based on the evidence from the phase III trials,[93,94,158] the NCCN panel lists single-agent lenalid-

omide as one of the preferred maintenance regimens (category 1). Lenalidomide lacks the neurologic toxicity seen with thalidomide. However, there seems to be an increased risk for secondary cancers, especially posttransplantation[93,94,159] or after treatment with a melphalan-containing regimen.[96] According to the results of the FIRST trial, in the continuous lenalidomide/dexamethasone arm, the absence of the alkylator melphalan seems to be more effective in terms of improving PFS and lowering incidence of second malignancies.[92]

A meta-analysis of 4 randomized controlled trials examined patients treated with lenalidomide maintenance versus those treated with no maintenance or placebo in both the transplant and non-transplant settings.[160] The analysis showed that patients treated with lenalidomide maintenance had significantly improved PFS (HR, 0.49; $P<.001$) and a trend toward OS (HR, 0.77; $P=.071$) versus no maintenance or placebo.[160] There was significantly more grade 3/4 neutropenia with the use of lenalidomide and a 2-fold increased risk of secondary malignancies.

The NCCN panel notes that the benefits and risks of maintenance therapy with lenalidomide versus secondary cancers should be discussed with patients.

Bortezomib as Maintenance Therapy After Autologous SCT

The results from the HOVON study show that maintenance with single-agent bortezomib after autologous SCT is well tolerated and is associated with improvement of ORR.[60] Patients in the HOVON trial were randomly assigned to 1 of the 2 arms consisting of either primary treatment with VAD followed by autologous SCT and maintenance with thalidomide or with PAD followed by autologous SCT and bortezomib as maintenance therapy for 2 years. The study reported high near-CR/CR rates after primary treatment with the bortezomib-based regimen. Bortezomib as maintenance therapy was well tolerated and associated with additional improvement of response rates[60] (see "Preferred Primary Therapy Regimens for Transplant Candidates," page 249).

A multicenter phase III trial in patients with newly diagnosed MM showed that consolidation with bortezomib after autologous SCT improved PFS only in patients not achieving at least a VGPR after autologous SCT.[161] No difference was seen in PFS in patients with a VGPR or better after autologous SCT.

Bortezomib as Maintenance Therapy After Non-Transplant Active Primary Treatment

The preliminary results of the phase III UPFRONT study also show that maintenance with single-agent bortezomib is well-tolerated when administered after treatment with bortezomib-based primary therapy.[162] Patients with newly diagnosed MM ineligible for high-dose therapy and SCT enrolled in the UPFRONT trial were randomized (1:1:1) and treated with one of the following bortezomib-based primary regimens: bortezomib and dexamethasone; bortezomib in combination with thalidomide and dexamethasone; or bortezomib with melphalan and prednisone followed by maintenance treatment with bortezomib. The updated results show that the response rates, including CR and VGPR or better, improved after bortezomib maintenance in all arms, with no concomitant increase in the incidence of PN.[162]

The NCCN panel members added bortezomib to the list of preferred maintenance regimens with a category 2A designation.

Adjunctive Treatment for MM

Important advances have been made in adjunctive treatment/supportive care of patients with MM. This involves careful patient education about the probable side effects of each drug, the drug combinations being used, and the supportive care measures required. Supportive care can be categorized into those measures required for all patients and those that address specific drugs.

Bony manifestations of myeloma, in the form of diffuse osteopenia and/or osteolytic lesions, develop in 85% of patients. Related complications are the major cause of limitations in quality of life and performance status in patients with MM. A large, double-blind, randomized trial has shown that monthly use of intravenous pamidronate (a bisphosphonate) can decrease pain and bone-related complications, improve performance status, and, importantly, preserve quality of life in patients with Durie-Salmon stage III MM and at least one lytic lesion.[163,164] Zoledronic acid has equivalent benefits.[165] Results from the study conducted by Zervas et al[166] show a 9.5-fold greater risk for the development of osteonecrosis of the jaw with zoledronic acid compared with

pamidronate. Patients who are on bisphosphonates should have their renal function monitored. They should have a dental examination before the start of bisphosphonate therapy and be monitored for osteonecrosis of the jaw.

The MRC Myeloma IX study examined effects of zoledronic acid versus clodronate (a bisphosphonate not currently FDA approved) in patients with MM initiating chemotherapy regardless of bone disease. The patients were randomized to receive zoledronic acid (n=981) or clodronic acid (n=979). Zoledronic acid was reported to reduce mortality and significantly improve PFS.[167] Patients on clodronate and zoledronic acid had similar occurrence of acute renal failure and treatment-related serious adverse events. Zoledronic acid was associated with higher rates of confirmed osteonecrosis of the jaw than was clodronic acid.[167–169] The study reanalyzed and recently reported survival outcomes. After an extended follow-up (median, 5.9 years), in addition to PFS, the OS was also significantly improved (52 vs 46 months; HR, 0.86; *P*=.01) compared with clodronic acid.[170] The long-term rates of osteonecrosis of the jaw were also observed to be higher with zoledronic acid compared with clodronate (3.7% vs 0.5%; *P*=.0001).[170]

A recent meta-analysis of 20 randomized controlled trials of comparing bisphosphonates with either placebo or a different bisphosphonate as a comparator concluded that adding bisphosphonates to the treatment of MM reduces vertebral fractures and probably reduces pain. Whether zoledronate is superior to pamidronate and other bisphosphonates remains to be determined.[171]

These NCCN Guidelines recommend bisphosphonates for all patients receiving myeloma therapy for symptomatic disease regardless of documented bone disease (category 1). In patients with smoldering or stage I MM, according to the NCCN panel, bisphosphonates may be considered but preferably in a clinical trial. Skeletal survey annually or as clinically indicated is recommended for these patients. Bone densitometry or other metabolic studies should be reserved for clinical trials.

Low-dose radiation therapy (10–30 Gy) is used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.[172] Limited involved fields should be used to limit the effect of irradiation on stem cell harvest or its effect on potential future treatments; the radiation doses administered should not preclude stem cell collection in potential candidates for high-dose therapy and hematopoietic SCT. Orthopedic consultation should be obtained for impending or actual fractures in weight-bearing bones, bony compression of the spinal cord, or vertebral column instability. Either vertebroplasty or kyphoplasty should be considered for symptomatic vertebral compression fractures.

Excess bone resorption from myeloma bone disease can lead to excessive release of calcium into the blood, contributing to hypercalcemia. Symptoms include polyuria and gastrointestinal disturbances, with progressive dehydration and decreases in glomerular filtration rate. Hypercalcemia should be treated with hydration and furosemide, bisphosphonates, steroids, and/or calcitonin. Among the bisphosphonates (zoledronic acid, pamidronate, and ibandronate), the NCCN panel members prefer zoledronic acid for treatment of hypercalcemia.[173–175]

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.[176] Institutions differ in their use of plasmapheresis for adjunctive treatment of renal dysfunction.

Erythropoietin therapy should be considered for anemic patients, especially those with renal failure. Measuring endogenous erythropoietin levels may also be helpful in treatment planning[177,178] (see the NCCN Guidelines for Cancer- and Treatment-Related Anemia, available at NCCN.org).

To prevent infection: (1) intravenous immunoglobulin therapy should be considered for recurrent, life-threatening infections; (2) pneumococcal and influenza vaccine should also be considered; and (3) *Pneumocystis carinii* pneumonia (PCP), herpes, and antifungal prophylaxis is recommended if a high-dose regimen is used. Bortezomib treatment has been associated with an incidence of herpes zoster.[47,48] Herpes prophylaxis is recommended in patients receiving bortezomib therapy.[46] (See the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections, available at NCCN.org).

Thrombosis is relatively common when thalidomide or lenalidomide is used with steroids, and is particularly frequent when treating newly diagnosed patients. Use of prophylactic anticoagulation agents (see NCCN Guidelines for Venous Thromboembolic Disease, available at NCCN.org) is recommended

when IMiDs are used in combination therapy during induction.[68,179,180]

Hydration should be maintained and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided to decrease the chances of renal dysfunction. According to the NCCN panel members, the use of plasmapheresis to improve renal function is a category 2B recommendation. The use of intravenous contrast media and NSAIDs should also be avoided in patients with renal impairment.

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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty conflict:
Leona Holmberg, MD, PhD: Up-To-Date