National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Multiple Myeloma

Version 1.2012

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Multiple Myeloma - Panel Members

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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.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

NCCN Guidelines™ Version 1.2012
Multiple Myeloma - Updates

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Discussion

Updates in Version 1.2012 NCCN Multiple Myeloma Guidelines from Version 1.2011 include:

MYEL-1

- Initial diagnostic workup:
  - Added [del 17p13].
  - Removed "for suspected vertebral compression" following MRI.

MYEL-2

- Follow-Up/Surveillance (these changes were made throughout the guideline for consistency).
  - Removed "Consider" before serum free light chain assay, bone marrow aspirate and biopsy, bone survery, and MRI, CT, PET/CT recommendations.
  - LDH and beta-2 microglobulin added "as clinically indicated."
  - Bone marrow added "aspirate and biopsy" as clinically indicated.

MYEL-3

- Renamed column header "Induction therapy" "Primary Treatment."
- Primary treatment:
  - Smoldering, removed (category 1) from recommendation to observe at 3-6 mo intervals and added "or clinical trial."
  - Active, changed "induction therapy" to "myeloma therapy."
- Follow-Up/Surveillance
  - Added "Multi-parameter flow cytology as clinically indicated."

MYEL-4

- Changed "induction therapy" to "primary treatment."
- Changed "plateau" to "best response."
- Modified footnote h: "A prospective trial by Bruno et al, found improved survival for patients receiving an autologous transplant followed by non-myeloablative allograft compared to patients who received tandem autologous grafts. In contrast, the IFM trial (99-03) by Garban et al, and the BMT-CTN 0102 trial by Stadtmauer et al reported no overall survival or progression free survival with autologous transplant followed by mini-allograft in high-risk myeloma patients.
  Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007;356:1110-1120.
  Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006;107:3474-3480.
  Stadtmauer EA, Krishnan A, Pasquini MC, et al. Tandem autologous stem cell transplants (auto-auto) with or without maintenance therapy versus single autologous transplant followed by HLA-matched sibling non- myeloablative allogeneic stem cell transplant (auto-allo) for patients (pts) with high risk (HR) multiple myeloma (MM): Results from the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) 0102 trial [abstract]. Blood 2010;116:Abstract 526."

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Updates in Version 1.2012 NCCN Multiple Myeloma Guidelines from Version 1.2011 include:

MYEL-5

- Post-autologous stem cell transplant: Progressive disease, added "Additional autologous stem cell transplant."
- Added footnote l: Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression.
- Post-allogeneic stem cell transplant: added "on clinical trial" after maintenance therapy

MYEL-B

- Modified footnote 1: "Other examples of active disease include: Repeated infections, amyloidosis, or hyperviscosity" deleted or hypogammoglubinanemia."

MYEL-C

- Removed pages: EMBT, IMBTR, and ABMTR criteria for evaluating disease response and progression in patient with multiple myeloma treated by high-dose therapy and haemopoietic stem-cell.

MYEL-D (1 of 2)

- Changed the page layout by putting information into a table format.
- Removed footnote: Bortezomib/liposomal doxorubicin is preferred to bortezomib single agent.
- Primary therapy for transplant candidates:
  - Bortezomib/lenalidomide/dexamethasone, changed from a category 2B to a category 2A.
- Primary therapy for non-transplant candidates:
  - Added (category1) to melphalan/prednisone/lenalidomide.
- Maintenance therapy:
  - Added bortezomib.
- Modified footnote 5: "There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

MYEL-D (2 of 2)

- Salvage therapy:
  - Bendamustine, changed from a category 2B to a category 2A.
  - Bortezomib/lenalidomide/dexamethasone, changed from a category 2B to a category 2A.
  - Removed cyclophosphamide VAD
  - Removed dexamethasone
  - Removed lenalidomide
  - Removed thalidomide
  - Added ± bortezomib to DT-PACE (VTD-PACE)
  - Added footnote 6: "Consider single agent lenalidomide or thalidomide for steroid-intolerant individuals."

MYEL-E

- Bisphosphonates:
  - Modified first bullet: "All patients receiving primary myeloma therapy should be given bisphosphonates (category1)."
- Added footnote 1: Both pamidronate and zoledronic acid have shown equivalence in terms of reducing risk of skeletal-related events in randomized trials. In a recent MRC IX trial, in addition to benefits for bone health, zoledronic acid reduced mortality by 16% versus clodronic acid and extended median overall survival by 5.5 months. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet 2010;376:1989-1999.
- Hypercalcemia:
  - Bisphosphonates, added (zoledronic acid preferred).
- Removed "consider" from PCP, herpes, and antifungal prophylaxis if high-dose dexamethasone regimen.
- Removed "consider" from herpes zoster prophylaxis for patients treated with bortezomib.

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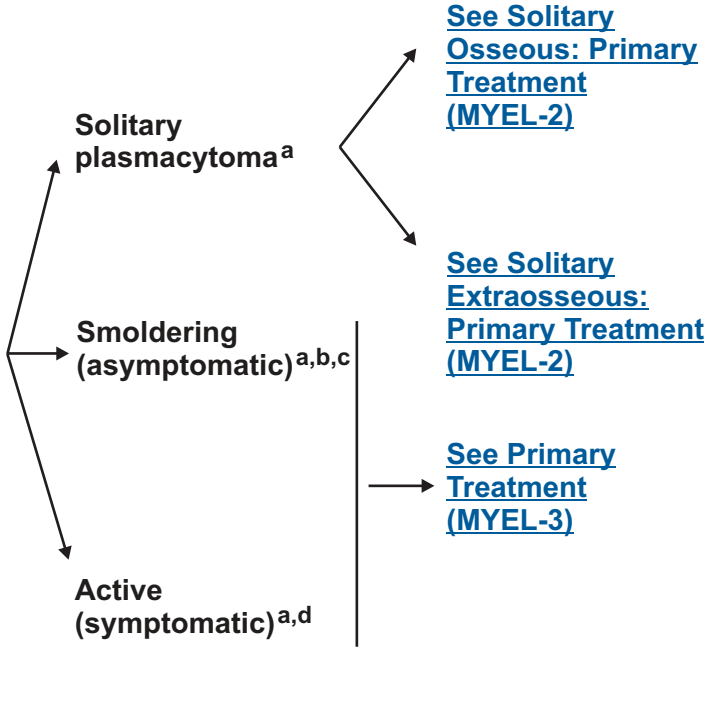
INITIAL DIAGNOSTIC WORKUP

- H&P
- CBC, differential, platelets
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- Serum free light chain assay
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24 h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 amplification]

Useful Under Some Circumstances

- MRI
- 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 viscosity
- HLA typing

CLINICAL PRESENTATION



[a] See Staging Systems for Multiple Myeloma (MYEL-A).
[b] See Smoldering Myeloma (Asymptomatic) (MYEL-B).
[c] Includes Durie-Salmon Stage I Myeloma.
[d] See Active Myeloma (Symptomatic) (MYEL-B).

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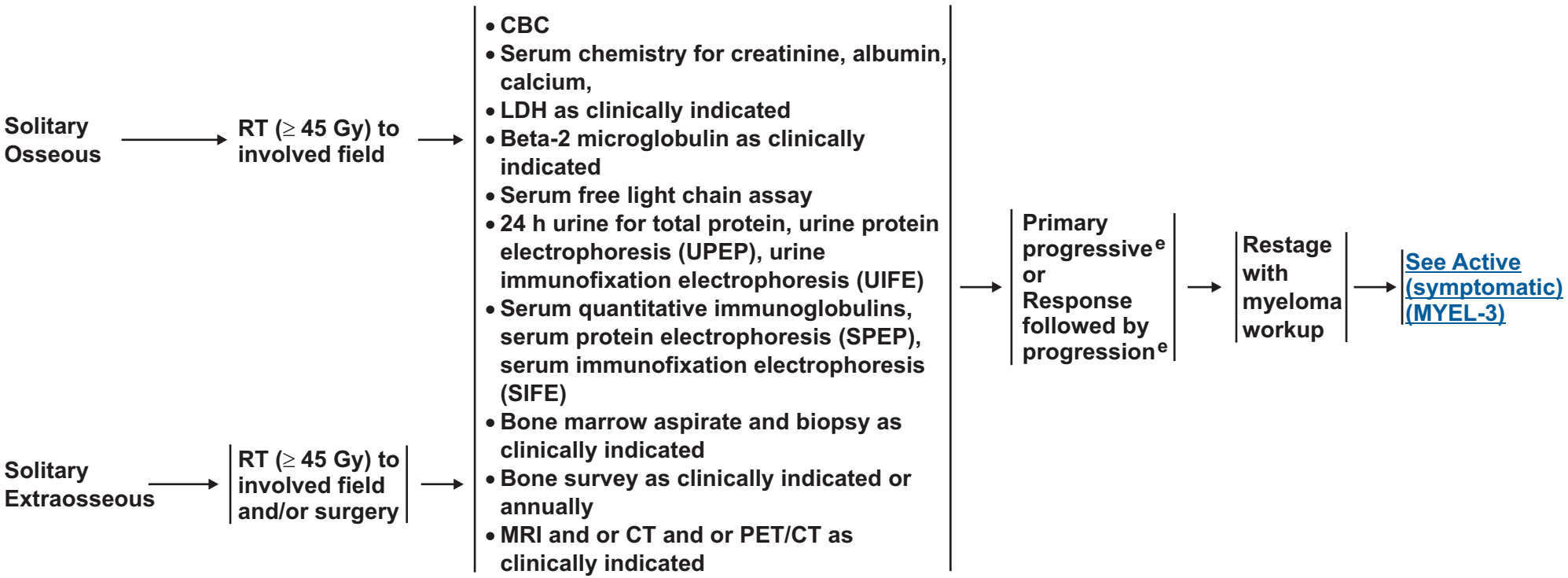

[e] See Response Criteria for Multiple Myeloma (MYEL-C).

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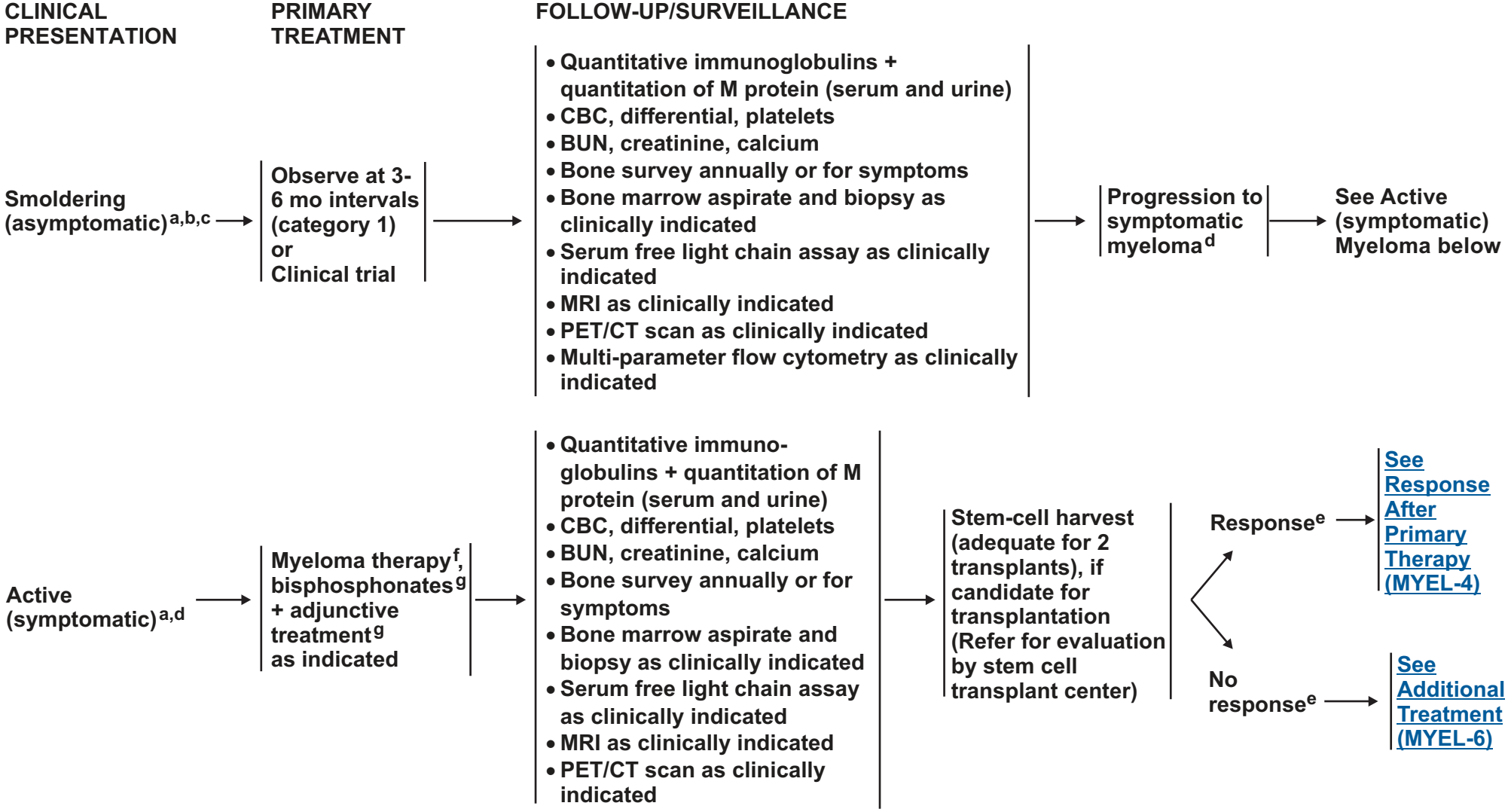

[a] See Staging Systems for Multiple Myeloma (MYEL-A).
[b] See Smoldering (Asymptomatic) Myeloma (MYEL-B).
[c] Includes Durie-Salmon Stage I Myeloma.
[d] See Active (Symptomatic) Myeloma (MYEL-B).
[e] See Response Criteria for Multiple Myeloma (MYEL-C).
[f] See Myeloma Therapy (MYEL-D).
[g] See Adjunctive Treatment (MYEL-E).

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ACTIVE (SYMPTOMATIC) MYELOMA

FOLLOW-UP/SURVEILLANCE

Response after primary therapy[e] →

- **Autologous[j,k] stem cell transplant (category 1)**
- **OR**
- **Allogeneic[h,i] stem cell transplant in clinical trial**
- **OR**
- **Continue myeloma therapy until best response[e]** → **Monitor as above and/or maintenance therapy[f]** → **See Additional Treatment (MYEL-6)**

→

- **Quantitative immunoglobulins + quantitation of M protein at least every 3 mo**
- **CBC, differential, platelets**
- **BUN, creatinine, calcium**
- **Bone survey annually or for symptoms**
- **Bone marrow aspirate and biopsy as clinically indicated**
- **Serum free light chain assay as clinically indicated**
- **MRI as clinically indicated**
- **PET/CT scan as clinically indicated**

→ **See Additional Treatment (MYEL-5)**

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

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

[h] A prospective trial by Bruno et al, found improved survival for patients receiving an autologous transplant followed by non-myeloablative allograft compared to patients who received tandem autologous grafts. In contrast, the IFM trial (99-03) by Garban et al, and the BMT-CTN 0102 trial by Stadtmauer et al reported no overall survival or progression free survival with autologous transplant followed by mini-allograft in high-risk myeloma patients.
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[i] 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.

[j] 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.
Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol. 2006;24:929-936.

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

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ACTIVE (SYMPTOMATIC) MYELOMA **ADDITIONAL TREATMENT**

Post-allogeneic stem cell transplant:

Progressive disease[e] → **Salvage therapy[f] on or off clinical trial or Donor lymphocyte infusion**

Response or stable disease[e] → **Maintenance therapy on clinical trial or Observe** → **Progressive disease[e]** → **Salvage therapy[f] on or off clinical trial or Donor lymphocyte infusion**

Post-autologous stem cell transplant:

Progressive disease[e] → **Salvage therapy[f] on or off clinical trial or Allogeneic stem cell transplant on clinical trial[i] (category 3 for conventional vs clinical trial) or Additional autologous stem cell transplant[l]**

Response or stable disease[e] → **Maintenance therapy[f] or Second tandem transplant or Observe** → **Progressive disease[e]** → **Salvage therapy[f] on or off clinical trial or Allogeneic stem cell transplant on clinical trial[i] or Additional autologous stem cell transplant[l]**

[e] See Response Criteria of Multiple Myeloma (MYEL-C).
[f] See Myeloma Therapy (MYEL-D).
[i] 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.
[l] Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression.

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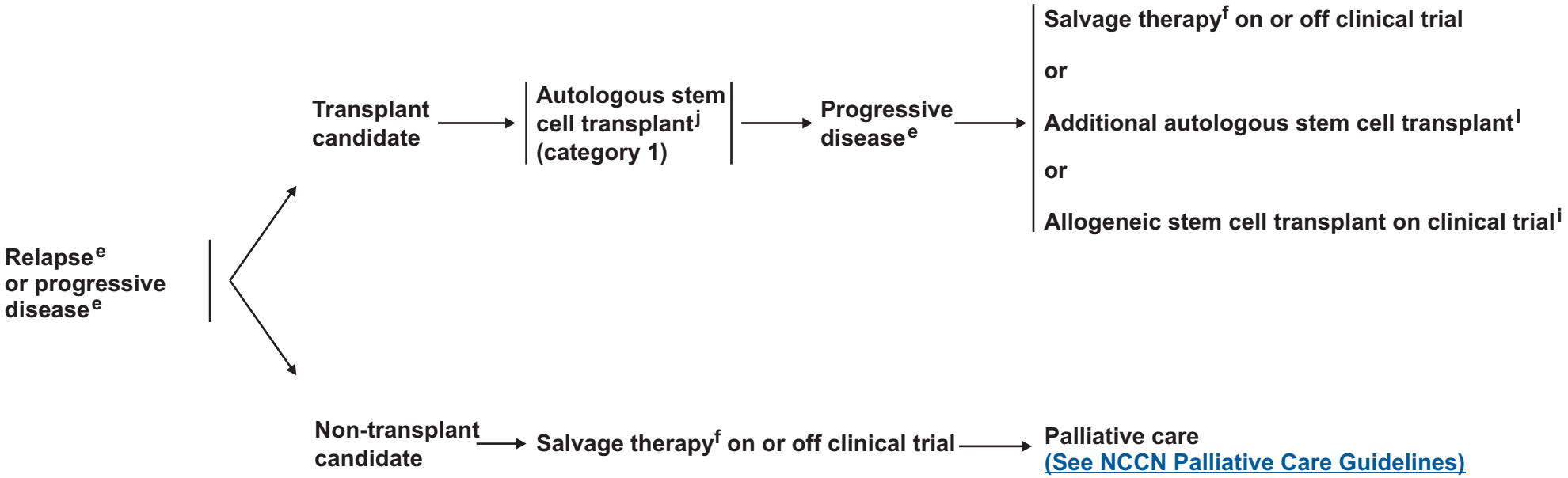
ACTIVE (SYMPTOMATIC) MYELOMA **ADDITIONAL TREATMENT**



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STAGING SYSTEMS FOR MULTIPLE MYELOMA

Stage	Durie-Salmon Criteria[1]	ISS Criteria[2]
I	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/24 h	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage 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/24 h	Serum beta-2 microglobulin ≥ 5.5 mg/L
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(9):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.

Return to Clinical Presentation (MYEL-1)

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DEFINITION OF MULTIPLE MYELOMA (SMOLDERING AND ACTIVE)

Smoldering (Asymptomatic) Myeloma

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.

Active (Symptomatic) Myeloma[1]

Requires one or more of the following:
- **Calcium elevation (>11.5m g/dL) [>2.65 mmol/L]**
- **Renal insufficiency (creatinine >2 g/L) [177 µmol/L or more]**
- **Anemia (hemoglobin < 10 g/dL or 2 g/dL < normal) [<12.5 mmol/L<normal]**
- **Bone disease (lytic or osteopenic)**

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

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(5):749-57.
Reprinted by permission from Macmillan Publishers Ltd. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA

International Myeloma Working Group Uniform Response Criteria - CR and Other Response Categories

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 h
PR, partial response	≥ 50% reduction of serum M-protein and reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to 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 two 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 upon 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

International Myeloma Working Group Uniform Response Criteria - Disease Progression and Relapse

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/24 h)** • **Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL.** • **Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[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 or 2.65 mmol/L) 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 at least 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) [2.65 mmol/L]** • **Decrease in hemoglobin of ≥ 2 g/dL [1.25 mmol/L]** • **Rise in serum creatinine by 2 mg/dL or more [177 µmol/L or more]**
Relapse from CR[1] (To be used only if the end point studied is DFS, 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 (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)**

[1] All relapse categories require two 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[1,2,3]

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

	Preferred Regimens	Other Regimens
Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide[4]/dexamethasone • Bortezomib/thalidomide/dexamethasone (category 1) • Lenalidomide[4]/dexamethasone (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Thalidomide/dexamethasone (category 2B)
Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone • Lenalidomide/low-dose dexamethasone (category 1) • Melphalan/prednisone/bortezomib (MPB) (category 1) • Melphalan/prednisone/lenalidomide (MPL) (category1) • Melphalan/prednisone/thalidomide (MPT) (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Melphalan/prednisone (MP) • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance Therapy	• Bortezomib • Lenalidomide[5] • Thalidomide (category 1)	• Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with bortezomib.
[3]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
[4]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.
[5]There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following-transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

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

MYELOMA THERAPY[1,2,3]

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

	Regimens
Salvage Therapy	• **Repeat primary induction therapy (if relapse at > 6 mo)** • **Bendamustine** • **Bortezomib (category 1)** • **Bortezomib/dexamethasone** • **Bortezomib/lenalidomide/dexamethasone** • **Bortezomib/liposomal doxorubicin (category 1)** • **Cyclophosphamide/bortezomib/dexamethasone** • **Cyclophosphamide/lenalidomide/dexamethasone** • **Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)** • **Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)** • **High-dose cyclophosphamide** • **Lenalidomide/dexamethasone[6] (category 1)** • **Thalidomide/dexamethasone[6]**

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with bortezomib.
[3]Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexamethasone.
[6]Consider single agent lenalidomide or thalidomide for steroid-intolerant individuals.

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

ADJUNCTIVE TREATMENT

Bone Disease

- Bisphosphonates (pamidronate and zoledronic acid)[1]
  - All patients receiving primary myeloma therapy should be given bisphosphonates (category 1)
  - Use of bisphosphonates in smoldering or stage I disease preferably in the context of a clinical trial. These patients should have bone survey annually and if symptoms
  - 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 (zoledronic acid preferred), steroids and/or calcitonin.

Hyperviscosity

- Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity

Anemia (See NCCN Cancer and Treatment Related Anemia Guidelines)

- Consider erythropoietin for anemic patients

Infection (See NCCN Prevention and Treatment of Cancer-Related Infections Guidelines)

- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection
- Consider pneumovax and influenza vaccine
- PCP, herpes, and antifungal prophylaxis if high-dose dexamethasone regimen
- Herpes zoster prophylaxis for patients treated with bortezomib

Renal Dysfunction

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

Coagulation/thrombosis

- Prophylactic anticoagulation recommended for patients receiving thalidomide-based, or lenalidomide with dexamethasone therapy

(See NCCN Venous Thromboembolic Disease Guidelines)

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

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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 has estimated 20,520 new cancer cases of MM in the United States in 2011, including 11,400 cases in men and 9,120 cases in women, with an estimated 10,610 deaths.[1] The mean age of affected individuals is 62 years for men (75% older than 70 years) and 61 years for women (79% older than 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 owing to newer and more effective treatment options available.[2, 3]

Multiple myeloma is typically sensitive to a variety of 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 of MM has been evolving rapidly due to the introduction of new drugs, such as thalidomide, lenalidomide, and bortezomib. In addition, there is emerging understanding of the microenvironment of the bone marrow, which creates the rationale for new combinations of therapies and new drug development.[4] Studies of the associated cytogenetic abnormalities indicate that MM is a heterogeneous disease suggesting that risk-adapted approaches and individualizing treatment will further help refine patient management.

These guidelines developed by the NCCN Multiple Myeloma Panel members address diagnosis, treatment and follow-up for patients with MM.

Initial Diagnostic Workup

The initial diagnostic workup in all patients should include a history and physical (H&P) examination and the following baseline blood studies and biological assessments to differentiate symptomatic and asymptomatic MM: a complete blood count (CBC) with differential and platelet counts; blood urea nitrogen (BUN); serum creatinine, and serum electrolytes; serum calcium; albumin; lactate dehydrogenase (LDH); beta-2 microglobulin. Increased BUN and creatinine indicate decreased kidney function, while LDH levels help assess tumor cell burden. The level of beta-2 microglobulin reflects the tumor mass and is now considered a standard measure of the tumor burden.

The monoclonal protein (M-protein) component in serum and urine is detected and evaluated by the following urine and serum analyses. Urine analysis as a part of the initial diagnostic workup includes

evaluating 24 hour urine for total protein; urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE).

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 M-protein, helps track the progression of myeloma disease and response to treatment. Use of serum free light chain (FLC) assay along with SPEP and SIFE yields high sensitivity while screening for MM and related plasma cell disorders.[5] Therefore, this assay is now included as a part of the initial diagnostic workup in the NCCN Multiple Myeloma Guidelines. The serum FLC assay also has prognostic value in plasma cell disorders, including monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, active myeloma, immunoglobulin light chain amyloidosis and solitary plasmacytoma.[5, 6] The serum FLC assay also allows for quantitative monitoring of patients with light chain amyloidosis and oligosecretory myeloma. In addition to all the above, the FLC ratio is required for documenting stringent complete response according to the International Myeloma Working Group Uniform Response Criteria.[7] The FLC assay cannot replace the 24-h urine protein electrophoresis for monitoring myeloma patients with measurable urinary M proteins.

Most patients have serum proteins with or without associated urinary protein. In the Mayo Clinic review of 1027 patients with newly diagnosed with MM, 20% of patients had secretory urinary proteins, however 3% of patients had neither serum nor urine proteins, therefore had nonsecretory myeloma.[8] Once the myeloma or M-protein is quantified, it is important to use the same test for serial studies to ensure accurate relative quantification.

To evaluate bone marrow plasma cell infiltration, bone marrow aspiration and biopsy is recommended to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells. To evaluate lytic bone lesions, full skeleton X-ray survey is recommended.

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

Deletion of chromosome 13 [del(13)] appears to have an amplifying effect on cell cycle gene expression and is reported to be associated with short event free survival and overall survival (OS).[9] Deletion of 17p13 (the locus for the tumor-suppressor gene, p53) leads to loss of heterozygosity of *TP53* and is considered high-risk feature in MM.[10-12] Other high-risk chromosomal aberrations in MM are characterized by structural changes that include specific rearrangements involving the IGH gene (encoding immunoglobulin heavy chain), located at 14q32. Several subgroups of patients are identified, on the basis of 14q32 translocations. The three main ones are the t(11;14)(q13;q32), t(4;14)(p16;q32) and t(14;16)(q32;q23). From a clinical point of view, t(4;14) is the most important one. A number of studies have confirmed that patients with this translocation have a poor prognosis.[13, 14]

Conflicting data exists regarding t(14;16); while one study showed no impact on prognosis,[15] some studies have shown a negative prognostic impact.[16, 17] A translocation between 11 and 14 [t(11;14)] has been reported to be associated with an improved survival.[18, 19] Abnormalities

of chromosome 1 are also among the frequent chromosomal alterations in MM.[20] The short arm is most often associated with deletions and the long arm with amplifications.[21] Gains/amplification of 1q21 increases the risk of MM progression and incidence of the amplification is higher in relapsed than in newly diagnosed.[20, 22]

Stratification of patients into various risk groups based on the chromosomal markers is being utilized by some centers for prognostic counseling, selection, and sequencing of therapy approaches.[23, 24] According to the NCCN Multiple Myeloma Panel members, the FISH Panel for prognostic estimation should include t(4;14), t(14;16), and 17p13 deletions, t(11;14), chromosome 13 deletion, and chromosome 1 amplification. The utility of this information is to determine biological subtype as well as for prognostic recommendations.

In addition to cytogenetic markers of prognosis, it is postulated that biological factors or gene expression signatures may be capable of discerning prognosis and helping rationale therapeutic decisions.[25, 26] Further understanding of the molecular subtypes of MM is emerging from the application of high-throughput genomic tools such as gene expression profiling (GEP).[27] With the currently available novel treatment approaches, majority of MM patients can now anticipate long-term disease control. However, patients with cytogenetically and molecularly defined high-risk disease do not receive the same benefit from current approaches as the low-risk patients. GEP is a powerful and fast tool with the potential to provide additional prognostic value to further refine risk-stratification, help therapeutic decisions, and inform novel drug design and development. At the present time, standardized testing for GEP is not available and there is inadequate data to determine how this prognostic information should be used to direct patient management.

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

Additional Diagnostic Tests

The NCCN Multiple Myeloma Panel recommends additional tests that maybe useful under some circumstances. These include magnetic resonance imaging (MRI),[28] computed tomography (CT), or positron emission tomography (PET)/CT scan. Active myeloma is positive on PET scan.[29, 30] PET-CT and MRI scans are more sensitive than plain radiographs and are indicated when symptomatic areas show no abnormality on routine radiographs.

A tissue biopsy may also be necessary to confirm the presence of plasmacytomas. Plasma cell labeling index may be helpful to identify the fraction of the myeloma cell population that is proliferating.[31] Also staining of bone marrow and fat pad for the presence of amyloid, and serum viscosity should be evaluated if hyperviscosity is suspected**.**

In selected patients with MM, physicians may use allogeneic (i.e., from someone else) transplantation. In this approach, physicians administer non-myeloablative therapy and infuse stem cells (i.e., peripheral blood or bone marrow) obtained from a donor, preferably a Human Leukocyte Antigen (HLA) -identical sibling. In such cases, the patient will need to be HLA-typed.

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

Diagnostic Categories

Based on the results of the clinical and laboratory evaluation discussed in previous sections, patients are initially classified as either having smoldering (asymptomatic) disease or active (symptomatic) disease. For definitions refer to NCCN Multiple Myeloma Guidelines section titled “Definition of Multiple Myeloma (Smoldering and Active)”.

The criteria agreed upon by the International Myeloma Working Group (IMWG) for smoldering (asymptomatic) patients includes low concentrations of M-protein (greater than or equal to 30 g/L) and/or bone marrow infiltration greater than or equal to 10% plasma cells; however, with no anemia, renal failure, hypercalcemia, or bone lesions.[32]

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)[33]. The ISS system is based on easily obtained laboratory measures (serum beta-2 -microglobulin and serum albumin) and is easier to use than the Durie-Salmon staging system for patients with previously untreated MM.

Response Criteria

Assessing the response to treatment is a key determinant of myeloma treatment.

The IMWG response criteria were developed from the European Group for Blood and Bone Marrow Transplant/ International Bone Marrow Transplant Registry/ American Bone Marrow Transplant Registry (EBMT/ IBMTR/ ABMTR) response criteria,[34] with revisions and improvements to help uniform reporting.

The updated IMWG response criteria definitions[35] for complete response (CR), stringent complete response (sCR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease are outlined in the NCCN Multiple Myeloma Guidelines section titled “Response Criteria for Multiple Myeloma”. It is recommended that the IMWG uniform response criteria should be used in future clinical trials.

Solitary Plasmacytoma

The diagnosis of solitary plasmacytoma requires a very thorough evaluation to rule out the presence of systemic disease because many patients presumed to have solitary plasmacytomas are found to have occult disease. 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.[36] However, the treatment and follow-up options for osseous and extraosseous plasmacytomas are similar.

Primary Therapy for Solitary Plasmacytoma

For those patients with osseous plasmacytoma, primary radiation therapy (45 Gy or more) to the involved field is the initial treatment and is potentially curative.[37, 38] Extraosseous plasmacytomas are treated initially with radiation therapy (45 Gy or more) to the involved field followed by surgery if necessary.

Surveillance/Follow-up Tests for Solitary Plasmacytoma

Follow-up and surveillance tests for both solitary plasmacytoma and extra-osseous plasmacytoma consist of blood and urine tests done every 4 weeks initially to monitor response to the primary radiation therapy. If the patient achieves complete disappearance of the paraprotein then the frequency could be reduced to every 3-6 months

or as indicated clinically. If the protein persists, then the monitoring should continue every 4 weeks.

The blood tests include CBC; serum chemistry for creatine, albumin, calcium; serum quantitative immunoglobulins, SPEP, and SIFE; and serum FLC assay. Testing for LDH levels and beta-2 microglobulin may be useful under some circumstances.

The urine tests include 24 hour urine assay for total protein, UPEP, and UIFE.

Bone marrow aspirate and biopsy, and imaging studies using MRI and/or CT and/or PET/CT are recommended as clinically indicated. PET imaging may detect early bone marrow involvement in patients with solitary plasmacytoma.[30, 39] Bone survey is recommended annually or as clinically indicated.

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

Smoldering (Asymptomatic) Myeloma

Smoldering (asymptomatic) myeloma describes a stage of disease for which there are no symptoms and no related organ or tissue impairment.[32] Patients with Durie-Salmon stage I myeloma also have low amounts of M-protein without significant anemia, hypercalcemia, or bone disease, would be included in this category. Patients with asymptomatic smoldering MM have an indolent course for many years without therapy.

Primary Therapy for Smoldering (Asymptomatic) MM

Patients with smoldering myeloma including Durie-Salmon stage I do not need primary therapy as it may take many months to years before the disease progresses. The risk of transformation to symptomatic myeloma[40] is life-long and patients should be closely.

The NCCN Multiple Myeloma Panel recommends that patient with smoldering myeloma should initially be observed at 3-6 months intervals (category 1 recommendation) or be enrolled in clinical trials.

Surveillance/Follow-up Tests for Smoldering (Asymptomatic) MM

The surveillance/follow-up tests include CBC; serum chemistry for creatine, albumin, LDH, calcium, beta-2 microglobulin; serum quantitative immunoglobulins, SPEP, and SIFE; and serum FLC assay. The urine tests include 24 hour urine assay for total protein, UPEP, and UIFE.

Bone survey is recommended annually or as clinically indicated. Bone marrow aspiration and biopsy and imaging studies with MRI and/or CT and/or PET/CT are recommended as clinically indicated. PET imaging appears to reliably predict active myeloma, by virtue of FDG uptake, low-level smoldering myeloma is consistently negative on the PET scan.[29] It can also assess the extent of active disease, detect extramedullary involvement or evaluate treatment response.[30, 41-43]

Multiparameter flow cytometry is a newly available tool that can help individualize the follow-up/surveillance strategy for patients with smoldering myeloma. It measures abnormal cells in the bone marrow and provides information regarding the risk of progression to active myeloma. A high proportion of abnormal plasma cells within the bone marrow plasma cell compartment (> 95%), has been shown to predict the risk of progression in both patients with smoldering myeloma or

MGUS.[44, 45] According to the NCCN Multiple Myeloma Panel members, multiple parameter flow cytometry information may be a useful consideration in the follow-up/surveillance plan of patients with smoldering myeloma. Since this test is not standardized and widely available, they recommend that it should only be performed in laboratories with experience.

If the disease progresses to symptomatic myeloma then patients should be treated according to the guidelines for symptomatic MM. The IMWG definition for progressive disease is in section titled “Response Criteria for Multiple Myeloma” in the NCCN Multiple Myeloma Guidelines.

Active (Symptomatic) Multiple Myeloma

Primary Therapy for Active (Symptomatic) MM

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and in selected patients primary therapy is followed by high dose chemotherapy with autologous stem cell support. 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 stem cell transplant (SCT). Therefore, one of the first steps in evaluating patients with advanced MM is to determine whether or not they would be considered a candidate for high dose therapy and transplant, based on age and co-morbidities. However, it should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant. It is also important to consider supportive care for all patients at the time of 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 section on Adjunctive Treatment below). In all patients, careful attention to supportive care is critical to avoid early complications that may compromise therapeutic outcome.

The page titled “Myeloma Therapy” in the Guidelines has a list of primary therapy regimens recommended by the NCCN Multiple Myeloma Panel members for transplant as well as non-transplant candidates and also lists drugs recommended for maintenance therapy. The list is selected and not inclusive of all regimens. The NCCN Multiple Myeloma Panel members have classified the regimens either as “preferred regimens” or “other regimens” on the basis of a balance of efficacy and toxicity. Research into various primary regimens has focused on improving the complete response rates in both transplant and non-transplant candidates. The NCCN Panel members have noted that it is important to assess for response to primary therapy after 2 cycles.

Lenalidomide is a potent analogue of thalidomide. Both lenalidomide and thalidomide possess immunomodulatory properties.[46] Prophylaxis with an anticoagulation agent is recommended for patients receiving thalidomide- or lenalidomide-based therapy.

Bortezomib-based regimens may be of value in patients with renal failure, and in those with certain adverse cytogenetic features.[47] Bortezomib treatment has been associated with an incidence of herpes zoster.[48] The incidence of bortezomib-associated herpes zoster may be reduced with the use of prophylactic acyclovir.[49] The risk of deep vein thrombosis (DVT) is low with bortezomib; however peripheral neuropathy and gastrointestinal disturbance can be higher. Bortezomib related adverse events are predictable and managed with patient monitoring and appropriate supportive care.[50]

Preferred Primary Therapy Regimens for Transplant Candidates

Bortezomib/Dexamethasone

Bortezomib is a proteasome inhibitor that not only directly targets the myeloma cell, but also targets the interaction between the tumor cell, and the bone marrow microenvironment. Bortezomib targets both intrinsic and extrinsic signaling pathways, while dexamethasone targets only the intrinsic pathway. This emerging understanding of the bone marrow microenvironment provides the rationale of combining these two drugs.

In the Intergroupe Francophone du Myelome (IFM) cooperative group trial, 482 patients were randomized to one of the following four arms: VAD (n = 121) alone, or VAD plus consolidation therapy with dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP; n = 121), or bortezomib/dexamethasone (n = 121) alone, or bortezomib/dexamethasone plus consolidation with DCEP (n = 119), followed by autologous stem-cell transplantation.[51] The primary end point was after primary therapy was CR/near CR rate. The investigators evaluated the response was evaluated according to modified EBMT criteria,[34] including additional categories of near CR (CR but immunofixation-positive)[52] and VGPR (serum M-protein reduction ≥ 90%; urine light chain < 100 mg/24 hours).[7]

After primary therapy, the rate of CR/near CR (14.8% vs 6.4%), rate of achieving at least a VGPR (37.7% vs 15.1%), and rate of overall response (78.5% vs 62.8%) were significantly higher with bortezomib plus dexamethasone versus VAD.[51] At a median follow-up of 32.2 months, median progression free survival (PFS) was modest not statistically significant, 36.0 months versus 29.7 months with bortezomib/dexamethasone versus VAD.[51] Use of DCEP as consolidation therapy following primary therapy did not have a significant impact on response rates.[51] Bortezomib/dexamethasone was equally effective in patients with high-risk MM, including those with ISS stage III disease and poor-risk cytogenetic abnormalities.

Another trial analyzed a large series of patients (younger 65 years) with newly diagnosed MM who were treated with primary therapy of bortezomib/dexamethasone versus VAD before high-dose melphalan treatment with hematopoietic stem-cell support.[47] The results demonstrated that bortezomib improves the prognosis (in terms of both event free survival and OS) of patients with t(4;14), compared with patients treated with VAD primary therapy. Also, primary therapy with bortezomib/dexamethasone significantly improved the outcome of patients including those with t(4;14) compared with VAD.[47]

Based on these data and the uniform consensus among the NCCN Multiple Myeloma Panel members, bortezomib/dexamethasone is listed a category 1 option as primary therapy for transplant candidates. Bortezomib treatment has been associated with an incidence of herpes zoster.[53, 54] Herpes prophylaxis is recommended in patients receiving bortezomib and in the post-transplant setting.[48]

Bortezomib/Doxorubicin/Dexamethasone

The updated results from the Dutch-Belgian Hemato-Oncology Cooperative Group HOVON-65/ GMMG-HD4 phase III trial of newly diagnosed patients with stage II/III myeloma demonstrated high response rates with the bortezomib/doxorubicin/dexamethasone versus VAD and this superior response rate was maintained even after SCT with significantly higher overall response rate (ORR).[55] No unexpected toxicities occurred, and deletion of chromosome 13q did not have a significant impact on response. Responses improved with bortezomib maintenance.[55] The PFS at 36 months was 46% for patients treated with bortezomib/doxorubicin/dexamethasone as primary therapy

followed by SCT and bortezomib maintenance versus 42% for patients treated with VAD followed by SCT and maintenance with thalidomide.[55]

Based on data from the HOVON-65/ GMMG-HD4 trial and the uniform consensus among the NCCN Multiple Myeloma Panel members, bortezomib/doxorubicin/dexamethasone is a category 1 option for primary therapy for transplant candidates.

Bortezomib/Thalidomide/Dexamethasone

The GIMEMA Italian Multiple Myeloma Network reported results of a phase III trial investigating bortezomib/thalidomide/dexamethasone (n = 241) versus thalidomide/dexamethasone (n = 239) as primary therapy, followed by tandem autologous SCT with high dose melphalan and then consolidation therapy with the same primary regimen.[56] The addition of bortezomib to thalidomide and dexamethasone significantly improved ORR both following primary treatment. After primary therapy, CR/near CR was achieved in 73 patients (31%, 95% CI 25·0–36·8) receiving bortezomib/thalidomide/dexamethasone, and 27 (11%, CI 7·3–15·4) on thalidomide/dexamethasone.[57] Rates of CR/near CR and VGPR or better continued to be significantly higher in the bortezomib/thalidomide/dexamethasone group than in the thalidomide/dexamethasone group after the first and second autologous SCT, and subsequent consolidation therapy.[57] Patients receiving the bortezomib containing regimen experienced grade 3/4 peripheral neuropathy.

Data from a single institution retrospective study are similar to the interim data from the GIMEMA trial.[58] The findings of this analysis demonstrate that with ORR after primary therapy with bortezomib/thalidomide/dexamethasone was 94% of the patients (32 of 34 patients showed some response, including a VGPR rate ≥ 56%).[58]

The results of the randomized phase III trial by the Spanish Myeloma Group (PETHEMA/GEM) also demonstrated a significantly higher CR rate with bortezomib/ thalidomide/dexamethasone as primary therapy in both the overall series and in patients with high-risk cytogenetics. Following autologous SCT, the CR rate continued to be significantly higher with bortezomib/thalidomide/dexamethasone than with thalidomide/dexamethasone.[59]

Based on the above data and the uniform consensus among the NCCN Multiple Myeloma Panel members, bortezomib/thalidomide/dexamethasone is a category 1 option as primary therapy for transplant candidates.

Bortezomib/Lenalidomide/Dexamethasone

Phase I/II study results have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is very active and well tolerated in newly diagnosed MM patients.[60-62] Response rate is 100% with 74% VGPR or better and 52% CR/near CR. Given this high extent and frequency of response, a randomized trial is now evaluating this regimen with or without high dose melphalan and stem cell support in newly diagnosed transplant candidates.

The benefits of bortezomib/lenalidomide/dexamethasone as primary therapy were also seen in the results of Phase II EVOLUTION trial[63] and the Phase II IFM 2008 trail.[64, 65] In the Evolution study, the ORR after primary treatment was 83% (14% stringent CR; 38% CR+ near CR; and 50% ≥ VGPR)[63] and in the Phase II IFM 2008 trial, the ORR after primary treatment was 97% (13% stringent CR; 16% CR; and 54% ≥ VGPR).[64]

Bortezomib/lenalidomide/dexamethasone regimen is included as a category 2A recommendation to the list of primary treatment options available for transplant candidates in the guidelines.

Cyclophosphamide/Bortezomib/Dexamethasone

Data from three phase II studies involving newly diagnosed MM patients (n = 495) has demonstrated high response rates with cyclophosphamide/bortezomib/dexamethasone *(*CyBorD) as primary treatment.[66-68] The trial by Reeder et al carried out in U.S. and Canada demonstrated ORR of 88% including a VGPR or greater of 61% and 39% CR/near CR with CyBorD primary regimen.[66] The depth of response seen after primary treatment was maintained after transplant as well, in those who underwent transplantation (70% rates of CR/near CR; rate of at least VGPR or better 74%).[66]

Analysis of the German DSMM XIa study also demonstrated high responses with CyBorD as primary treatment (ORR was 84%; with 74% PR rate and 10% CR rate). High response rates were also seen in patients with unfavorable cytogenetics.[67] In the updated results of the Phase II EVOLUTION study, primary treatment with CyBorD demonstrated ORR of 78% (3% stringent CR; 31% CR + near CR; and 41% ≥ VGPR).[63] Based on data from these three phase II studies, the NCCN Multiple Myeloma Panel has now included the combination of cyclophosphamide/bortezomib/dexamethasone as a category 2A recommendation to the list of primary treatment options available for transplant candidates.

Lenalidomide/Dexamethasone

Lenalidomide is a potent analogue of thalidomide. Like thalidomide it is believed to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis and cytokine circuits, among others. Lenalidomide received approval from the U.S. Food and Drug Administration (FDA) for the treatment of relapsed/refractory MM in combination with dexamethasone (discussed further below under Salvage Therapy). However, lenalidomide and dexamethasone have been investigated as primary therapy. The Phase III randomized controlled study, S0232, by Southwest Oncology Group (SWOG) compared dexamethasone alone with a combined therapy of dexamethasone plus lenalidomide for patients newly diagnosed with MM.[69] 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 one year survival results from the Eastern Cooperative Oncology Group (ECOG) phase III study (E4A03).[70, 71] At the time the SWOG trial was halted, lenalidomide plus dexamethasone arm showed improved CR rate compared to dexamethasone alone (22% vs. 4%).[69]

In a recent open label trial, 445 newly diagnosed MM patients were randomly assigned high-dose or low-dose regimens. The response was superior with high-dose dexamethasone. One hundred and sixty nine (79%) of 214 patients receiving high-dose therapy and 142 (68%) of 205 patients on low-dose therapy had complete or partial response within four cycles.[72] However, the high response rates did not result in superior time to progression, PFS, or OS compared with low-dose dexamethasone. The trial was stopped after one year and patients on high-dose therapy were allowed crossed over as the OS rate was significantly higher in the low dose arm. At 1 year interim analysis, OS was 96% in the low-dose dexamethasone group compared with 87% in the high-dose group (P = .0002); 2- year OS was 87% versus 75% respectively.

The cause of inferior overall survival with high-dose dexamethasone seems to be related to increased deaths due to toxicity. Fifty two

percent on the high-dose regimen compared with 35% on the low-dose regimen had grade three or worse toxic effects in the first 4 months, including deep-vein thrombosis (26% vs. 12%); infections including pneumonia (16 vs. 9%); and fatigue (15% vs. 9%). The 3-year OS of patients who received four cycles of primary treatment with either dose followed by autologous SCT was 92%, suggesting that lenalidomide/dexamethasone is a reasonable for primary therapy prior to SCT.

A retrospective analysis of 411 newly diagnosed patients treated with either lenalidomide/dexamethasone (n = 228) or thalidomide/dexamethasone (n = 183) was performed at the Mayo Clinic.[73] In a matched-pair analysis, the differences between the two arms were similar for age, sex, transplantation status, and dexamethasone dose. The proportion of patients achieving at least a PR to lenalidomide/dexamethasone was 80.3% versus 61.2% with thalidomide/dexamethasone; VGPR rates were 34.2% and 12.0%, respectively. Patients receiving lenalidomide/dexamethasone had longer time to progression (median, 27.4 vs. 17.2 months; *P* = .019), longer PFS (median, 26.7 vs. 17.1 months; *P* = .036), and better OS (median not reached vs. 57.2 months; *P* = .018).[73] Grade 3 or 4 adverse event (57.5% vs. 54.6%, *P* = .568) were seen in similar proportion of patients in both the groups. Main grade 3 or 4 toxicities of lenalidomide/dexamethasone were hematologic, mainly neutropenia (14.6% vs. 0.6%, *P* < .001); the most common toxicities in thalidomide/dexamethasone were venous thromboembolism (15.3% vs. 9.2%, *P* = .058) and peripheral neuropathy (10.4% vs. 0.9%, *P* < .001). Based on the results of this meta-analyses lenalidomide/dexamethasone appears well tolerated and more effective than thalidomide/dexamethasone.[73] However, randomized prospective trials are needed to confirm these results.

A decrease in CD34-positive cells collected after prolonged lenalidomide treatment has been reported.[74, 75] Guidelines by the IMWG suggest that patients on lenalidomide in combination with dexamethasone should have stem cells collected within the first 4 cycles of therapy.[76]

The NCCN Multiple Myeloma Panel recommend harvesting peripheral blood early in the courses of primary treatment with lenalidomide. Lenalidomide/dexamethasone is listed as a category 1 primary treatment option in the NCCN Guidelines. The Panel recommends appropriate prophylaxis for patients receiving this therapy.

The incidence of deep vein thrombosis is low with single agent lenalidomide or lenalidomide plus low-dose dexamethasone, but risk rises when combined with high-dose dexamethasone. According to a recent report patients treated with lenalidomide and high-dose dexamethasone who developed a venous thromboembolism (VTE) did not experience shorter OS or time to progression.[77] Prophylactic anticoagulation is recommended in patients receiving this therapy.[50, 78]

Other Primary Therapy Regimens for Transplant Candidates

Thalidomide/Dexamethasone

Thalidomide attacks multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis and cytokine circuits, among others. Rajkumar et al reported the results of a study involving 207 patients with newly diagnosed MM randomized to receive thalidomide/dexamethasone or dexamethasone alone.[79] The response rate to the combined therapy was significantly higher compared to those receiving dexamethasone alone (63% vs. 41%, respectively). Stem cells for subsequent transplant were also successfully collected. However, increased toxicity is associated with

thalidomide; specifically DVT, therefore prophylactic anticoagulation is recommended if thalidomide and dexamethasone are given.[78] Other side effects of thalidomide included rash, gastrointestinal disturbance, peripheral neuropathy, or somnolence.[50] The use of thalidomide requires individual patient consideration and the higher response rate of the thalidomide/dexamethasone combination must be weighed against the increased side effects. Thalidomide in combination dexamethasone as primary regimen is a category 2B recommendation in the NCCN Guidelines. The Panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Single agent Dexamethasone
Dexamethasone alone maybe an option as short term primary therapy for highly selected group of patients (eg, in those with renal failure, hypercalcemia, cord compromise requiring radiation therapy, cytopenia). Single agent dexamethasone as primary treatment is a category 2B recommendation in the NCCN Guidelines.

Liposomal Doxorubicin/Vincristine/ Dexamethasone (DVD) regimen
In a non-inferiority trial newly diagnosed, active MM patients (n = 192) were randomized to receive pegylated liposomal doxorubicin/vincristine/dexamethasone regimen or vincristine/doxorubicin/dexamethasone regimen.[80] The primary endpoints were response and toxicity. Objective response, PFS, and OS were similar between the treatment groups. However, pegylated liposomal doxorubicin/vincristine/dexamethasone was associated with less toxicity compared with vincristine/doxorubicin/dexamethasone.[80] Data from recent studies suggest that vincristine/doxorubicin/dexamethasone no longer be recommended as most patients respond to induction regimen based on novel drug combinations. Liposomal doxorubicin/vincristine/dexamethasone regimen is listed as a category 2B recommendation for primary treatment in the NCCN Guidelines.

Preferred Primary Therapy Regimens for Nontransplant Candidates

All of the regimens described above for transplant candidates are also options for nontransplant candidates. The regimens containing melphalan compromise stem cell reserve, and thus are options only for nontransplant candidates.

Melphalan/Prednisone/Thalidomide
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 OS of 24 to 36 months.[81] Palumbo and colleagues were the first to report that when thalidomide was combined with melphalan and prednisone (MPT), combined near CR and CR rates were 27.9% for MPT compared to 7.2% for MP.[82] Subsequently, a number of phase III trials have reported significant higher ORR with MPT versus MP (57-76% vs. 31-48%), including a higher CR or VGPR rate (7-15.5%).[83-88] The impact of MPT on survival is not clear as only the IFM studies[83, 84] have reported a survival advantage in patients on MPT. The HOVON group carried out a phase III study to compare the standard MP versus MPT in 333 newly diagnosed elderly patients with MM.[89] Significantly higher responses rates were seen with MPT treated patients compared to MP and were comparable with response rates seen in the French and Italian trial described above. Overall response rate with MPT (CR+VGPR+PR) was 66% versus 45% with MP. The number of patients not responding to therapy or patients with progressive disease was 55% with MP and 34% with MPT. The vent-free survival was 13 months with MPT versus 9 months with MP and OS was 40 months with MPT versus 31 months with MP.[89] Comparisons between these studies are difficult because of

differences in patient populations, duration of treatment and use of maintenance regimens.

Due to the significantly higher ORR consistently seen in all these studies, MPT is a category 1 recommendation as primary treatment in patients not eligible for transplant. There is a significant risk of DVT with thalidomide-based therapy, therefore use of prophylaxis in patients on MPT therapy is highly recommended.

Melphalan/Prednisone/Bortezomib

Addition of bortezomib to MP (MPB) was investigated in a large randomized international phase III VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) trail.[90] The trial evaluated MP (n = 338) versus MPB (n = 344) in previously untreated patients with MM who were 65 years of age or older, or patients younger than 65 years of age and transplant ineligible. The addition of bortezomib resulted in highly significant increases in time to disease progression, PFS, OS, time to next treatment, and complete response. Importantly, 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 with a median follow-up of 36.7 months show a 35% reduced risk of death with MPB versus MP.[91] The 3-year OS rate was 68.5% in the MPB arm compared to 54% in the MP arm. With MPB, time to progression and OS was unaffected by advanced age, renal impairment, and adverse cytogenetics (t[4;14], t[14;16], del[17p]).The adverse events were higher in the MPB arm; however, discontinuation of treatment due to adverse events was reported to be similar in both arms. Improvement in peripheral neuropathy in patients treated with MPB was seen within a median of 1.9 months; 60% completely resolved within a median of 5.7 months.[91]

Another interesting finding from this study was that patients relapsing after bortezomib-based therapy are not more resistant to subsequent therapies and can be as successfully treated with subsequent immunomodulatory drug-based therapies. The median survival from start of subsequent therapy was 30.2 months for those treated initially with MPB versus 21.9 months for those with MP.[91] Response rates to second-line bortezomib-, thalidomide-, and lenalidomide-based therapies were 41%, 37%, and 73%, respectively after MPB, and 59%, 47%, and 67%, respectively, after MP.[91] This finding supports the strategy of using bortezomib-based treatment as first-line therapy instead of reserving it as salvage after upfront conventional therapy. Based on the VISTA trial results, the MPB regimen is now a NCCN category 1 recommendation as primary treatment in patients not eligible for transplant.

Advantages of MPB over MPT include more rapid response and higher rates of CR, which is associated with improved survival in the nontransplant setting.[92, 93] Results of VISTA also support use of MPB in patients with high-risk cytogenetics and/or impaired renal function. There is no randomized head-to-head study comparing MPT and MPB; however, a meta-analysis of the phase III studies has demonstrated that better response rates could be expected with MPB than with MPT.[94] Yeh et al compared the existing data (on MP, MPT, and MPB) and calculated an 81% probability that MPB was the most efficacious among the three regimens in terms of ORR and a greater than 99% probability that it was also the most efficacious in terms of CR. No difference was seen in OS and PFS between MPB and MPT regimens.

Melphalan/Prednisone/Lenalidomide

Melphalan and prednisone in combination with lenalidomide (MPL) was studied in 54 patients with newly diagnosed MM.[95] Although there were concerns about myelosuppression with lenalidomide, therapy with oral MPL produced very high response rates. Eighty one percent of patients achieved at least a PR, 47.6% achieved a VGPR, and 24% achieved a complete immunofixation-negative response. 1 year event free survival in all patients was 92% and OS was 100%. Common grade 3/4 toxicities seen were neutropenia (in 52%), thrombocytopenia (in 24%), and anemia (in 5 %).

A subsequent analysis of the kinetics of neutropenia and thrombocytopenia as well as the safety and efficacy of MPL showed that the hematological toxicities are manageable and median PFS was 28.5 months, and 2-year OS was 91%.[96] The investigators suspect that cytoxicity of bone marrow is related to melphalan in the regimen.

In another phase I/II trial of newly diagnosed MM patients not eligible for autologous SCT (median age 74 years), MPL regimen showed substantial activity (CR was 12%, ORR was 69%) with a manageable toxicity profile.[97] The most common grade 3/4 toxicities were neutropenia (58% of patients) and thrombocytopenia (27%).[97]

The phase III MM-015 study is evaluating 459 patients (median age 65) with newly diagnosed MM randomly assigned to MPL followed by lenalidomide maintenance or MPL followed by placebo maintenance, or MP followed by placebo maintenance.[98] The updated results show that overall, MPL plus lenalidomide maintenance reduced the risk of disease progression by 58% compared with MP with a higher 2-year PFS rate (55% vs 16%).[99] The MPL regimen is a category 1 option as primary treatment option for patients ineligible for transplant in the NCCN Multiple Myeloma Guidelines.

Lenalidomide/Low-dose Dexamethasone

Based on the results of the SWOG SO232 trial,[69] which included nontransplant candidates and the results of ECOG E4A03 trial[70] which included elderly patients as well, lenalidomide in combination with low dose- dexamethasone is a well tolerated and effective regimen for elderly. In the study (discussed in the previous section) the OS rate was significantly higher in the lenalidomide plus low dose arm compared to lenalidomide plus high-dose dexamethasone arm.[72] The inferior survival outcome seen with high dose dexamethasone was greatest in patients 65 years and older. At 2 years, patients who did not proceed to transplant had an OS rate of 91% with lenalidomide and low dose dexamethasone.[72] Therefore, lenalidomide in combination with low dose dexamethasone considered a category 1 option by the NCCN Multiple Myeloma Panel for nontransplant candidates. The Panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Bortezomib/Dexamethasone

A U.S. community-based, randomized, open-label, multicenter phase IIIb UPFRONT trial, is comparing safety and efficacy of three highly active bortezomib-based regimens one of which is bortezomib/dexamethasone.

Bortezomib/thalidomide/dexamethasone; bortezomib/dexamethasone; and MPB are being compared with each other in previously untreated elderly patients with MM ineligible SCT.[100] The updated results demonstrate that all three regimens are active with good response rates with predictable and similar rates of toxicities reported for all arms. [100, 101] The study also showed that bortezomib maintenance was well tolerated and resulted in increased rates of very good PRs in all three arms. The NCCN Multiple Myeloma Panel has included

bortezomib/dexamethasone as a category 2A primary therapy option for patients ineligible for transplant.

Other Primary Therapy Regimens for Nontransplant Candidates

Compared to MP, both MPT and MPB regimens have reported superior responses compared to MP. However, MP may still have a role in patients who do not have access to novel agents. According to the NCCN Multiple Myeloma Panel, MP is a category 2A recommendation. The other NCCN category 2B options for patients not eligible for SCT include thalidomide/dexamethasone, single agent dexamethasone, liposomal doxorubicin/vincristine/dexamethasone (DVD), and vincristine/doxorubicin/dexamethasone (VAD).

Follow-Up After Primary Therapy for Transplant and Nontransplant Candidates

Following primary therapy, patients are re-evaluated (after 2 cycles) with the laboratory tests, bone survey and bone marrow aspiration and biopsy to determine whether there has been a treatment response, or whether primary progressive disease is present. Potential transplant candidates undergo a stem cell harvest, collecting enough stem cells for two transplants in anticipation of a tandem transplant or a second transplant as salvage therapy. Autologous and allogeneic transplants are discussed further below. Alternatively, all patients may consider continuation of primary therapy till the best response is reached. The optimal duration of primary therapy following maximal response is unknown, hence, maintenance therapy, or observation can be considered 2 cycles beyond maximal response.

Stem Cell Transplants

Introduction

High dose therapy with stem cell support is a critical component in the treatment plan for eligible newly diagnosed MM patients. The types of SCT may be single autologous SCT, a tandem SCT (a planned second course of high dose therapy and SCT within 6 months of the first), or an allogeneic SCT. An allogeneic SCT can be either done after prior myeloablative therapy, or after nonmyeloablative therapy. Nonmyeloablative therapy, also referred to as “mini transplant” has been investigated as a technique to decrease toxicity of the allotransplant while preserving the alloimmune graft-versus-myeloma effect.[102, 103] An allogeneic SCT may also follow an autologous SCT.

The NCCN Multiple Myeloma Guidelines indicate that all types of SCT are appropriate in different clinical settings; these indications are discussed further below. However, in general, all candidates for high-dose chemotherapy must have sufficient liver, renal, pulmonary, and cardiac function. Earlier studies of autologous transplant included total body irradiation (TBI) as component of the preparative regimen. Regimens with chemotherapy only have recently been shown to have equivalent efficacy and less toxicity than TBI. TBI regimens have now been abandoned,[104] but newer, potentially less toxic radiation techniques aimed to deliver total marrow irradiation (TMI) while reducing toxicities to non-target organs, are currently undergoing evaluation in clinical trials.[105]

Autologous Stem Cell Transplants

Autologous SCT results in high response rates and remains the standard of care following primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous SCT is associated with statistically significant higher response rates as well as increased overall and

event-free survival when compared with the response of similar patients treated with conventional therapy.[106] In 2003, results of a second trial comparing high-dose therapy to standard therapy showed an increase in the complete response rate and an improvement in OS (54 months in the high-dose group compared to 42 months for standard therapy).[107] The benefit was more pronounced for higher risk patients. Barlogie and colleagues reported on the results of an American trial that randomized 510 patients to receive high dose therapy with autologous stem cell support or standard therapy.[108] With a median follow-up of 76 months, there were no differences in response rates, PFS, or OS between the two groups. The reason for the discrepant results are not clear, but may be related to differences in the specific high dose and conventional regimens between the American and French study. For example, the American study included TBI as part of the high dose regimen; TBI has subsequently been found to be inferior to high dose melphalan.[106]

Another trial included 190 patients aged 55 to 65 randomized to standard or high dose therapy.[109] This study was specifically designed to include older patients, since the median age of the participants in other trials ranged from 54-57 years while the median age in this trial was 61 years. After 120 months of follow up, there was no significant difference in OS, although there was a trend toward improved event free survival in the high dose group (P = .7). Additionally, the period of time without symptoms of treatment or treatment toxicity (TWiSTTs) was significantly longer in the high dose group. The study concluded that the equivalent survival suggests that the treatment choice between high dose and conventional dose chemotherapy should be based on personal choice in older patients. For example, an early transplant may be favored because patients can enjoy a longer interval of symptom free time. However, this study[56] also showed that a transplant performed at the time of relapse (as salvage therapy) has a similar OS compared to an early transplant. The choice of early versus late transplant was examined in a randomized French trial, and the results in both arms are comparable with respect to OS.[110] However, early SCT was superior in terms of quality of life, assessed as time without symptoms and side effects from therapy. [110]

It should be noted that all randomized studies of autologous SCT following primary therapy were designed and implemented prior to the availability of thalidomide, lenalidomide or bortezomib. Therefore, the role of transplant may evolve in the future. Results from the IFM 2005/01 study of patients with symptomatic myeloma receiving primary therapy with either bortezomib/dexamethasone versus VAD showed a marked improvement in ORR with bortezomib/dexamethasone over VAD (discussed in sections above).[111] 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).[111] In the bortezomib plus dexamethasone arm 34% required a second SCT, compared with 47% of patients in the VAD arm.[111] With a median follow-up of 32.2 months, PFS after primary treatment with bortezomib and dexamethasone versus VAD group was 36.0 and 29.7 months respectively.[111] Responses were evaluated post primary treatment and post-autologous SCT. Progression free survival was significantly longer in patients achieving greater than or equal to a VGPR after autologous SCT than in the 188 patients achieving less than VGPR (median 41.1 vs. 33.5 months). Also, PFS was also significantly longer in the patients achieving greater than or equal to a VGPR after primary treatment than in patients achieving a less than VGPR (median 41.1 vs. 29.0 months).[112]

In another study, 474 patients were randomized to primary therapy with bortezomib/dexamethasone/thalidomide (n = 236) or thalidomide/dexamethasone (n = 238) prior to double autologous

SCT.[113] The three drug yielded high response rates compared with the two drug regimen, with CR rate of 19% (vs. 5%) and ≥ VGPR of 62% (vs. 31%). After SCT, improved incremental responses were still seen with bortezomib/dexamethasone/thalidomide compared with thalidomide plus dexamethasone. Taken together these studies suggest that improved responses with the primary regimen results in improved outcomes after transplantation.

Studies have found that progressive disease emerging after primary therapy does not preclude a good response to autologous SCT.[108, 114, 115] For example, Kumar and colleagues reported on a case series of 50 patients with primary progressive MM receiving an autologous SCT.[115] Results were compared to 100 patients with responsive disease undergoing autologous SCT. The one year PFS from the time of transplant was 70% in the primary progressive group compared to 83% in the chemosensitive group. For this reason, the guidelines indicate autologous SCT as a category 1 option for treatment of primary progressive or refractory disease post primary treatment.

Tandem Stem Cell Transplants

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**.** The IFM94 trial reported by Attal et al randomized newly diagnosed myeloma patients to single or tandem autologous transplants.[116] A total of 78% of patients assigned to the tandem transplant group received the second transplant at a median time of 2.5 months after the first. A variety of options for salvage therapy were provided. For example relapsing patients in either group underwent either no therapy, additional conventional therapy or another SCT. The probability of surviving event free for seven years after the diagnosis was 10% in the single transplant group compared to 20% in the double transplant group. An accompanying editorial by Stadtmauer questions whether the promising results might be related to regimens used, rather than the effect of two courses of high dose therapy.[117] For example, patients in the single transplant arm received 140 mg/m^2 melphalan plus TBI, while those in the tandem arm received the same dose without TBI for the initial transplant and with TBI for the second transplant. As noted above, 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, those patients who did not achieve a complete CR or a VGPR within 3 months after the first transplant appeared to benefit the most from a second transplant. The authors of the IFM94 study have suggested that the improvement in projected survival associated with tandem transplant is related not to improved response rates, but to longer durations of response. Four other randomized trials have compared single versus tandem transplant.[109, 118-120] None of these trials showed a significant improvement in OS. However, since the median follow-up in these trials ranged from 42 to 53 months, the lack of significant improvement is not surprising. The trial by Cavo et al[118] found that patients not in CR or near CR after the first transplant benefited the most from a second transplant. This confirms the observations of the IFM94 trial using non-TBI based high dose regimens.

In both the French and Italian trials, the benefit of a second autologous SCT was seen in patients failing to achieve a complete response or very good partial response (greater than 90% reduction in M protein level) with the first procedure. These two studies were not adequately powered to evaluate the equivalence of one versus two transplants in patients achieving a CR or VGPR after the first transplantation.

A review of long-term outcomes of several trials of autologous transplantation by Barlogie et al found that tandem transplantations were superior to both single transplantations and standard therapies.[121] Also, post relapse survival was longer when event-free survival was sustained for at least 3.5 years after tandem transplantation.[121] The NCCN Multiple Myeloma Panel recommends collecting enough stem cells for two transplants in *all* eligible patients. According to the NCCN Multiple Myeloma Panel, a tandem transplant can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT. The benefit from the second transplant in patients, who are in CR, or VGPR, and also in those who achieve less than VGPR after the first SCT, should preferably be answered in a clinical trial. In fact, such a randomized prospective NIH and Intergroup-supported trial is currently ongoing. The other options for this group of patients include maintenance therapy or observation.

The NCCN Multiple Myeloma algorithms identify the following situations where a repeat autologous SCT as salvage therapy may be considered either on or off clinical trial depending on the time interval between the preceding stem cell transplant and documented progression: 1) In patients initially treated with primary therapy alone followed by the first autologous SCT when the disease relapsed, who now have progressive disease following the first autologous SCT (category 2A recommendation on or off a clinical trial). 2) In patients who have progressive disease after first autologous transplant (category 2A recommendation on or off a clinical trial). A retrospective case-matched control analysis was performed comparing patients who underwent a second autologous SCT to those treated with conventional chemotherapy for relapsed MM.[122] Similar to previously published smaller studies,[123-125] this retrospective analysis demonstrated that a second autologous SCT is associated with superior relapse-associated mortality compared with conventional chemotherapy (68% vs 78%), along with improved OS (32% vs 22%) at 4 years. In this analysis, factors associated with improved OS and PFS included younger age (< 55 years), beta-2 microglobulin <2.5 mg/L at diagnosis, a remission duration of >9 months and a greater than PR to their first ASCT. Indicating that, a second autologous transplant for relapsed or progressive MM patients may be an option for carefully selected patients. 3) In patients with initial CR or near CR to an initial single/tandem autologous SCT who then develop progressive disease. Some of these patients can achieve durable complete or partial remission.[125, 126] and for this reason the NCCN Multiple Myeloma Panel members consider it a category 2A and recommend it in the setting of standard therapy or as part of clinical trial.

Allogeneic Stem Cell Transplant

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

Given the small candidate pool, it is not surprising that there have been no randomized clinical trials comparing myeloablative allogeneic to autologous SCT, but multiple case series have been published describing allogeneic SCT as an initial or salvage therapy for MM. In a 1999 review, Kyle reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured.[127] Other reviews have also reported increased morbidity without convincing proof of improved survival.[114, 128] However, there is intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.[108] The original trial had an ablative, allogeneic transplant group in which patients with HLA identical siblings were assigned. Only 36 patients received allografts, and because of the high 6 month mortality of 45% the allogeneic arm was closed. With seven years of follow-up the OS of the conventional chemotherapy, autologous and allogeneic arms are all identical at 39%. The autologous and conventional chemotherapy arms do not demonstrate a plateau, however, while the allogenic curve is flat at 39%. This suggests that a proportion of these patients are long term survivors. Thus, there is ongoing interest in myeloablative allogeneic SCT, particularly given that lack of a significant cure rate for single or tandem autologous SCT. Therefore, the NCCN Guidelines consider myeloablative allogeneic SCT an accepted option, only in the setting of a clinical trial in patients responding to primary therapy; or primary progressive disease, or as salvage therapy in patients with progressive disease following an initial autologous SCT.

Another strategy that has been investigated is, initial autologous SCT followed by a mini-allogeneic transplant. A prospective trial by Bruno et al[129] showed that, among patients (under 65 years) with HLA-matched siblings who received an autograft-allograft regimen, CR rate after allografting was 55%, compared with 26% after double autograft in patients without HLA-matched siblings. Median OS was higher (80 vs. 54 months). In the prospective PETHEMA trial, in patients failing to achieve at least near CR with a first autologous SCT although no significant difference in OS was observed between double autologous SCT and autologous SCT followed by mini-allogeneic transplant, a trend toward a longer PFS was observed.[130] In contrast, the IFM trial (99-03) by Garban et al[131], and the BMT-CTN 0102 trial by Stadtmauer et al[132] reported no OS or PFS with autologous transplant followed by mini-allogeneic transplant in high-risk myeloma patients.

Mini- allogeneic transplants have also been investigated as salvage therapy by virtue of its graft-versus myeloma effect. Responsive disease to prior transplantation and younger age are associated with better response and OS rates.[133-136] In a case series report, 54 patients with previously treated relapsed or progressive disease were treated with an autologous-SCT followed by a mini-allogeneic transplant.[134] There was a 78% OS at a median 552 days after the mini-allogeneic transplant, with a 57% complete response rate and an ORR of 83%. This study concluded that this approach reduced the acute toxicities of a myeloablative allogeneic-SCT while preserving anti-tumor activity. The largest case series was reported by the EBMT.[135] In this heterogeneous population of 229 patients, the 3 year OS and PFS were 41% and 21%, respectively. Adverse OS was associated with chemoresistant disease, more than 1 prior transplant, and improved OS was associated with graft versus host disease, confirming the importance of a graft versus leukemia effect. This study concluded that mini-allogeneic transplantation is feasible, but heavily pretreated patients and patients 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 in

order to stimulate a beneficial graft-versus-myeloma effect[137-144] or salvage therapy on or off a clinical trial.

Maintenance Therapy

Thalidomide as Maintenance Therapy After Autologous SCT
Thalidomide as maintenance therapy after a prior autologous SCT has been studied in retrospective as well as independent randomized trials. In a retrospective review of 112 patients undergoing autologous SCT, Brinker and colleagues reported on the outcomes of 36 patients who received thalidomide as maintenance or salvage therapy compared to 76 patients who received no post transplant therapy.[145] The median survival in the thalidomide group was 65.5 months compared to 44.5 months in the no treatment group (P = .9). Attal et al randomized 597 patients to one of three different strategies following tandem autologous SCT, either no maintenance, pamidronate alone, or pamidronate combined with thalidomide.[146] There was a highly significant event free and OS advantage in the thalidomide and pamidronate arm. The group that appeared to benefit the most was one that had patients who achieved 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 versus prednisone alone as maintenance therapies post autologous SCT. The results confirm that thalidomide added to maintenance is superior to prednisone alone.[147] In another randomized trial, thalidomide maintenance induced improvement in PFS in patients achieving less than a VGPR following autologous SCT with no survival benefit.[148] Thalidomide has also been used before, during, and after tandem autologous SCT.[108, 149] In a randomized study of 668 newly diagnosed patients, half received thalidomide throughout the course of the tandem autologous SCT, i.e. thalidomide was incorporated into primary therapy, continued between the tandem autologous SCT, and was incorporated into consolidation therapy and continued as maintenance therapy.[149] The group that was not treated with thalidomide received the same core therapy. After a median follow up of 42 months, the group that received thalidomide had improved complete response rates (62% vs. 43%) and five year event free survival rates (56% vs. 44%). However, the OS rate was approximately 65% in both groups. Patients who did not receive thalidomide throughout therapy benefited from thalidomide at the time of relapse. The results of this study suggest that sequencing drugs may be important. For example, if thalidomide is used as part of up front therapy, another drug should be considered for maintenance therapy.

Based on the above evidence, according to the NCCN Multiple Myeloma Panel thalidomide alone is a category 1 recommendation and one of the preferred maintenance regimens. Thalidomide in combination with prednisone is a category 2A recommendation as maintenance therapy. There are concerns about the cumulative toxicity with thalidomide. For example, peripheral neuropathy observed with thalidomide is related to the duration of treatment and is cumulative. The benefits and risks of maintenance therapy with thalidomide should be discussed with patients.

Lenalidomide as Maintenance Therapy After Autologous SCT
Lenalidomide has been evaluated in two independent randomized phase III studies as maintenance following autologous transplantation. The CALGB 100104 trial compared lenalidomide versus placebo as maintenance therapy after prior autologous SCT.[150] The encouraging preliminary interim results led to un-blinding of this trial. The updated interim results show that patients receiving lenalidomide maintenance following a autologous SCT had a significant reduction in the risk of disease progression or death when compared to patients receiving placebo.[151] The benefit of lenalidomide maintenance therapy was

observed among those either achieving a complete response or not after autologous SCT.

Data from the international, randomized, double-blind phase III IFM 2005-02 trial show that following autologous SCT, patients treated with lenalidomide as consolidation therapy followed by lenalidomide as maintenance therapy had upgraded responses. The final analysis of the IFM 2005-02 trial performed after a median follow up of 34 months from randomization and 44 months from diagnosis showed that maintenance with lenalidomide improved the PFS. The median PFS was 24 months from randomization in patients in the placebo arm versus 42 months from randomization with lenalidomide maintenance.[152]

Lenalidomide as Maintenance Therapy After Nontransplant Active Primary Treatment

Data from the Phase III MM-015 study shows that lenalidomide maintenance following MPL primary therapy significantly reduced the risk of disease progression and also increased PFS.[99] In this study, newly diagnosed patients with MM (n = 459) aged ≥65 years were randomized to receive MP followed by placebo until progression, or MPL until progression, or MPL followed by lenalidomide until progression. The primary comparison for this trial was the MPL followed by lenalidomide maintenance arm versus MP followed by placebo arm. The results show MPL followed by lenalidomide maintenance resulted in rapid and higher rates ORR (77% vs 50%, *P* <.001) compared with MP alone. Maintenance with lenalidomide also reduced the risk of disease progression by 58% compared with MP along with a higher 2-year PFS rate (55% vs 16%).[99]

The analysis comparing MPL followed by lenalidomide maintenance arm to MPL followed by placebo arm at the beginning of cycle 10 demonstrated that maintenance lenalidomide resulted in a 69% reduced risk of progression compared with placebo (HR = 0.314, *P* < .001).[99]

Based on the above evidence the NCCN Multiple Myeloma Panel members have listed single agent lenalidomide as maintenance therapy as one of the preferred maintenance regimens. However pending peer reviewed publications of the above mentioned phase III trial results and the safety/efficacy data of lenalidomide in this setting, the current NCCN category of evidence and consensus for recommending lenalidomide as maintenance therapy is category 2A. Lenalidomide lacks the neurologic toxicity seen with thalidomide. However, there appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance therapy following SCT. The benefits and risks of maintenance therapy with lenalidomide versus secondary cancers should be discussed with patients. A recent report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option following mini-allogeneic SCT.[153]

Bortezomib as Maintenance Therapy After Autologous SCT

Bortezomib as maintenance therapy is being investigated in phase III trials. The preliminary results from the HOVON study show that maintenance with single agent bortezomib following autologous SCT is well tolerated and is associated with improvement of overall response rates.[55] Patients in the HOVON trail were randomly assigned to one of the two arms consisting of either primary treatment with vincristine/doxorubicin/dexamethasone followed autologous SCT and maintenance with thalidomide or with bortezomib/doxorubicin/dexamethasone followed autologous SCT and bortezomib as maintenance therapy. Maintenance therapy in both arms was given for 2 years. The study reported high near CR/CR rates after primary treatment with bortezomib-based regimen. Bortezomib as

maintenance therapy was well tolerated and associated with additional improvement of response rates.[55]

Bortezomib as Maintenance Therapy After Nontransplant Active Primary Treatment

The preliminary results of the phase III UPFRONT study also show that maintenance with single agent bortezomib is well tolerated when administered after treatment with bortezomib-based primary therapy.[100] Newly diagnosed MM patients ineligible for high-dose therapy and stem cell transplantation enrolled in the UPFRONT trial were randomized (1:1:1) and treated with one of the following bortezomib-based primary regimens: bortezomib/dexamethasone, bortezomib/thalidomide/dexamethasone, and bortezomib/melphalan/prednisone followed by maintenance treatment with bortezomib. The updated results show that the response rates, including CR and ≥VGPR, improved after bortezomib maintenance in all arms with no concomitant increase in the incidence of peripheral neuropathy [100]

The NCCN Multiple Myeloma Panel members have added bortezomib to the listed of preferred maintenance regimens with a category 2A designation.

Other Maintenance Therapy Regimens After Autologous SCT

A number of other maintenance therapies, such as steroids (dexamethasone) and interferon, have been investigated in patients whose disease responds to high-dose therapy followed by autologous or allogeneic SCT.[154] At the present time, the role of interferon[155] or steroid maintenance therapy[156] in general is uncertain, and for this reason these are category 2B recommendations as maintenance therapy in the NCCN Multiple Myeloma Guidelines.

Treatment of Progressive or Relapsed Myeloma

Salvage Therapy

Salvage therapy is considered in the following clinical situations: for patients with relapsed disease following allogeneic or autologous SCT; for patients with primary progressive disease following initial autologous or allogeneic SCT; for patients ineligible for SCT with progressive or relapsing disease after initial primary therapy.

A variety of therapies are available as options for salvage therapy. If the relapse occurs at greater than 6 months after completion of the initial primary therapy, patients may be retreated with the same primary regimen.

The phase III APEX trial compared bortezomib versus high dose dexamethasone as salvage therapy.[54] Among the 669 participants, patients randomized to bortezomib had a combined complete and partial response rate of 38% compared to 18% for those receiving dexamethasone, improved median time to progression (6.22 vs. 3.49 months) and one year survival (80% vs. 66%). In an updated efficacy analysis,[157] 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 OS was 29.8 months with bortezomib and 23.7 months with dexamethasone, despite nearly two thirds of patients' crossing over to bortezomib. Survival rates after one year were 80% and 67%, respectively ($P = .00002$). Patients with poor prognostic factors also benefited from bortezomib. Patients with deletion of chromosome 13 had worse survival when treated with dexamethasone than those without the deletion. However for bortezomib-treated patients, the outcome was the same for those with or without the deletion.[158] Based on the above phase III trial data, the NCCN Multiple Myeloma Panel members have included bortezomib

monotherapy as a category 1 salvage therapy option for patients with relapsed/refractory myeloma. A randomized trial, MMY-3021 of 222 patients compared single-agent bortezomib administered by the conventional intravenous route versus by subcutaneous route.[159] The results showed no significant differences in terms of time to progression or in one year OS between groups.[159] However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy.

The FDA approved the regimen for combining bortezomib with pegylated liposomal doxorubicin (PLD) as a treatment option for MM patients who have not previously received bortezomib and have received at least 1 prior therapy. The approval was based on a priority review of data from an international phase III trial (n = 646), showing that use of the combination significantly extended the median time to disease progression compared with bortezomib alone (9.3 vs. 6.5 months).[160] Median duration of response was increased from 7.0 months to 10.2 months with the combination therapy. Based on these results, the NCCN Multiple Myeloma Panel considers bortezomib with pegylated liposomal doxorubicin regimen as a category 1 salvage therapy option for patients with relapsed/refractory myeloma.

Addition of dexamethasone to bortezomib in patients with relapsed/ refractory myeloma who had progressive disease during bortezomib monotherapy, resulted in improvement of response in 18-34% of patients.[161-163] The NCCN Multiple Myeloma Panel members have included bortezomib/dexamethasone regimen as a category 2A salvage therapy option for patients with relapsed/refractory myeloma.

Lenalidomide combined with dexamethasone received approval from the FDA as treatment option for patients with MM who had received at least one prior treatment. This was based on the results of two studies of total 692 patients randomized to receive either dexamethasone with or without lenalidomide. The primary efficacy endpoint in both studies was time to progression. A pre-planned interim analysis of both studies reported that the median time to progression was significantly longer in the lenalidomide arm compared to the control group.[164, 165] The updated clinical data from the pivotal North American Phase III trial (MM-009) in 353 previously treated MM patients reported increased OS, as well as median time to disease progression in patients receiving lenalidomide plus dexamethasone compared to patients receiving dexamethasone plus placebo.[165] Similar results were seen in the international trial MM-010.[164] Patients in both these trials had been heavily treated prior to enrollment, many having failed three or more rounds of therapy with other agents and more than 50 percent of patients had undergone SCT.[164, 165] Most adverse events and Grade 3/4 adverse events were more frequent in MM patients who received the combination of (lenalidomide/ dexamethasone compared to placebo and dexamethasone. Thrombocytopenia (61.5%) and neutropenia (58.8%) were the most frequently reported adverse events observed. The NCCN Multiple Myeloma Panel now considers this regimen as a category 1 option as salvage therapy for patients with relapsed/refractory myeloma. Lenalidomide monotherapy has also been investigated and found effective in patients with relapsed/refractory myeloma.[166] The NCCN Multiple Myeloma Panel suggests considering lenalidomide monotherapy for steroid-intolerant individuals.

Data from preclinical studies showed lenalidomide sensitizes myeloma cells to bortezomib and dexamethasone. The results of phase 1 and phase II studies show that bortezomib/lenalidomide/dexamethasone is well tolerated and very active with durable responses seen in patients with heavily pretreated relapsed and/or refractory myeloma, including

patients who have had prior lenalidomide, bortezomib, thalidomide and SCT.[167, 168] The updated data after over 2 years of follow-up report a median PFS of 9.5 months and median OS of 26 months, with respective 12- and 24-month OS rates of 86% and 55% respectively.[169] The NCCN Multiple Myeloma Panel members have now included bortezomib/lenalidomide/dexamethasone as category 2A option for relapsed/refractory myeloma.

The effects of adding of an alkylating agent (such as cyclophosphamide) and a novel agent (such as lenalidomide or bortezomib) to dexamethasone have been investigated for patients with relapsed/refractory myeloma. A retrospective analysis to assess the efficacy of lenalidomide in combination with cyclophosphamide and dexamethasone showed that this regimen is effective in heavily pre-treated patients with manageable adverse effects.[170] The combination of bortezomib, dexamethasone and cyclophosphamide was found effective in relapsed/refractory myeloma patients with an acceptable toxicity profile.[171, 172] The NCCN Multiple Myeloma Panel members have included cyclophosphamide/dexamethasone in combination with either lenalidomide or bortezomib to the list of options for relapsed/refractory myeloma.

The addition of dexamethasone to thalidomide to treat relapsed/refractory myeloma patients, has been reported to have higher response rates of about 50%, when compared to thalidomide alone.[173-176] Furthermore, combination therapy of dexamethasone/thalidomide along with infusional chemotherapy such as cisplatin, doxorubicin cyclophosphamide and etoposide (DT-PACE regimen) was also found effective especially in patients with progressive disease.[177] Both the above regimens have been included NCCN Multiple Myeloma Guidelines as category 2A options for relapsed/refractory myeloma. Thalidomide monotherapy has also been shown to be effective in refractory/relapsed myeloma with 20-48% of the patients obtaining at least a PR.[178-182] Thalidomide-based combination regimens are more effective than thalidomide monotherapy however for steroid-intolerant individuals, the NCCN Multiple Myeloma Panel suggests considering thalidomide monotherapy.

In a trial by Knop and colleagues, 31 patients who had experienced relapse after high-dose chemotherapy and autologous transplantation were enrolled to receive increasing doses of bendamustine.[183] The ORR was 55% with a median PFS 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. A retrospective analysis of 39 patients has reported that bendamustine is effective and tolerable in patients with advanced progressive myeloma with an ORR of 36%.[184] Bendamustine is currently a NCCN category 2A treatment option for relapsed/refractory myeloma.

Other salvage options in the NCCN Multiple Myeloma Guidelines, include high-dose (non-marrow ablative) cyclophosphamide[185]; DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) [186, 187]; and VTD-PACE (bortezomib/thalidomide/dexamethasone- cisplatin, doxorubicin cyclophosphamide and etoposide.[17]

Adjunctive Treatment for Multiple Myeloma

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

Bony manifestations of myeloma, in the form of diffuse osteopenia and/or osteolytic lesions, develop in 85% of patients. Related complications are the major cause of limitations in quality of life and performance status in patients with MM. A large, double-blind, randomized trial has shown that monthly use of intravenous pamidronate (a bisphosphonate) can decrease pain and bone-related complications, improve performance status, and, importantly, preserve quality of life in patients with Durie-Salmon stage III myeloma and at least one lytic lesion.[188, 189] Zoledronic acid is more potent, can be administered more rapidly, and has equivalent benefits.[190] Results from the study conducted by Zervas et al[191] show a 9.5 fold greater risk for the development of osteonecrosis of the jaw with zoledronic acid compared to pamidronate. Patients who are on bisphosphonates should have their renal function monitored. They should be monitored for osteonecrosis of the jaw.

The MRC Myeloma IX study examined effects of zoledronic acid versus clodronate (a bisphosphonate not currently FDA approved) in MM patients initiating chemotherapy regardless of whether they had bone disease. The patients were randomized to received zoledronic acid (n = 981) or clodronic acid (n = 979). Zoledronic acid was reported to reduce mortality and significantly improve PFS.[192] Patients on clodronate and zoledronic acid had similar occurrence of acute renal failure and treatment-related serious adverse events. Zoledronic acid was associated with higher rates of confirmed osteonecrosis of the jaw than was clodronic acid.[192-194]

The NCCN Multiple Myeloma Guidelines now recommend bisphosphonates for all patients receiving myeloma therapy for symptomatic disease (category 1 recommendation).

In patients with smoldering or stage I MM, bisphosphonates may be considered but preferably in a clinical trial. Skeletal survey annually or as clinically indicated is recommended for these patients. Bone densitometry or other metabolic studies should be reserved for clinical trials.

Low-dose radiation therapy (10-30 Gy) is used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.[38] Limited involved fields should be used to limit the effect of irradiation on stem cell harvest or its effect on potential future treatments; the radiation doses administered should not preclude stem cell collection in potential candidates for high-dose therapy and hematopoietic SCT. Orthopedic consultation should be obtained for impending or actual fractures in weight-bearing bones, bony compression of the spinal cord, or vertebral column instability. Either vertebroplasty or kyphoplasty should be considered for symptomatic vertebral compression fractures.

Excess bone resorption from myeloma bone disease can lead to excessive release of calcium into the blood, contributing to hypercalcemia. Symptoms include polyuria and gastrointestinal disturbances, with progressive dehydration and decreases in glomerular filtration rate. Hypercalcemia should be treated with hydration and furosemide, bisphosphonates, steroids, and/or calcitonin. Among the bisphosphonates (zoledronic acid, pamidronate, and ibandronate), the NCCN Multiple Myeloma Panel members prefer zoledronic acid for treatment of hypercalcemia.[195-197]

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.[198] Institutions differ in their use of plasmapheresis for adjunctive treatment of renal dysfunction.

Erythropoietin therapy should be considered for anemic patients, especially those with renal failure. Measuring endogenous erythropoietin levels may also be helpful in treatment planning[199, 200] (see NCCN Cancer and Treatment Related Anemia Guidelines).

To prevent infection (1) intravenous immunoglobulin therapy should be considered in the setting of recurrent, life-threatening infections; (2) pneumococcal and influenza vaccine should also be considered; and (3) *Pneumocystis carinii* pneumonia (PCP), herpes, and antifungal prophylaxis is recommended, if a high-dose regimen is used. Bortezomib treatment has been associated with an incidence of herpes zoster.[53, 54] Herpes prophylaxis is recommended in patients receiving bortezomib and in the post-transplant setting.[48] (see NCCN Prevention and Treatment of Cancer Related Infections Guidelines).

Thrombosis is relatively common when thalidomide or lenalidomide is used with steroids, and is particularly frequent when treating newly diagnosed patients. Use of prophylactic anticoagulation agents (see NCCN Venous Thromboembolic Disease Guidelines) is recommended when immunomodulatory drugs are used in combination therapy during induction.[78, 201, 202]

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

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