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The NCCN

Multiple Myeloma

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. The American Cancer Society estimates that 20,580 new cases of MM will occur in the United States in 2009, including 11,680 in men and 8900 in women, with an estimated 10,580 deaths.[1] The mean age of affected individuals is 62 years for men (75% > 70 years) and 61 years for women (79% > 70 years). The treatment of MM has dramatically improved over the past decade. The 5-year survival rate reported in the Surveillance Epidemiology and End Results database has increased from 25% in 1975 to 34% in 2003 because of the availability of newer and more effective treatment options.[2,3]

Multiple Myeloma Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, multiple myeloma, Waldenström's monoclonal protein, C-reactive protein, combination chemotherapy, stem cell transplant, primary amyloidosis, cytogenetics, proteasome inhibitor, immunomodulatory drugs, bisphosphonates, supportive therapies, novel therapies (*JNCCN* 2009;7:908–942)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

These 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 these 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 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.

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Disclosures for the NCCN Multiple Myeloma Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Multiple Myeloma Guidelines Panel members can be found on page 942. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at NCCN.org.)

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

MM is typically sensitive to various cytotoxic drugs, both as initial treatment or as treatment of relapsed disease. Unfortunately, responses are transient, and MM is not considered curable with current approaches. However, over the past few years treatment has been evolving rapidly because of the introduction of new drugs, such as bortezomib, thalidomide, and lenalidomide. In addition, understanding of the microenvironment of the bone marrow is emerging, creating a rationale for new combinations of therapies and new drug development.[4] Studies of the associated cytogenetic abnormalities also indicate that MM is a heterogeneous disease. These factors suggest that future risk-adapted approaches will further refine patient management.

These guidelines address diagnosis, treatment, and follow-up for multiple myeloma, systemic light chain amyloidosis, and the related Waldenström's macroglobulinemia.

Initial Diagnostic Workup

The initial diagnostic workup (page 910) in all patients should include a history and physical examination and the following baseline blood studies: CBC with differential and platelet counts; blood urea nitrogen (BUN); serum creatinine and serum electrolytes; serum calcium; albumin; lactate dehydrogenase (LDH); and β_2-microglobulin. Increased BUN and creatinine indicate decreased kidney function, whereas LDH levels help assess tumor cell burden in lymphoma-like or plasmablastic myeloma. The level

Text continues on p. 925

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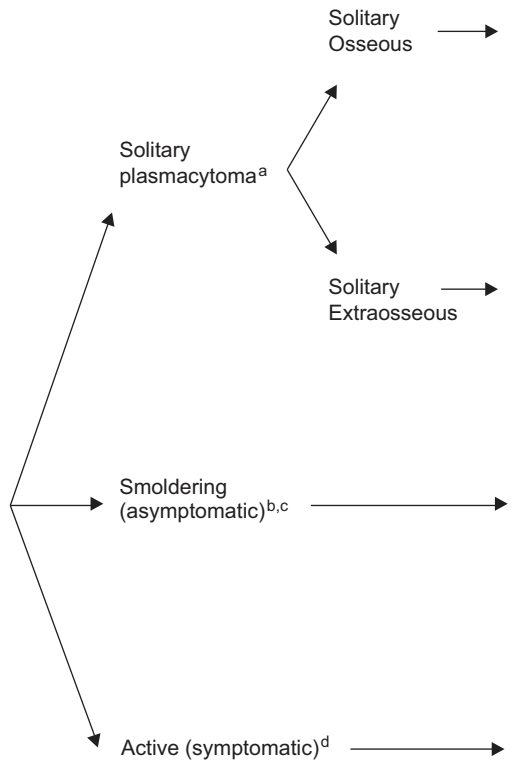
INITIAL DIAGNOSTIC WORKUP

- H&P
- CBC, differential, platelets
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- 24 hour urine total protein
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24 hour urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- FISH [del 13, del 17, t(4;14), t(11;14), t(14;16)]

Useful Under Some Circumstances

- MRI for suspected vertebral compression
- CT scan (avoid contrast)
- PET/CT scan
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Bone densitometry
- Plasma cell labeling index
- Staining of marrow and fat pad for amyloid
- Serum free light chain assay
- Serum viscosity
- HLA typing

CLINICAL PRESENTATION



[a] See Staging Systems for Multiple Myeloma (page 914).
[b] See Smoldering Myeloma (Asymptomatic; page 915).
[c] Includes Durie-Salmon stage I myeloma.
[d] See Active Myeloma (Symptomatic; page 915).

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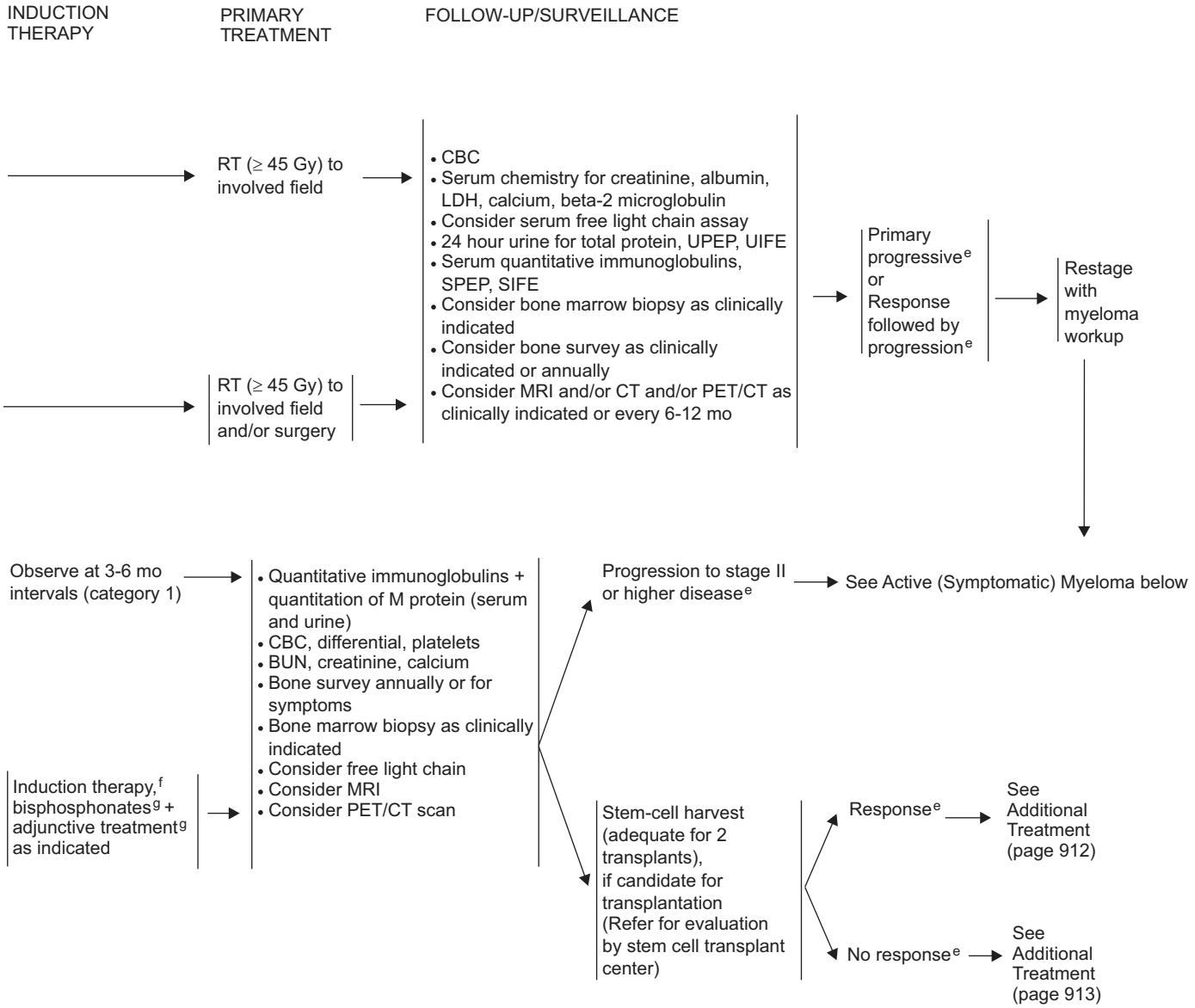

[e] See Response Criteria for Multiple Myeloma (pages 916–919).
[f] See Myeloma Therapy (page 920).
[g] See Adjunctive Treatment (page 921).

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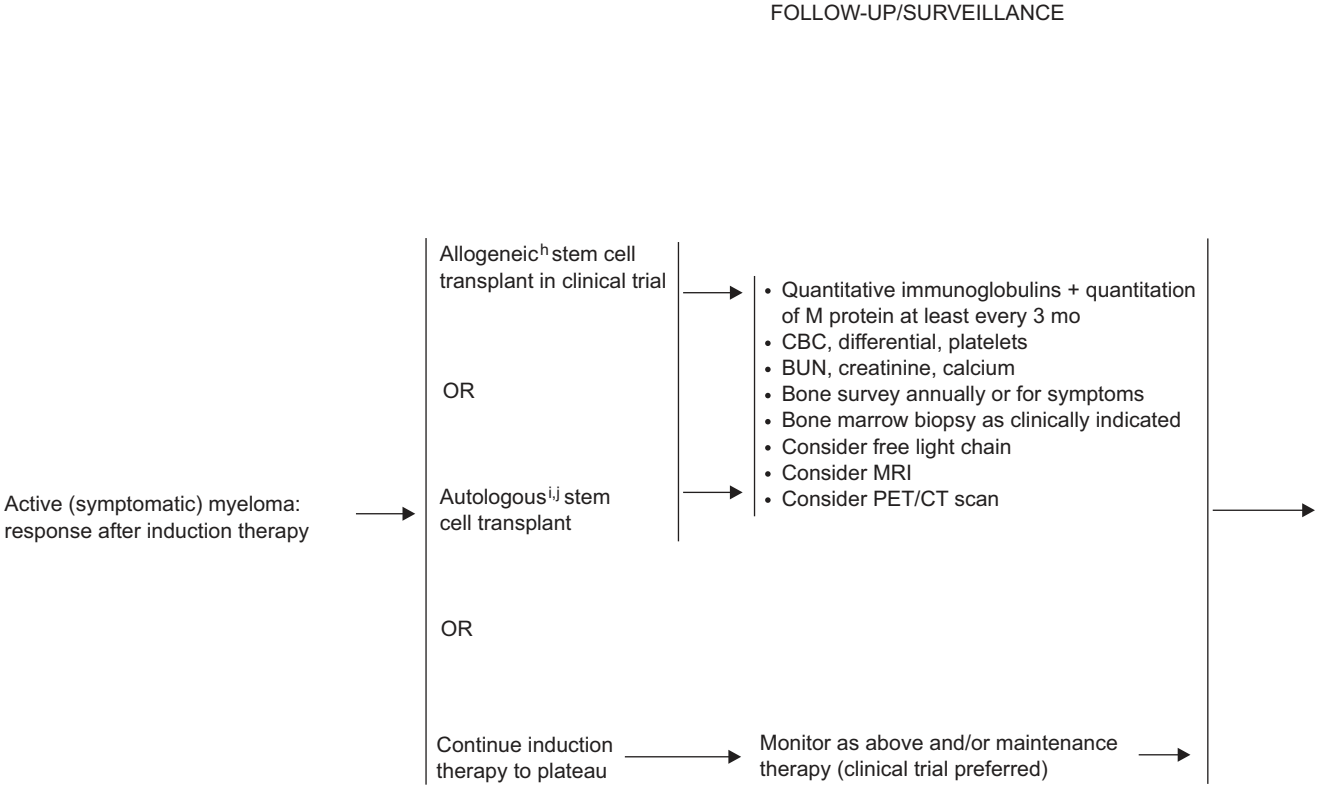

[h] A prospective trial by Bruno B, Rotta M, Patriarca F, et al. N Engl J Med 2007;356:1110-1120, found improved survival for patients receiving an autologous transplant followed by non-myeloablative allograft compared to patients who received tandem autologous grafts. The IFM trial (99-03) by Garban F, Attal M, Michallet M, et al. Blood 2006;107:3474-3480, reported no overall survival or progression free survival with autologous transplant followed by mini allograft in high-risk myeloma patients. Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative on a clinical trial (off-trial category 3). Current data do not support miniallografting alone.

[i] Single 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. Fermand JP, Katsahian S, Divine M, et al. High dose therapy and autologous blood stem cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005;23:9227-9233; and Barlogie B, Kyle RA, Anderson KC, et al. Comparable survival of patients with multiple myeloma treated with autotransplant-supported melphalan -TBI or standard VBMCP consolidation and no role of interferon maintenance: final results of US Intergroup Trial S9321. J Clin Oncol 2006;24:929-936..

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

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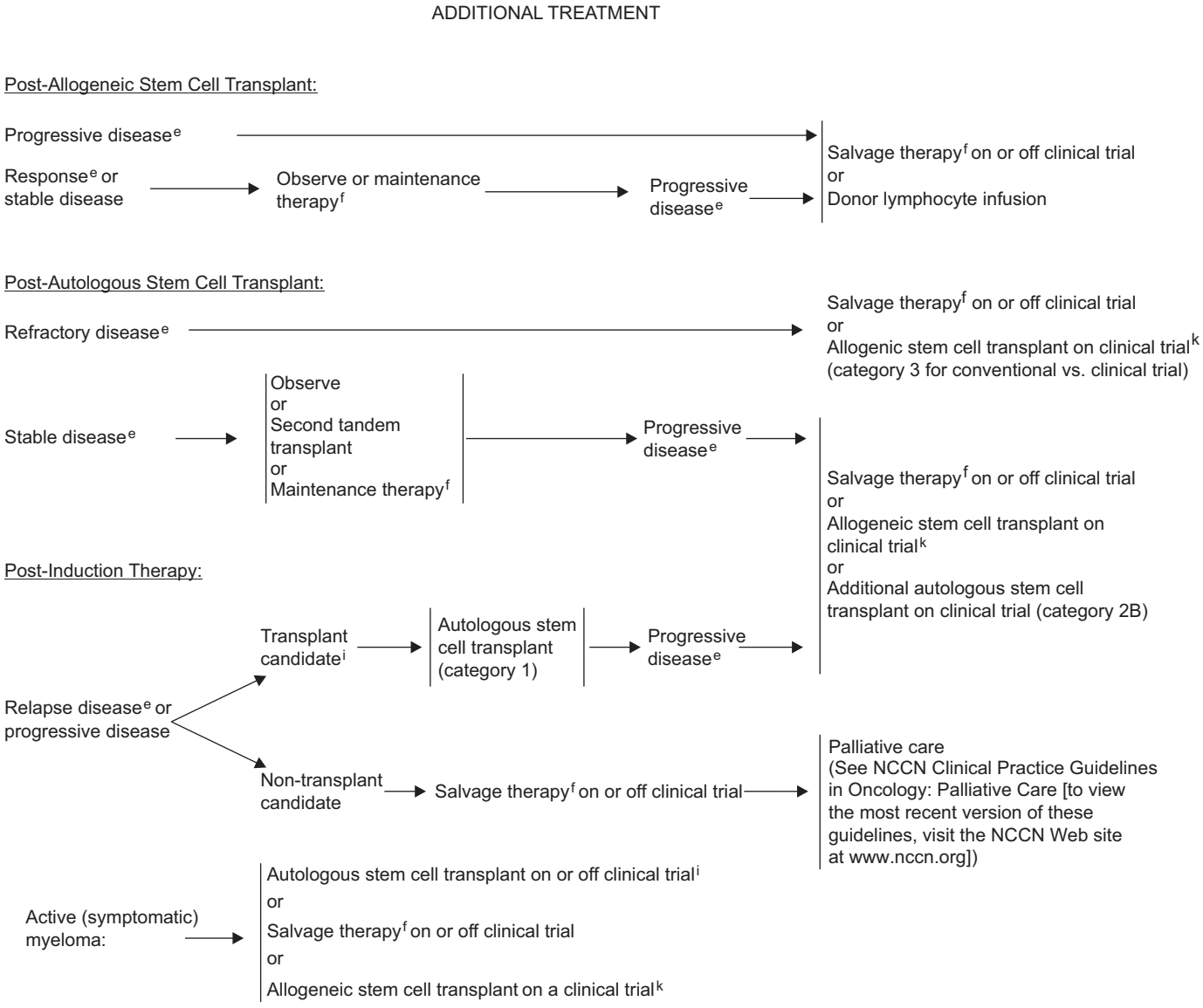

[e] See Response Criteria of Multiple Myeloma (pages 916-919).
[f] See Myeloma Therapy (page 920).
[k] Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative on a clinical trial (off-trial category 3). Current data do not support miniallografting alone.
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STAGING SYSTEMS FOR MULTIPLE MYELOMA

Stage	Durie-Salmon Criteria[1]	ISS Criteria[2]
I[2]	All of the following: • Hemoglobin value > 10 g/dL • Serum calcium value normal or ≤ 12 mg/dL • Bone x-ray, normal bone structure, or solitary bone plasmacytoma only • Low M-component production rate ➤ IgG value < 5 g/dL ➤ IgA value < 3 g/dL ➤ Bence-Jones protein < 4 g per 24 hour	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither stage I or III	Neither stage I or III
III	One or more of the following: • Hemoglobin value < 8.5 g/dL • Serum calcium value > 12 mg/dL • Advanced lytic bone lesions • High M-component production rate ➤ IgG value > 7 g/dL ➤ IgA value > 5 g/dL ➤ Bence-Jones protein > 12 g per 24 hour	Serum beta-2 microglobulin ≥ 5.5 mg/dL
Subclassification Criteria A Normal renal function (serum creatinine level < 2.0 mg/dL) B Abnormal renal function (serum creatinine level ≥ 2.0 mg/dL)		

[1] Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. Cancer 1975;36:842-854. Copyright© 1975; American Cancer Society . Reproduced with permission of John Wiley & Sons, Inc.
[2] Greipp P, San Miquel J, Durie B, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412-3420.

DEFINITION OF MULTIPLE MYELOMA (SMOLDERING AND ACTIVE)

Smoldering (Asymptomatic) Myeloma	Active (Symptomatic) Myeloma[a]
M-protein in serum ≥ 30 g/L and/or Bone marrow clonal plasma cells ≥ 10% No related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms	Requires one or more of the following: • Calcium elevation (> 11.5 g/dL) • Renal insufficiency (creatinine > 2 mg/dL) • Anemia (hemoglobin < 10 or 2 g < normal) • Bone disease (lytic or osteopenic)

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

International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121:749-757.

International Uniform Response

Reprinted by permission from Macmillan Publishers Ltd. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-1473.

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA

EBMT, IBMTR, and ABMTR criteria for definition of response, relapse, and progression in patients with multiple myeloma treated with high-dose therapy and stem cell transplant.

Complete response (CR) requires all of the following:
- Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- < 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks, it is not necessary to repeat the bone marrow, except in patients with nonsecretory myeloma in whom the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
- Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, of the criteria for CR are fulfilled are classified as partial response (PR), providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.
PR requires all of the following:
- ≥ 50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.
- Reduction in 24 hour urinary light chain excretion either by ≥ 90% or to 200 mg, maintained for a minimum of 6 weeks.
- For patients with nonsecretory myeloma only, ≥ 50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
- ≥ 50% reduction in the size of soft tissue plasmacytomas (according to radiography or clinical examination).
- No increase in size or number of lytic bone lesions (development of a compression fractures does not exclude response).

Patients in whom some, but not all, of the criteria for PR are fulfilled are classified as minimal response (MR), provided the remaining criteria satisfy the requirements for MR. MR requires all of the following:
- 25% to 49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
- 50% to 89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg per 24 hours, maintained for a minimum of 6 weeks.
- For patients with nonsecretory myeloma only, 25% to 49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
- 25% to 49% reduction in the size of soft tissue plasmacytomas (according to radiography or clinical examination).
- No increase in size or number of lytic bone lesions (development of a compression fractures does not exclude response).

No change: not meeting the criteria of either minimal response or progressive disease.

Plateau: stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.
Time point for assessing response:
- Response to the transplant procedure is assessed through comparison with results immediately before conditioning.
- If transplant is part of a treatment program, response to the whole treatment program is assessed through comparison with the results at the start of the program.

Relapse from CR requires at least one of the following:
- Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
- ≥ 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.9 mmol/L) not attributable to any other cause.

Reproduced with permission from The International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121:749-757.

RESPONSE CRITERIA FOR MULTIPLE MYELOMA (continued)

Progressive disease (for patients not in CR) requires one or more of the following:

- > 25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed by at least one repeated investigation.
- > 25% increase in the 24 hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg per 24 hours and confirmed by at least one repeated investigation.
- > 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L) not attributable to any other cause.

Reproduced with permission from Blade J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patient with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Br J Haematol 1998;102:1115-1123.

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA (continued)

International Myeloma Working Group Uniform Response Criteria

Response Category	Response Criteria[1]
sCR, stringent complete response	CR as defined below plus: Normal free light chain (FLC) ratio and absence of clonal cells in bone marrow[2] by immunohistochemistry or immunofluorescence[3]
CR, complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[2]
VGPR, very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours
PR, partial response	≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours 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 the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD, 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 CR, VGPR, PR, or progressive disease

[1] All response categories require 2 consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[2] Confirmation with repeat bone marrow biopsy not needed.

[3] Presence/absence of clonal cells is based on the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is of > 4:1 or < 1:2.

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA (continued)

International Myeloma Working Group Uniform Response Criteria

Relapse Subcategory	Relapse Criteria
Progressive disease[1] (to be used for calculation of time to progression and progression-free survival and points for all patients, including those in CR; includes primary progressive disease and disease progression on or off therapy)	Progressive disease: requires any one or more of the following: Increase of ≥ 25% from baseline in: • Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[2] • Urine M-component and/or (the absolute increase must be ≥ 200 mg per 24 hours • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[3] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[1]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[2] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions • 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 sum of the products of the cross-diameters of the measurable lesion • Hypercalcemia (> 11.5 mg/dL) • Decrease in hemoglobin of ≥ 2 g/dL • Rise in serum creatinine by 2 mg/dL or more
Relapse from CR[1] (to be used only if the end point studied is disease-free survival)[4]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow[3] • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

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

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MYELOMA THERAPY[1–4]

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

- Primary induction therapy for transplant candidates:
  - Bortezomib/dexamethasone (category 1)
  - Bortezomib/doxorubicin/dexamethasone (category 1)
  - Bortezomib/lenalidomide[5]/dexamethasone (category 2B)
  - Bortezomib/thalidomide/dexamethasone (category 1)
  - Dexamethasone (category 2B)
  - Liposomal doxorubicin/vincristine/dexamethasone (DVD; category 2B)
  - Lenalidomide[5]/dexamethasone (category 1)
  - Thalidomide/dexamethasone (category 2B)

- Primary induction therapy for nontransplant candidates:
  - Dexamethasone (category 2B)
  - Lenalidomide/low-dose dexamethasone (category 1)
  - DVD (category 2B)
  - Melphalan/prednisone (MP)
  - Melphalan/prednisone/bortezomib (MPB; category 1)
  - Melphalan/prednisone/thalidomide (MPT; category 1)
  - Thalidomide/dexamethasone (category 2B)
  - Vincristine/doxorubicin/dexamethasone (VAD; category 2B)

- Maintenance therapy:
  - Interferon (category 2B)
  - Steroids (category 2B)
  - Thalidomide (category 1) ± prednisone (category 2B)

- Salvage:
  - Bendamustine (category 2B)
  - Bortezomib[6] (category 1)
  - Bortezomib/dexamethasone
  - Bortezomib/lenalidomide/dexamethasone (category 2B)
  - Bortezomib/liposomal doxorubicin[6] (category 1)
  - Cyclophosphamide-VAD
  - Dexamethasone
  - Dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP)
  - Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE)
  - High-dose cyclophosphamide
  - Lenalidomide/dexamethasone (category 1)
  - Lenalidomide
  - Repeat primary induction therapy (if relapse at > 6 month)
  - Thalidomide
  - Thalidomide/dexamethasone

[1]Selected, but not inclusive of all regimens.
[2]Treatments are listed alphabetically and do not imply preference.
[3]Consider herpes zoster prophylaxis for patients treated with singe-agent bortezomib.
[4]Prophylactic anticoagulation recommended for patients undergoing thalidomide-based therapy or lenalidomide with dexamethasone therapy.
[5]Consider harvesting peripheral blood stem cells before prolonged exposure to lenalidomide.
[6]Bortezomib/liposomal doxorubicin is preferred to single-agent bortezomib.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

ADJUNCTIVE TREATMENT

Bone Disease
- Bisphosphonates (pamidronate and zolendronic acid)
  - All patients with documented bone disease, including osteopenia (category 1)
  - Use of bisphosphonates in smoldering or stage I disease preferrably in the context of a clinical trial. These patients should have bone survey yearly
  - Monitor for renal dysfunction with use of bisphosphonates
  - Monitor for osteonecrosis of the jaw
- Radiation Therapy
  - Low-dose radiation therapy (10–30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture or 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, steroids, and/or calcitonin

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

Anemia (see NCCN Clinical Practice Guidelines in Oncology: Cancer- and Treatment-Related Anemia*)
- Consider erythropoietin for anemic patients

Infection (see NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections*)
- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection
- Consider pneumovax and influenza vaccine
- Consider PCP, herpes, and antifungal prophylaxis if high-dose dexamethasone regimen
- Consider herpes zoster prophylaxis for patients treated with bortezomib

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

Coagulation/Thrombosis
- Prophylactic anticoagulation recommended for patients thalidomide-based therapy or lenalidomide with dexamethasone therapy

*To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

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INITIAL DIAGNOSTIC WORKUP

Clinical and amyloid-related assessment
- Orthostatic vital signs
- History and physical
- Abdominal fat pad aspirate or involved organ biopsy
- Hereditary amyloid testing (for African-American and peripheral neuropathy patients at minimum)

Hematologic
- CBC with differential
- Prothrombin time (PT), partial thromboplastin time (PTT), Factor X (if indicated)

Plasma cell disease
- Bone marrow aspirate and biopsy with immunohistochemical staining for kappa and lambda and Congo red staining amyloid
- Electrophoresis of serum and urine
- Immunoelectrophoresis serum and urine
- Serum free light chains

Renal
- Blood urea nitrogen, creatinine
- 24 hour urinary protein
- Creatinine clearance

Cardiac
- EKG
- Echocardiogram
- Chest x-ray
- Brain natriuretic peptide and troponin

Liver and GI tract
- Alkaline phosphatase, liver enzymes, bilirubin
- Stool guaiacs
- Gastric emptying scan (if gastroparesis present)
- Ultrasound or CT scan to document craniocaudal liver span
- Random serum cortisol and thyroid-stimulating hormone (TSH)

Peripheral Nervous System
- EMG (if clinically significant peripheral neuropathy)

Other
- Endocrine testing: TSH, cortisol
- Pulmonary testing: pulmonary function tests

CLINICAL FINDINGS[a]

Renal involvement only

Cardiac involvement

Multiorgan involvement

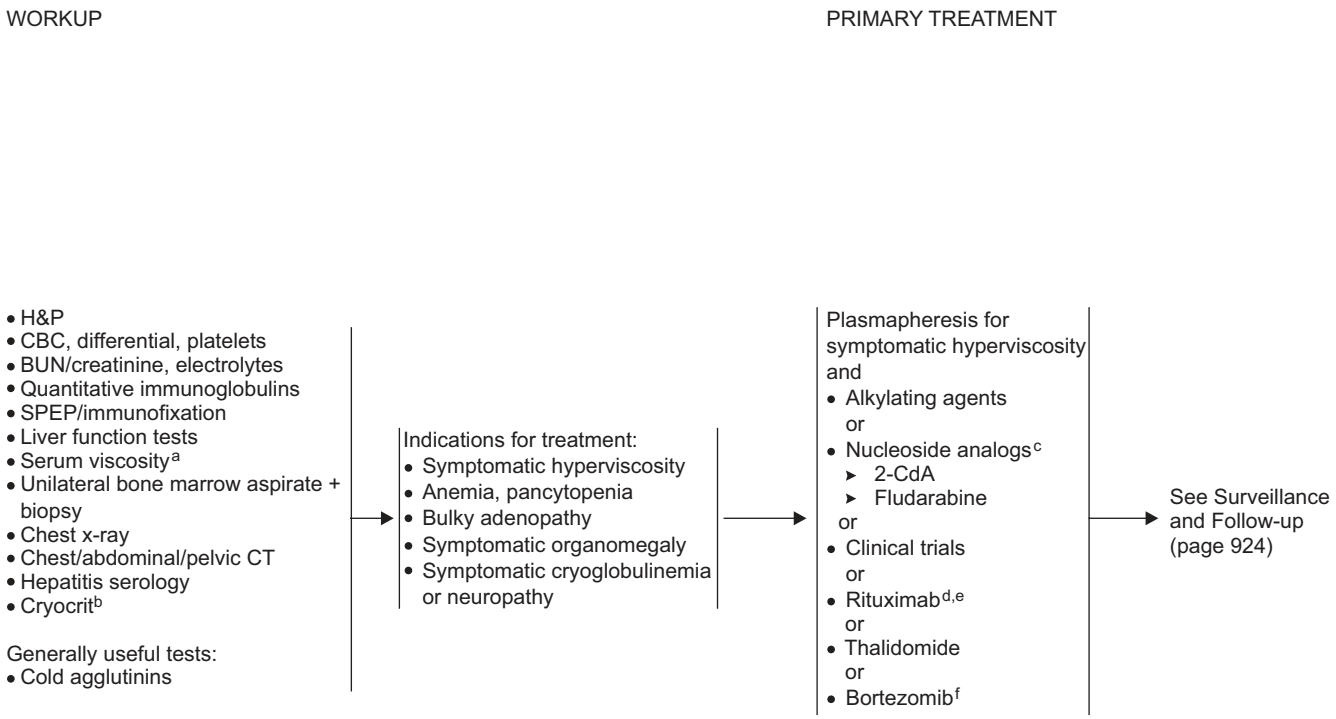
PRIMARY TREATMENT

Data are insufficient to indicate the optimal treatment of amyloidosis and, therefore, all patients should be treated in the context of a clinical trial when possible

Therapeutic options include:
- Oral melphalan and dexamethasone
- Intermediate- or high-dose melphalan with stem cell transplant
- Dexamethasone and alpha-interferon
- Thalidomide and dexamethasone
- Single-agent bortezomib[b]
- Lenalidomide/dexamethasone
- Best supportive care

[a] Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis. Am J Hematol 2005;79:319-328.

[b] Consider herpes zoster prophylaxis for patients treated with bortezomib.



Proposed Criteria for the Diagnosis of Waldenström's macroglobulinemia
- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes, plasmacytoid cells, and plasma cells
- Diffuse, interstitial, or nodular pattern of bone marrow infiltration
- Surface Ig+, CD5-, CD10-, CD19+, CD20+, CD23- immunophenotype

Reprinted from Owen RG. Developing diagnostic criteria in Waldenstrom's macroglobulinemia. Semin Oncol 2003;30:196-200. Copyright (2003), with permission from Elsevier.

[a] Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity.
[b] If cryocrit positive, then initial and follow-up sample should be measured under warm conditions.
[c] Avoid nucleoside analogs if a stem cell transplant is considered.
[d] Preliminary data indicate significant response with minimal toxicity. Long-term results are unknown.
[e] For patients with M-protein > 5 g/dL, use of rituximab alone is discouraged, reports of transient increase in M-protein have been noted with use of rituximab alone.
[f] Consider herpes zoster prophylaxis for patients treated with bortezomib.

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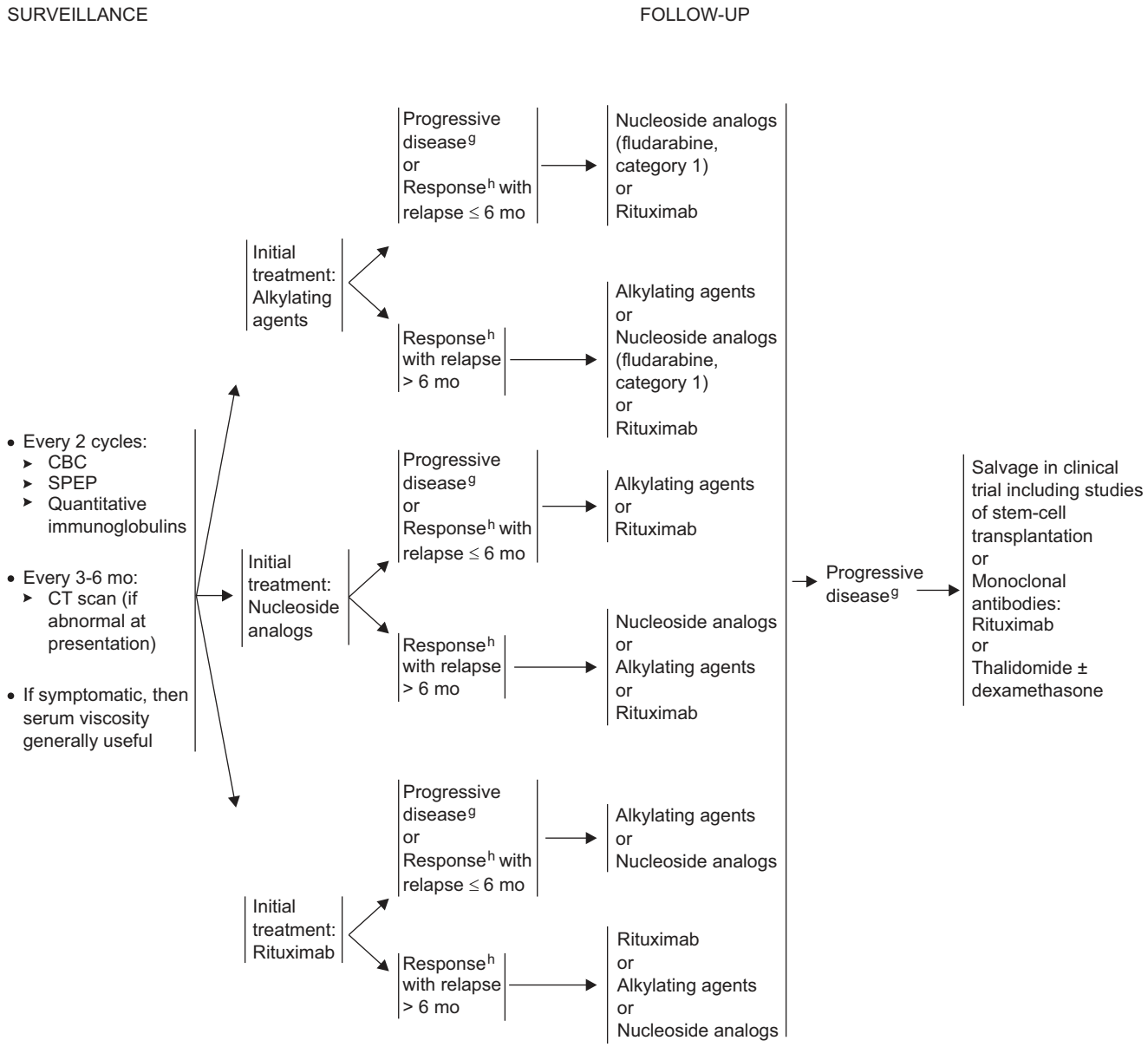

[g] Disease progression: defined by a sustained ≥ 25% rise in M-protein in serum or urine, adenopathy or organomegaly.
[h] Disease partial response: defined by at least 50% reduction in all measurable disease, confirmed with a second measurement at ≥ 4 weeks later.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

Text continued from p. 909

of β_2-microglobulin reflects the tumor mass and is now considered a standard measure of the tumor burden. Serum analysis also includes quantitative immunoglobulins levels of different types of antibodies (IgG, IgA, and IgM), serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE) to obtain more specific information about the type of abnormal antibodies present. Assessing changes and proportions of various proteins, particularly the monoclonal protein (M-protein), helps track progression of myeloma disease and response to treatment. Urine analysis includes evaluation of a 24-hour urine sample for total protein; a urine protein electrophoresis (UPEP); and a urine immunofixation electrophoresis (UIFE).

Most patients have serum proteins with or without associated urinary protein. In the Mayo Clinic review of 1027 patients with newly diagnosed MM, 20% of patients had secretory urinary proteins, but 3% had neither serum nor urine proteins and therefore had nonsecretory myeloma.[5] Once the myeloma or M-protein is quantitated, the same test must be used for serial studies to ensure accurate relative quantitation.

Other tests include skeletal survey, unilateral bone marrow aspirate, and biopsy. Chromosomal analysis using conventional karyotyping (cytogenetics) and fluorescence in situ hybridization (FISH) may be performed in the plasma cells obtained from bone marrow aspiration. Cytogenetics and FISH may detect chromosomal abnormalities, frequently involving translocations of the immunoglobulin heavy chain genes. Specific chromosomal abnormalities identified include a deletion in chromosome 13 [del(13)] and a translocation between chromosomes 4 and 14 [t(4;14)], which are both associated with a poor prognosis. A translocation between 11 and 14 [t(11;14)] may be associated with improved survival.[6,7] Other chromosomal abnormalities include deletion in chromosome 17 [del(17)] and translocation between 14 and 16 [t(14;16)].

Currently, data are inadequate to determine how this prognostic information should be used to direct patient management. Furthermore, the adverse impact of these cytogenetic abnormalities has been established in the context of conventional therapies and stem cell transplant (SCT) but not with novel treatments.

Bone marrow immunohistochemistry sometimes may be useful to confirm the presence of monoclonal plasma cells to more accurately measure plasma cell involvement, and bone marrow flow cytometry can help define the disease.

Additional tests useful under some circumstances include MRI,[8] CT, and PET/CT scan. Active myeloma is positive on PET scan.[9,10] A tissue biopsy may also be necessary to confirm the presence of plasmacytomas. Under some circumstances, use of an assay for serum free light chain (FLC) along with the aforementioned workup procedures is recommended. The serum FLC assay in combination with SPEP and SIFE yields high sensitivity.[11] It is useful to diagnose and monitor monoclonal gammopathies, especially nonsecretory myeloma and AL amyloidosis.[12,13]

The panel also recommends plasma cell labeling index to identify the fraction of the myeloma cell population that is proliferating,[14] and also staining of bone marrow and fat pad to detect the presence of amyloid. Serum viscosity should also be assessed if hyperviscosity is suspected.

Selected patients may undergo allogeneic (i.e., from someone else) transplantation, wherein physicians administer nonmyeloablative therapy and infuse stem cells (i.e., peripheral blood or bone marrow) obtained from a donor, preferably a human leukocyte antigen (HLA)-identical sibling. This technique requires patient to be HLA-typed.

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

Diagnostic Categories

Based on the results of the clinical and laboratory evaluation, patients are initially classified as either having smoldering (asymptomatic) or active (symptomatic) disease (page 914). Those with active disease are then further categorized according to stage, based on either the Durie-Salmon staging system or the International Staging System (ISS; page 915).[15] The ISS is based on easily obtained laboratory measures (serum β_2-microglobulin and serum albumin) and is easier to use than the Durie-Salmon staging system for patients with previously untreated MM.

Solitary plasmacytomas are further categorized as osseous or extraosseous. *Osseous plasmacytoma* is defined as a plasmacytoma emanating from bone without other evidence of disease. Solitary plasmacytomas derived from soft tissue are termed *extraosseous*.[16] However, treatment and follow-up options for

osseous and extraosseous plasmacytomas are similar. The diagnosis of plasmacytoma requires a thorough evaluation to rule out the presence of systemic disease, because many patients presumed to have solitary plasmacytomas are found to have occult disease.

Response Criteria

Assessing the response to treatment is a key determinant of myeloma treatment. Pages 916 through 919 list 2 different sets of response criteria, one developed by the European Group for Bone and Marrow Transplant (EBMT; page 916) and the other by the International Myeloma Working Group (IMWG; page 918). The EBMT criteria categorize response as complete response (CR), partial response, minimal response, relapse, and progressive disease, whereas the IMWG criteria categorize response as stringent CR, CR, very good partial response (VGPR), partial response, and stable disease. Because the IMWG criteria were recently developed and are not yet validated, the EBMT criteria are more commonly used.

Primary Treatment

Solitary Plasmacytoma

For patients with osseous plasmacytoma, primary radiation therapy (≥ 45 Gy) to the involved field constitutes initial treatment and is potentially curative.[17,18] Extraosseous plasmacytomas are treated initially with radiation therapy (≥ 45 Gy) to the involved field and/or with surgery. Follow-up and surveillance for both solitary plasmacytoma and extraosseous plasmacytoma consist of blood and urine tests every 4 weeks initially to monitor response to the radiation therapy. If the paraprotein completely disappears, then the frequency of the tests could be reduced to every 3 to 6 months and as clinically indicated. If the protein persists, then monitoring should continue every 4 weeks.

Blood tests include a CBC; serum chemistry for creatine, albumin, LDH, calcium, and β_2-microglobulin; serum quantitative immunoglobulins; SPEP; and SIFE. Serum FLC assay may also be considered. Urine tests include a 24-hour urine assay for total protein, UPEP, and UIFE.

Bone marrow biopsy should be considered as clinically indicated, and bone survey may be considered annually or as clinically indicated. MRI and/or CT and/or PET/CT may also be considered every 6 to 12 months or as clinically indicated. PET imaging may detect early bone marrow involvement in patients with solitary plasmacytoma.[19,20]

If progressive disease emerges, then the patient should be re-evaluated for recurrent extraosseous plasmacytoma or myeloma, with systemic therapy administered as indicated.

Smoldering (Asymptomatic) Myeloma

Patients with asymptomatic smoldering MM have an indolent course for many years without therapy (see page 911). These patients have low concentrations of M-protein (≥ 30 g/L) and bone marrow infiltration of 10% plasma cells or more; however, they do not have anemia, renal failure, hypercalcemia, or bone lesions. Patients with Durie-Salmon stage I MM (page 915) also have low amounts of M-protein without significant anemia, hypercalcemia, or bone disease. Patients with smoldering myeloma, including those with Durie-Salmon stage I, do not need primary therapy because they can do well for many months to years before the disease progresses. These patients should initially be observed at 3- to 6-month intervals (category 1 recommendation).

Blood tests include a CBC; serum chemistry for creatine, albumin, LDH, calcium, and β_2-microglobulin; serum quantitative immunoglobulins; SPEP; and SIFE. Serum FLC assay may also be considered. Urine tests include a 24-hour urine assay for total protein, UPEP, and UIFE.

Bone marrow biopsy should be considered as clinically indicated, and bone survey may be considered annually or as clinically indicated. MRI and/or CT and/or PET/CT may also be considered as clinically indicated. PET imaging seems to reliably predict active myeloma through determination of fluorodeoxyglucose uptake; low-level smoldering myeloma is consistently negative on PET scan.[9] It can also assess the extent of active disease, detect extramedullary involvement, and evaluate treatment response.[21–24]

If the disease progresses to stage II or higher, then patients should be treated according to the guidelines for advanced MM (see page 911). Disease progression is defined as a sustained 25% or greater increase in M-protein in serum or urine, greater than 25% increase in plasma cells in bone marrow aspirate or on trephine biopsy, development of new sites of lytic disease, hypercalcemia, or increase size of bone lesions or in tumor volume in plasmacytomas.

Active (Symptomatic) Multiple Myeloma

Induction Chemotherapy: Patients presenting with active (symptomatic) myeloma are initially treated with induction chemotherapy followed by high-dose chemotherapy and autologous stem cell support in selected patients. 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 transplantation. Therefore, a first step in evaluating patients with advanced MM is to determine whether they would be considered candidates for high-dose therapy and transplantation based on age and comorbidities. However, advanced age and renal dysfunction are not absolute contraindications to transplant. Supportive care should also be considered for all patients at diagnosis. For example, 80% of patients have bone disease and up to 33% have renal compromise. Bone disease, renal dysfunction, and other complications, such as hypercalcemia, hyperviscosity, and coagulation/thrombosis, should be treated with appropriate adjunctive measures (see Adjunctive Treatment, page 935, and page 921 in the algorithm).

Induction regimens for potential transplant candidates and options for those who are not are listed on page 920. Research into various induction regimens has focused on improving CR rates in patients, regardless of transplantation eligibility.

Primary Induction Therapy for Transplantation Candidates: Bortezomib/dexamethasone and related bortezomib-based regimens, lenalidomide/dexamethasone, and thalidomide/dexamethasone are among the panel's current choices for induction therapy associated with high response rates (see page 920).

Bortezomib-Based Regimen: Bortezomib is another relatively new agent, a first-in-its-class proteasome inhibitor that not only directly targets the myeloma cell but also targets the interaction between the tumor cell and the bone marrow microenvironment. For example, apoptotic signaling of the myeloma cells can be triggered in various ways. Bortezomib targets both intrinsic and extrinsic pathways, whereas dexamethasone targets only the intrinsic pathway. This emerging understanding of the bone marrow microenvironment provides the rationale for combining these drugs.

The Intergroupe Francophone du Myelome (IFM) cooperative group trial randomized 482 patients to either bortezomib and dexamethasone regimen or VAD (vincristine, doxorubicin, and dexamethasone) regimen as induction therapy before SCT.[25] The bortezomib and dexamethasone arm showed a better CR rate compared to VAD.[25]

During the 2008 American Society of Hematology (ASH)/ASCO Joint Symposium, Harousseau et al. reported updated results from the IFM 2005/01 trial. Post-induction CR/near CR rates were 15% in the bortezomib plus dexamethasone arm compared with 7% in the VAD arm (P = .0035). Higher response rates translated to higher rates of progression-free survival in bortezomib and dexamethasone arms. The median progression-free survival was not reached for the bortezomib plus dexamethasone group. However, the projected 2-year progression-free survival rate was 69% in the bortezomib plus dexamethasone arm, compared with 60% in the VAD arm (P = .0115). Among patients who proceeded to high-dose therapy and SCT, those who received bortezomib and dexamethasone had a higher probability of achieving VGPR or better.

Serious adverse events were reported in 27% of the patients treated with bortezomib plus dexamethasone, compared with 34% of those treated with VAD. Based on the IFM trial data and uniform consensus among the panel members, bortezomib plus dexamethasone is a category 1 option for induction therapy for transplantation candidates.

At the 2008 ASH annual meeting, interim results were presented from the phase III HOVON-65/GMMG-HD4 trial, which randomized 300 patients with newly diagnosed stage II/III myeloma to induction bortezomib, doxorubicin, and dexamethasone (PAD) versus VAD.[26] A significant number of patients in the PAD arm experienced at least a VGPR after induction therapy (42% vs. 15%; $P < .000001$) and at least a partial response rate or better in 83% versus 59% in the VAD arm. Similar response rates were seen after transplantation (> VGPR; 80% vs. 50%; P = .0019) and at least a partial response or better in 93% in PAD versus 80% in the VAD arm. No unexpected toxicities occurred, and deletion of chromosome 13q did not have a significant impact on response. Responses improved with bortezomib maintenance. Based on interim data from the HOVON-65/GMMG-HD4 trial and uniform consensus among panel members,

PAD is a category 1 option for induction therapy in transplantation candidates.

The GIMEMA Italian Multiple Myeloma Network reported updated results for a phase III trial investigating bortezomib, thalidomide, and dexamethasone versus thalidomide and dexamethasone induction therapy, followed by double autologous SCT with high-dose therapy (melphalan, 200 mg/m^2), and consolidation therapy with the same induction regimen.[27] The addition of bortezomib to thalidomide and dexamethasone significantly improved response rates after induction and first and second SCT. Two-year progression-free survival rates were significantly improved in the patients treated with bortezomib, thalidomide, and dexamethasone (progression-free survival, 90% vs. 80%; P = .009). However, overall survival at 2 years was not significantly different (96% vs. 91%). The superior response with bortezomib, thalidomide, and dexamethasone induction was seen across poor prognostic subgroups. Patients undergoing this induction therapy experienced grade 3/4 peripheral neuropathy; however, response rates remained high for those continuing treatment. Based on GIMEMA trial data and uniform consensus among the panel members, bortezomib added to thalidomide and dexamethasone is a category 1 option for induction therapy for transplantation candidates.

A phase I/II study results show that lenalidomide, bortezomib, and dexamethasone is very active and well tolerated in patients with newly diagnosed MM.[28,29] This regimen is included as induction therapy for transplantation candidates but, because the data are preliminary, it is a currently a category 2B recommendation.

Bortezomib treatment has been associated with an incidence of herpes zoster.[30,31] The incidence of bortezomib-associated herpes zoster may be reduced with the use of prophylactic acyclovir.[31] The risk for deep vein thrombosis is low with bortezomib; however, peripheral neuropathy can be higher. Bortezomib-based regimens may be of value in patients with renal failure and in those with adverse cytogenetic features.

Lenalidomide-Based Regimen: Lenalidomide, a potent analogue of thalidomide, received FDA approval for the treatment of relapsed/refractory MM in combination with dexamethasone (see Salvage Therapy, page 933). However, lenalidomide and dexamethasone have also been investigated as induction therapy. The phase III randomized controlled study by SWOG (S0232) compared dexamethasone with combined therapy of dexamethasone plus lenalidomide for patients with newly diagnosed MM.[32] This trial was halted at interim analysis and patients on dexamethasone alone were allowed to switch to lenalidomide with dexamethasone. The SWOG Data and Safety Monitoring Committee based its recommendation to permanently close enrollment based on the preliminary 1-year survival results from the ECOG phase III study (E4A03).[33,34] When the SWOG trial was halted, patients in the lenalidomide plus dexamethasone arm showed improved an CR rate compared with those treated with dexamethasone alone (22% vs. 4%).[32]

Updated results for the ECOG E4A03 trial for patients with newly diagnosed MM were also presented at the 2008 ASH/ASCO Joint Symposium. The primary analysis in this study evaluated lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in 445 patients. At a median follow-up of 3 years, patients in the lenalidomide plus high-dose dexamethasone arm showed a superior overall response rate (79% vs. 68%; P = .008). This result did not translate to an improvement in overall survival (75% vs. 74%; P = .46) or time-to-progression, because toxicity rates are significantly higher with lenalidomide and high-dose dexamethasone.

Recent reports[35–37] indicate a decrease in CD34-positive cells collected after prolonged lenalidomide treatment, and therefore the panel recommends harvesting peripheral blood early in the courses of induction with lenalidomide. The incidence of deep vein thrombosis is low with single-agent lenalidomide or lenalidomide plus low-dose dexamethasone, but rises when combined with high-dose dexamethasone. Prophylactic anticoagulation is also recommended when lenalidomide and dexamethasone is given.[38]

Thalidomide-Based Regimen: Thalidomide attacks multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others. Rajkumar et al.[39] reported the results of a study involving 207 patients with newly diagnosed MM randomized to receive thalidomide and dexamethasone or dexamethasone alone. The response rate to the combined therapy was significantly higher than for dexamethasone alone (63% vs. 41%, respectively). Stem cells

for subsequent transplantation were also successfully collected. However, increased toxicity is associated with thalidomide; specifically deep vein thrombosis, and therefore prophylactic anticoagulation is recommended if thalidomide and dexamethasone are given. Other side effects of thalidomide included rash, neuropathy, or bradycardia. The use of thalidomide requires individual patient consideration, and the higher response rate of the thalidomide and dexamethasone combination must be weighed against the increased side effects.

Dexamethasone as a single agent (category 2B) may be a reasonable option as short-term induction therapy for a highly selected group of patients.

Data from recent studies suggest that VAD may no longer be recommended because most disease responds to induction regimens based on novel drug combinations. Another category 2B recommendation is liposomal doxorubicin/vincristine/dexamethasone (DVD).[40]

Primary Induction Therapy for Nontransplantation Candidates: All the regimens described for transplantation candidates are also options for nontransplantation candidates. The following regimens compromise stem cell reserve and are therefore options only for nontransplantation candidates.

Melphalan and prednisone (MP) has been a standard treatment of MM since 1960. A review of the clinical trials reported that MP results in a 60% response rate with duration of 18 months and an overall survival of 24 to 36 months.[41] More recently, Palumbo et al.[42] were the first to report that combined near CR and CR rates were 27.9% for thalidomide in combination with melphalan and prednisone (MPT) compared with 7.2% for MP.

Subsequently, several phase III trials have reported significant higher overall response rates with MPT versus MP (57%–76% vs. 31%–48%), including higher CR or VGPR rates (7%–15.5%).[43–47] The impact of MPT on survival is unclear because only the IFM studies[43,44] reported a survival advantage in patients on MPT. Comparisons between these studies are difficult because of differences in patient populations, duration of treatment, and use of maintenance regimens. However, because of the significantly higher overall response rates consistently seen in these studies, MPT is a category 1 recommendation for patients not eligible for transplantation.

Addition of bortezomib to MP (MPB) was investigated in the large, randomized, international phase III VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) trial.[48] This study evaluated MP (n = 338) versus MPB (n = 344) in previously untreated patients with MM who were 65 years of age or older, or those younger than 65 years and ineligible for transplantation. The addition of bortezomib resulted in highly significant increases in time to disease progression, progression-free survival, overall survival, time to next treatment, and CR. Adverse cytogenetics, advanced age, and renal function had no impact on the efficacy of the bortezomib-containing regimen, which was well tolerated. Updated results from the phase III VISTA trial were reported at the 2008 ASH annual meeting.[49] The 3-year overall survival rate was 72% in the MPB arm compared with 59% in the MP arm ($P = .0032$). Median treatment-free intervals were also superior in the MPB arm (28.1 vs. 19.2 months and 16.6 vs. 8.4 months, respectively; $P < .000001$).

Furthermore, time-to-progression and overall survival was unaffected by advanced age, renal impairment, and adverse cytogenetics (t[4;14], t[14;16], del[17p]) in patients in the MPB arm. These data confirm the superiority of MPB over MP alone in patients with MM ineligible for transplantation. Based on the VISTA trial results, the MPB regimen is now a category 1 recommendation.

Both MPT and MPB regimens have shown superior responses compared with MP; therefore, the panel has designated MP a category 2A recommendation.

Based on the results of the SWOG SO232 trial,[32] which included nontransplantation candidates, and the ECOG E4A03 trial,[33] which also included elderly patients, lenalidomide in combination with low-dose dexamethasone is considered a category 1 option.

The older regimens, such as dexamethasone alone, thalidomide with dexamethasone, VAD, and DVD, are category 2B options.

Follow-Up After Induction Therapy: After initial induction chemotherapy, patients are re-evaluated with laboratory tests, bone survey, and bone marrow biopsy listed on page 911 to determine whether they have experienced a treatment response or if primary progressive disease is present. Primary progressive myeloma is defined on pages 916 through 919. A stem cell harvest is performed on potential transplantation candidates, with enough stem cells

collected for 2 transplants in anticipation of a tandem transplant or a second transplant as salvage therapy. Autologous and allogeneic transplants are discussed further later. Alternatively, patients may consider continuation of conventional chemotherapy to reach a treatment plateau. Treatment should be continued for, at most, 2 cycles beyond maximal response; continued treatment does not prolong the duration of the plateau phase.

SCTs

High-dose chemotherapy and SCTs can be classified as a single autologous SCT, a tandem SCT, or an allogeneic SCT. An allogeneic SCT can be performed after either myeloablative therapy or nonmyeloablative therapy. Nonmyeloablative therapy, also referred to as a *mini transplant*, has been investigated as a technique to decrease toxicity of the allotransplant while preserving the alloimmune graft-versus-myeloma effect.[50–52] An allogeneic SCT may also follow an autologous SCT.

These guidelines indicate that all types of SCT are appropriate in different clinical settings. However, in general, all candidates for high-dose chemotherapy must have sufficient liver, renal, pulmonary, and cardiac function. Earlier studies of autologous transplantation included total body irradiation (TBI) as a component of the preparative regimen. Because chemotherapy-only regimens have recently been shown to have equivalent efficacy and less toxicity than TBI, TBI regimens have now been abandoned.[53]

Autologous SCTs

Single Transplant: Autologous SCT results in high response rates and remains the standard of care after induction therapy for eligible patients. In 1996, results of the first randomized trial showed that autologous SCT is associated with statistically significant higher response rates and increased overall and event-free survival compared with similar patients treated with conventional therapy.[54] In 2003, results of a second trial showed that patients treated with high-dose therapy had an increased CR rate and improved overall survival compared with those treated with standard therapy (54 vs. 42 months).[55] The benefit was more pronounced in higher-risk patients.

However, in an American trial randomizing 510 patients to either high-dose therapy with autologous stem cell support or standard therapy, with a median follow-up of 76 months, Barlogie et al.[56] reported no differences in response rates, progression-free survival, or overall survival.

The reason for these discrepant results between the American and French studies are unclear, but may be related to differences in the specific high-dose and conventional regimens used. For example, the American study included TBI as part of the high-dose regimen, and TBI was subsequently found to be inferior to high-dose melphalan.[53]

Another trial randomized 190 patients aged 55 to 65 years to either standard or high-dose therapy.[57] This study was specifically designed to include older patients, with a median age of 61 years compared with 54 to 57 years in other trials. After 120 months of follow-up, no significant difference was seen in overall survival, although a trend was seen toward improved event-free survival 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 treatment choice between high- and conventional-dose chemotherapy should be based on personal preference in older patients. For example, an early transplant may be favored because patients can experience a longer symptom-free interval. However, this study[57] also showed that a transplant performed at relapse (as salvage therapy) has a similar overall survival to an early transplant.

All randomized studies of autologous SCT after induction therapy were designed and implemented before the availability of thalidomide, lenalidomide, or bortezomib. Therefore, the role of transplant may evolve in the future. Updated results from the IFM 2005/01 study[25] of patients with symptomatic MM showed that those undergoing induction therapy with bortezomib/dexamethasone before autologous SCT had a marked improvement in overall response rate compared with those treated with VAD. After the first autologous SCT, CR/near CR rates were 40% in the bortezomib plus dexamethasone arm, compared with 22% in the VAD arm ($P = .0001$). In the bortezomib plus dexamethasone arm, 34% required a second SCT compared with 47% in the VAD arm.

In another study, bortezomib and dexamethasone with thalidomide was compared with thalidomide/dexamethasone for induction therapy before

SCT in 450 patients.[27] The 3-drug regimen yielded high response rates compared with the 2-drug regimen, with CR/near CR of 32% (vs. 12%) and VGPR of 62% (vs. 29%). After SCT, improved responses were still seen with bortezomib, dexamethasone, and thalidomide compared with thalidomide plus dexamethasone (CR/near CR, 55% vs. 29%; VGPR, 76% vs. 53%). Taken together, these studies suggest that improved responses with the new induction regimen are associated with improved outcomes after transplantation.

Furthermore, interest has been shown in further defining the quality of a complete remission to better predict who would best benefit from transplantation. For example, PCR techniques to detect immunoglobulin gene rearrangements can better define molecular remissions. In one study of 70 patients who had undergone an allogeneic transplant, those who had negative PCR results had a significantly lower risk for relapse.[58]

Studies have found that progressive disease emerging after initial induction chemotherapy does not preclude a good response to autologous SCT.[55,59,60] For example, in a case series involving 50 patients with primary progressive MM and 100 patients with responsive disease, Kumar et al.[59] compared the results of autologous SCT. The 1-year progression-free survival from the time of transplant was 70% in the primary progressive group compared with 83% in the chemosensitive group. For this reason, the guidelines indicate that autologous SCT is the preferred option for treating primary progressive or refractory disease compared with either allogeneic SCT or conventional-dose salvage therapy (page 913).

Tandem or Repeat SCTs: Tandem SCT refers to a planned second course of high-dose therapy and SCT within 6 months of the first. Planned tandem transplants have been studied in several randomized trials. In the IFM94 trial, Attal et al.[61] randomized newly diagnosed myeloma patients to single or tandem autologous transplants. Among patients assigned to the tandem transplant group, 78% underwent the second transplant at a median time of 2.5 months after the first.

Various options for salvage therapy were provided. For example, patients experiencing relapse in either group underwent either no therapy, additional conventional therapy, or another stem cell transplant. The probability of surviving event-free for 7 years after diagnosis was 10% in the single transplant group compared with 20% in the double transplant group.

An accompanying editorial by Stadtmauer[62] questions whether the promising results might be related to regimens used, rather than 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. 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, patients who did not experience a CR or VGPR within 3 months after the first transplant seemed to benefit the most from a second transplant. The authors of IFM94 suggested that the improvement in projected survival associated with tandem transplant is not related to improved response rates but rather to longer durations of response. Four other randomized trials have compared single versus tandem transplantation,[63–66] with none showing a significant improvement in overall survival. 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.[66] found that patients not in CR or near CR after the first transplant benefited the most from a second transplant. This finding confirms the observations of the IFM94 trial using non-TBI–based high-dose regimens.

Taken together, the following conclusions can be drawn from these trials:

- Attainment of a CR or near CR is important for survival benefit.
- Patients who attain a CR or near CR after an initial autotransplant do not benefit from a second autotransplant.
- Only patients with partial response or stable disease after the first autotransplant derive benefit from a second autotransplant.

According to the panel, a tandem transplant within 6 months of the initial transplant is an option for patients with partial response or stable disease after the first autologous SCT. However, because results were inconsistent among the randomized trials,

this recommendation is category 2A.

The algorithms identify 2 situations in which a repeat salvage autologous SCT is recommended: 1) in patients initially treated with induction therapy alone, followed by an autologous SCT after disease relapse, who then experience progressive disease after a first autologous SCT; and 2) in patients with initial CR or near CR after an initial single autologous SCT who develop progressive disease. Fewer data are available on the latter population than for those who undergo autologous SCT for responsive or primary progressive disease, partly because of patient age and extensive prior treatment. However, a systemic review sponsored by the American Society for Blood and Marrow Transplant (ASBMT) reported that some of these patients can experience durable complete or partial remission.[60] For this reason, this recommendation is category 2B and participation in a clinical trial is encouraged.

Allogeneic SCT: Allogeneic SCT includes either myeloablative or nonmyeloablative (i.e., "mini") transplants. Allogeneic SCT has been investigated as an alternative to autologous SCT to not only avoid contamination of reinfused autologous tumor cells but also take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, the lack of a suitable donor and the increased morbidity have limited this approach, particularly for the typical older population with MM. Nonmyeloablative transplants are designed to decrease the morbidity of high-dose chemotherapy while preserving the beneficial graft-versus-tumor effect. Therefore, the principle difference between myeloablative and nonmyeloablative transplants relates to the chemotherapy regimen used. Specific preparatory regimens were not a focus of these guidelines, and therefore no distinction is made between these approaches.

Given the small candidate pool, it is not surprising that there have been no randomized clinical trials comparing myeloablative allogeneic with autologous SCT, but multiple case series have described allogeneic SCT as an initial or salvage therapy for MM. In a 1999 review, Kyle[67] reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40%; few patients were cured. Other reviews also reported increased morbidity without convincing proof of improved survival.[60,68]

However, the SWOG randomized trial of autologous transplant versus conventional chemotherapy presents intriguing data.[56] The original trial had an ablative, allogeneic transplant group consisting of patients with HLA-identical siblings. Only 36 patients received allografts, and because of the high 6-month mortality rate of 45%, the allogeneic arm was closed. With 7 years of follow-up, the overall survival of the conventional chemotherapy, autologous, and allogeneic arms are all identical at 39%. The autologous and conventional chemotherapy arms do not show a plateau, however, whereas the allogenic curve is flat at 39%. This finding suggests that a proportion of these patients are long-term survivors. Thus, interest in myeloablative allogeneic SCT is ongoing, particularly given the lack of a significant cure rate for single or tandem autologous SCT. Therefore, these guidelines consider myeloablative SCT an accepted option in the setting of a clinical trial (category 2A) in patients with responsive or primary progressive disease, or as salvage therapy in patients with progressive disease after an initial autologous SCT.

Another strategy that has been investigated is an initial autologous SCT followed by a mini-allogeneic transplant. A prospective trial by Bruno et al.[69] showed that patients (aged < 65 years) who had an HLA-matched sibling and received an autograft–allograft regimen had a CR rate of 55% after allografting compared with 26% after double autograft in patients without HLA-matched siblings. Median overall survival was higher (80 vs. 54 months). In contrast, a comparison of tandem autologous SCT versus initial autologous SCT followed by a mini-allogeneic transplant in high-risk patients in the IFM99-03 and IFM 99-04 studies[70] showed no significant difference in overall and event-free survival.

Mini-transplants have also been investigated as salvage therapy. In a case series report, 54 patients with previously treated relapsed or progressive disease underwent treatment with an autologous-SCT followed by a mini-allotransplant.[71] At a median 552 days after the mini-allotransplant, patients had an overall survival rate of 78%, a CR rate of 57%, and an overall response rate 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.[72] In this heterogeneous population of 229 patients, the 3-year overall and progression-free sur-

vival rates were 41% and 21%, respectively. Adverse overall survival was associated with chemoresistant disease and more than one prior transplant, and improved overall survival was associated with graft-versus-host disease, confirming the importance of a graft-versus-leukemia effect. This study concluded that mini-allotransplantation is feasible, but that heavily pretreated patients and those with progressive disease 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.[73]

Maintenance Therapy After Transplantation

Various maintenance therapies, such as dexamethasone and interferon, have been investigated in patients whose disease responds to high-dose therapy with autologous or allogeneic SCT.[74] Prior editions of these guidelines considered dexamethasone as a category 1 recommendation for maintenance therapy.[75] However, further trials have not shown this maintenance therapy to be associated with significant reductions in disease recurrence. Therefore, the role of interferon,[76] or steroid maintenance therapy in general, is currently uncertain, and is a category 2B recommendation (page 920).

Interest has also been shown in thalidomide as maintenance therapy after a prior autologous SCT. In a retrospective review of 112 patients undergoing autologous SCT, Brinker et al.[77] reported on the outcomes of 36 patients who received thalidomide as maintenance or salvage therapy compared with 76 who underwent no posttransplant therapy. Median survival in the thalidomide group was 65.5 months compared with 44.5 months in the no-treatment group ($P = .9$).

Thalidomide maintenance was also studied in randomized trials. One study randomized 597 patients to 1 of 3 different strategies after tandem autologous stem cell transplantation: no maintenance, pamidronate alone, or pamidronate combined with thalidomide.[78] A highly significant event-free and overall survival advantage was seen in the thalidomide/pamidronate arm. The group that seemed to benefit most included patients who experienced only a partial response after transplantation. However, peripheral neuropathy is a challenge with low-dose thalidomide, and may preclude long-term maintenance. An Australian study compared thalidomide plus prednisone with prednisone alone. Results confirm that thalidomide added to maintenance is superior to prednisone alone.[79]

Thalidomide has also been used before, during, and after tandem autologous SCT.[80,81] In a randomized study of 668 patients with newly diagnosed MM, half received thalidomide throughout the course of the tandem autologous SCT (i.e., thalidomide was incorporated into induction therapy, continued between the tandem autologous SCTs, and incorporated into consolidation therapy and continued as maintenance therapy).[81] The no-thalidomide group underwent the same core therapy. After a median follow-up of 42 months, the thalidomide group had improved complete response rates (62% vs. 43%) and 5-year event-free survival rates (56% vs. 44%). However, the overall survival rate was approximately 65% in both groups. Patients who did not receive thalidomide throughout therapy benefited from thalidomide at relapse. The results of this study suggest that sequencing drugs may be important. For example, if thalidomide is used as part of upfront therapy, another drug should be considered for maintenance therapy.

Based on this evidence, the panel assigned thalidomide alone a category 1 recommendation and thalidomide with prednisone a category 2A recommendation as maintenance therapy.

Lenalidomide and bortezomib are other maintenance therapies under investigation. CALGB 100104 is comparing lenalidomide versus placebo as maintenance therapy after prior autologous SCT, with a planned accrual of 462 patients. The HOVON 65MM study is randomizing patients who have undergone autologous SCT to undergo maintenance therapy with either thalidomide or bortezomib for 2 years.

Salvage Therapy

Conventional-dose salvage therapy is considered in the following clinical situations:

- Patients with progressive disease after allogeneic or autologous SCT
- Patients with primary progressive disease after initial autologous or allogeneic SCT
- Nontransplantation candidates with progressive or relapsing disease after initial induction therapy

Various therapies are available for conventional-dose salvage therapy (page 920). If relapse occurs

more than 6 months after completion of the initial induction therapy, patients may be retreated with the same induction regimen.

Bortezomib is considered a category 1 recommendation for salvage therapy based on the results of a phase III trial (APEX) comparing bortezomib and high-dose dexamethasone as salvage therapy.[30] Among the 669 participants, patients randomized to bortezomib had a combined complete and partial response rate of 38% compared with 18% for those receiving dexamethasone, and improved median time-to-progression (6.22 vs. 3.49 months) and 1-year survival rate (80% vs. 66%). When combined with dexamethasone, bortezomib is considered a category 2A recommendation.

In an updated efficacy analysis,[82] the response rate was 43% with bortezomib versus 18% for dexamethasone ($P < .0001$). A CR or near CR was observed in 16% versus 0% of relapsed patients, respectively. Median overall survival was 29.8 months with bortezomib and 23.7 months with dexamethasone, despite nearly two thirds of patients crossing over to bortezomib, and 1-year survival rates were 80% and 67%, respectively ($P = .00002$). Patients with poor prognostic factors also benefited from bortezomib. Deletion of chromosome 13 made a difference in patients treated with dexamethasone, because it was associated with worse survival, but had no impact in patients treated with bortezomib.[83]

The FDA has approved a new regimen combining bortezomib with pegylated liposomal doxorubicin (PLD) injection for treating MM in patients who did not previously receive bortezomib and have undergone at least 1 prior therapy. The FDA approval was based on a priority review of interim data from an international phase III trial (n = 646), showing that use of the drug combination significantly extended the median time to disease progression compared with bortezomib alone (9.3 vs. 6.5 months).[84] Median response duration increased from 7.0 to 10.2 months with combination therapy. The most commonly reported grade 3 or 4 adverse reactions associated with use of doxorubicin liposome and bortezomib were neutropenia (32%), thrombocytopenia (24%), anemia (9%), fatigue (7%), asthenia (6%), diarrhea (7%), peripheral neuropathy (7%), and hand–foot syndrome (6%). Other commonly reported events (any grade) were pyrexia (31%), nausea (48%), vomiting (32%), constipation (31%), stomatitis (20%), and rash (22%). Based on these results, the panel considers this regimen a category 1 recommendation. PLD with bortezomib is superior to bortezomib monotherapy for treating patients with relapsed/refractory MM.

Lenalidomide combined with dexamethasone has received FDA approval based on the results of 2 studies of 692 patients with MM who had undergone at least 1 prior treatment and were randomized to receive either dexamethasone with or without lenalidomide. The primary efficacy end point in both studies was time-to-progression. A preplanned interim analysis of both studies reported that patients in the lenalidomide arm had a significantly longer median time-to-progression than those in the control group.

The updated clinical data from the pivotal North American Phase III trial (MM-009) in 353 patients with previously treated MM reported increased overall survival and median time to disease progression in patients receiving lenalidomide plus dexamethasone compared with those receiving dexamethasone plus placebo. Similar results were also shown in the trial from the international study MM-010. Patients in both trials had been heavily treated before enrollment, many whose disease had failed to respond to 3 or more rounds of therapy with other agents. In addition, more than 50% of patients in the study had undergone SCT.[85,86] Most adverse events and grade 3/4 adverse events were more frequent in patients with MM who received the combination of lenalidomide and dexamethasone compared with those who received placebo and dexamethasone. Thrombocytopenia (61.5%) and neutropenia (58.8%) were the most frequently reported adverse events observed. The panel now considers this regimen a category 1 recommendation. Lenalidomide monotherapy has also been investigated and is considered a category 2A recommendation.[87]

Thalidomide has also been investigated as a salvage therapy, either as monotherapy[88] or in combination with various agents, including dexamethasone or in combination with dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE).[89] Thalidomide has been shown to induce responses in 30% of patients with progressive myeloma.[90] In another study of 65 patients with relapsed or progressive disease, 34% experienced a minor (14%), partial (14%), or complete (6%) response; response was noted by 3 to 5 weeks of treatment.[91]

Mohty et al.[92] reported on thalidomide as salvage therapy in 31 patients with MM that relapsed after an initial allogeneic SCT, with 9 (29%) experiencing an objective response.

Other salvage regimens, all considered category 2A, include cyclophosphamide-VAD (C-VAD); high-dose (non–marrow ablative) cyclophosphamide; dexamethasone; DT-PACE; and DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin).

In another trial, Knop et al.[93] enrolled 31 patients who experienced relapse after high-dose chemotherapy and autologous transplantation to receive increasing doses of bendamustine. The overall response rate was 55%, with a median progression-free survival of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90–100 mg/m^2). Toxicity was mild and mainly hematologic.

Data from preclinical studies showed that lenalidomide sensitizes MM cells to bortezomib and dexamethasone. The results of phase I and II studies show that this regimen is well tolerated and very active, with durable responses seen in patients with heavily pretreated relapsed and/or refractory MM, including those who have undergone treatment with lenalidomide, bortezomib, thalidomide, and STC.[94,95]

Adjunctive Treatment

Important advances have been made in adjunctive treatment of patients with MM and are listed on page 921. Additions include a recommendation to consider herpes simplex virus prophylaxis in patients receiving bortezomib (page 920). In addition, anticoagulant prophylaxis is recommended for patients receiving thalidomide or lenalidomide in combination with dexamethasone.[38,96,97]

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 quality of life and performance status limitations 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 myeloma and at least one lytic lesion.[98,99]

Zoledronic acid is more potent, can be administered more rapidly, and has equivalent benefits.[100] Based on published data and clinical experience, the guidelines recommend the use of bisphosphonates for all patients with MM who have bone disease, including osteopenia (category 1).[101,102] Results from the study conducted by Zervas et al.[103] show a 9.5-fold greater risk for the development of osteonecrosis of the jaw in patients treated with zoledronic acid than with pamidronate. Therefore, pamidronate may be preferred over zoledronic acid until further published data become available on these adverse effects. In 10% to 20% of patients with earlier-stage disease who do not have bone disease, bisphosphonates may be considered, but preferably in a clinical trial. An annual skeletal survey is recommended for follow-up of bone disease. Bone densitometry or other metabolic studies should be reserved for clinical trials. Chronic bisphosphonate users should be monitored for renal function and osteonecrosis of the jaw.

Low-dose radiation therapy (10–30 Gy) is used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.[18] Limited involved fields should be used to limit the effect of irradiation on stem cell harvest or 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.

Other Complications

Hypercalcemia should be treated with hydration and furosemide, bisphosphonates, steroids, and/or calcitonin. Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity[104] (see Waldenström's Macroglobulinemia on page 923). Erythropoietin therapy should be considered for anemic patients, especially those with renal failure. Measuring endogenous erythropoietin levels may also be helpful in treatment planning.[105,106] To prevent infection, the following interventions should be considered: 1) intravenous immunoglobulin therapy in the setting of recurrent, life-threatening infections; 2) pneumococcal and influenza vaccine;

and 3) *Pneumocystis carinii* pneumonia, herpes, and antifungal prophylaxis if a high-dose dexamethasone regimen is used. Herpes prophylaxis should also be considered in patients receiving bortezomib.[107] Hydration should be maintained and nonsteroidal anti-inflammatory agents (NSAIDs) should be avoided to decrease the chances of renal dysfunction; however, renal dysfunction is not a contraindication for transplantation. The use of intravenous contrast media and NSAIDs should also be avoided in patients with renal impairment. Institutions differ in their use of plasmapheresis (category 2B) for adjunctive treatment of renal dysfunction. Prophylactic anticoagulation should also be considered if a thalidomide-based therapy is used.[38]

Systemic Light Chain Amyloidosis

Systemic light chain amyloidosis is characterized by decreased numbers of monoclonal plasma cells in the bone marrow; however, the protein produced by these plasma cells has an affinity for visceral organs (e.g., kidney, heart, liver, spleen) and causes related end-organ dysfunction.[108]

Workup

The initial diagnostic workup includes a history and physical examination; CBC with differential and platelets; BUN; serum creatinine; and electrolytes. The diagnosis of amyloidosis requires the identification of amyloid deposits in tissues either by aspiration of abdominal subcutaneous fat or biopsy of the organs involved. The characterization of amyloidosis as asystemic light chain type requires the demonstration of the underlying plasma cell clone. Monoclonal plasma cell population can be detected in bone marrow aspirates through immunohistochemical staining. Screening with serum electrophoresis alone may be inadequate, because it does not show a monoclonal spike in nearly 50% of cases. Therefore, all patients should undergo immunofixation electrophoresis of both serum and urine, which could detect a monoclonal component. The measurement of circulating FLC is a useful diagnostic complement. Because treatment is different for the various types of systemic amyloidosis, genetic testing must be performed to identify the specific mutation in the hereditary forms, especially in African-Americans and patients with peripheral neuropathy.

Treatment

Treatment of systemic light chain amyloidosis should occur in a clinical trial because data are insufficient to identify optimal treatment of the underlying plasma cell disorder. Most of the treatment strategies used are derived from MM regimens. Treatment (page 922) of selected patients (n = 394) with primary systemic amyloidosis using high-dose melphalan and SCT resulted in hematologic remission, improved 5-year survival, and reversal of amyloid-related disease in a substantial proportion. A complete hematologic response, defined as no evidence of an underlying plasma cell dyscrasia 1 year after treatment, occurred in 40% of patients and was associated with prolonged survival.[109]

High-dose chemotherapy with peripheral blood SCT has been associated with higher response rates and seemingly higher overall survival than standard chemotherapy.[110] Additional new therapies look promising.[111] Promising results have been shown in patients with primary amyloidosis who are ineligible for SCT when treated with combination melphalan and high-dose dexamethasone. A hematologic response was obtained in 67% patients, and complete remission in 33%.[112] This regimen is well tolerated in these patients.

Other treatment options include oral melphalan and dexamethasone;[112] intermediate-dose melphalan or high-dose melphalan therapy with autologous SCT;[113] dexamethasone and alpha-interferon;[114] lenalidomide and dexamethasone;[115,116] and single-agent bortezomib.[117]

Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia is characterized by hypersecretion of immunoglobulin M (IgM) in the serum; excess lymphoplasmacytoid cells in the bone marrow; and, in contrast to MM, involvement of visceral organs, including the liver and spleen.[118,119]

Workup

The initial diagnostic workup includes a history and physical examination; CBC with differential and platelets; BUN; serum creatinine; and electrolytes. Quantitative immunoglobulins, SPEP, and immunofixation should be used to identify and quantify the M-protein (which is IgM), as is done in patients with MM. IgM is a pentamer and common cause of hyperviscosity. Therefore, evaluation for

characteristic clinical signs and symptoms of serum viscosity should be performed at diagnosis. Waldenström's macroglobulinemia has been associated with underlying hepatitis C.[118] Therefore, liver function tests and hepatitis C serology also should be obtained. A unilateral bone marrow aspirate and biopsy will confirm excess lymphoplasmacytoid cells. CT scans of the chest, abdomen, and pelvis can assess organ involvement in patients who are symptomatic and are used to follow-up patients with known visceral involvement. In patients with suggestive symptoms, useful tests include cold agglutinins or a cryocrit (page 923).[120]

Treatment

Indications for the treatment of Waldenström's macroglobulinemia include symptomatic hyperviscosity; anemia; pancytopenia; bulky adenopathy; and symptomatic organomegaly, cryoglobulinemia, or neuropathy (page 923). Primary treatment for patients who require systemic therapy includes alkylating agents,[118] nucleoside analogs,[121] rituximab,[122] thalidomide,[123] and bortezomib.[124] Treatment of Waldenström's macroglobulinemia is discussed in detail in several reviews.[125–127] Cladribine can induce CRs when used as both initial and salvage therapy.[121,128] However, nucleoside analogs should be avoided if SCT is considered. Preliminary rituximab data indicate significant response with minimal toxicity; however, long-term results are not known.

Treatment is typically continued until maximal response occurs, and then is discontinued. Plasmapheresis is indicated for treatment of symptomatic hyperviscosity, usually as a supplement to conventional systemic therapies. Plasmapheresis removes 80% of the IgM protein and is therefore effective in relieving the related signs and symptoms of hyperviscosity.[118]

Follow-up and Surveillance

Follow-up should include a CBC, quantitative immunoglobulins, and SPEP after every 2 treatment cycles. The same test should be used serially to ensure accurate quantitation of IgM protein. Serum viscosity is generally useful to assess symptomatic patients. If the CT was abnormal at presentation, it should be repeated at 3- to 6-month intervals (page 924).

Disease either responds or progresses after it is treated primarily with alkylating agents. Patients whose disease responds should be followed up expectantly without any maintenance therapy. Progression is defined by a sustained 25% or more increase in M-protein in serum or urine, adenopathy, or organopathy. If the disease progresses after 6 months or more, alkylating agents can be restarted, or nucleoside analogs[129,130] (fludarabine, category 1) or rituximab can be initiated; however, nucleoside analogs (fludarabine, category 1) or rituximab should be used to treat earlier progressions.

A similar treatment strategy is used for those treated primarily with nucleoside analogs (i.e., when progression occurs after 6 months, the nucleoside analogs used earlier can be restarted, or an alkylating agent or rituximab can be started). Earlier progressions should be treated with alkylating agents or rituximab. Similarly, patients treated initially with rituximab who experience relapse after 6 months or more should be treated with rituximab, alkylating agents, or nucleoside analogs; these patients who experience progressive disease or early relapse should be treated with alkylating agents or nucleoside analogs. Patients whose disease progresses after second-line therapy are candidates for salvage therapies (e.g., hematopoietic SCT; monoclonal antibodies such as rituximab;[131] thalidomide with or without dexamethasone) in the context of clinical trials. Ongoing trials are evaluating lenalidomide and bortezomib, alone and in combination, for treating Waldenström's macroglobulinemia.

Summary

Although MM is sensitive to both chemotherapy and radiation therapy, it remains incurable. However, treatment algorithms (based on published data and clinical experience) can be developed to optimize therapy, which include not only therapy for the underlying disease but also supportive therapy to enhance quality of life. Because myeloma is incurable, these guidelines prominently identify the clinical settings appropriate for treating patients enrolled in clinical research protocols.

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