National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Multiple Myeloma

Version 1.2011

NCCN.org

02/22/11

Table of contents

NCCN Multiple Myeloma Panel Members

Kenneth C. Anderson, MD/Chair α β *
Dana-Farber/Brigham and Women's Cancer Center

Melissa Alsina, MD β
H. Lee Moffitt Cancer Center & Research Institute

William Bensinger, MD α ξ
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

J. Sybil Biermann, MD λ
University of Michigan Comprehensive Cancer Center

Asher Chanan-Khan, MD α
Roswell Park Cancer Institute

Adam D. Cohen, MD α
Fox Chase Cancer Center

Steven Devine, MD α
The Ohio State University Comprehensive Cancer Center
- James Cancer Hospital and Solove Research Institute

Benjamin Djulbegovic, MD, PhD α β ξ
H. Lee Moffitt Cancer Center & Research Institute

Edward A. Faber, Jr., DO, MS β
UNMC Eppley Cancer Center at The Nebraska Medical Center

Carol Ann Huff, MD α
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Adetola Kassim, MD, MS β ξ
Vanderbilt-Ingram Cancer Center

Gwynn Long, MD α ξ ◊
Duke Cancer Institute

Bruno C. Medeiros, MD β
Stanford Comprehensive Cancer Center

Ruby Meredith, MD, PhD ¥
University of Alabama at Birmingham Comprehensive Cancer Center

Noopur Raje, MD α β
Massachusetts General Hospital Cancer Center

Jeffrey Schriber, MD β ξ
City of Hope Comprehensive Cancer Center

Seema Singhal, MD β
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

George Somlo, MD α β ◊
City of Hope Comprehensive Cancer Center

Keith Stockerl-Goldstein, MD α ξ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Steven P. Treon, MD, PhD α
Dana-Farber/Brigham and Women's Cancer Center

Guido Tricot, MD, PhD β
Huntsman Cancer Institute at the University of Utah

Donna Weber, MD α β ◊
The University of Texas MD Anderson Cancer Center

Joachim Yahalom, MD ¥
Memorial Sloan-Kettering Cancer Center

Furhan Yunus, MD β
St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute

NCCN
Rashmi Kumar, PhD
Dorothy A. Shead, MS

α Medical oncology
β Hematology
ξ Bone marrow transplantation
λ Surgery/Surgical oncology
¥ Radiotherapy/Radiation oncology
€ Pediatric oncology
◊ Internal medicine
* Writing committee member

NCCN Guidelines Panel Disclosures

Summary of the Guidelines Updates

Updates in Version 1.2011 NCCN Multiple Myeloma Guidelines from Version 3.2010 include:

Multiple Myeloma

Initial diagnostic workup (p. 3)
- Moved serum free light chain assay from useful under some circumstances to initial diagnostic workup.
- Added FISH for 1q21 amplification

Smoldering (asymptomatic) follow-up (p. 5)
- Changed "Progression to stage ll or higher disease" to "Progression to symptomatic myeloma."

Response criteria for multiple myeloma (p. 11)
- Under time point for assessing response added the following bullet: "Some responses can occur late post-transplant."

Myeloma therapy (p. 15)
- Bortezomib/cyclophosphamide/dexamethasone combination was added to primary induction therapy for transplant candidates.
- Bortezomib/dexamethasone combination was added to primary induction therapy for nontransplant candidates.
- Melphalan/prednisone/lenalidomide combination was added to primary induction therapy for nontransplant candidates.
- Cyclophosphamide/bortezomib/dexamethasone combination was added to salvage therapy.
- Cyclophosphamide/lenalidomide/dexamethasone combination was added to salvage therapy.
- Footnote 'h' is new to the page: These are representative regimens combining standard agents with novel agents.

Systemic Light Chain Amyloidosis

Primary treatment (p. 18)
- Added bortezomib with dexamethasone to primary treatment.
- Added cyclophosphamide/thalidomide/dexamethasone combination to primary treatment.

Multiple Myeloma

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) – Version 1.2011

1 Initial Diagnostic Workup

- H&P
- CBC, differential, platelets
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- 24 h urine total protein
- 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 17, t(4;14), t(11;14), t(14;16), 1q21 amplification]

Useful Under Some Circumstances

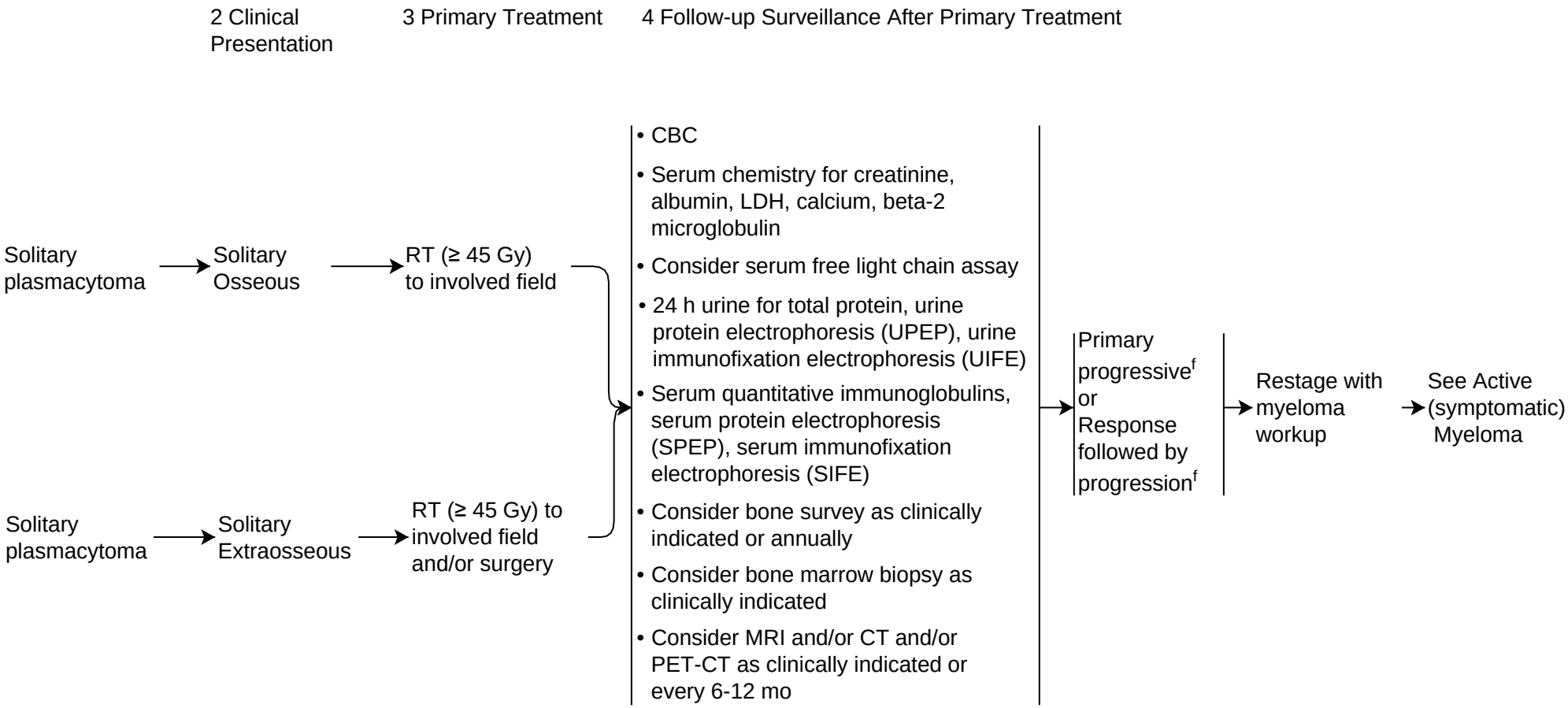
- MRI for suspected vertebral compression
- CT scan (avoid contrast)
- PET-CT scan
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Bone densitometry
- Plasma cell labeling index
- Staining of marrow and fat pad for amyloid
- Serum viscosity
- HLA typing

2 Clinical Presentation

- Solitary plasmacytoma[a] → See: Primary Treatment for Solitary Osseous and Solitary Extraosseous (p.4)
- Smoldering (asymptomatic)[a,b,c] → See: 3 Primary Treatment (p.5)
- Active (symptomatic)[a,b] → See: 3 Primary Treatment (p.5)

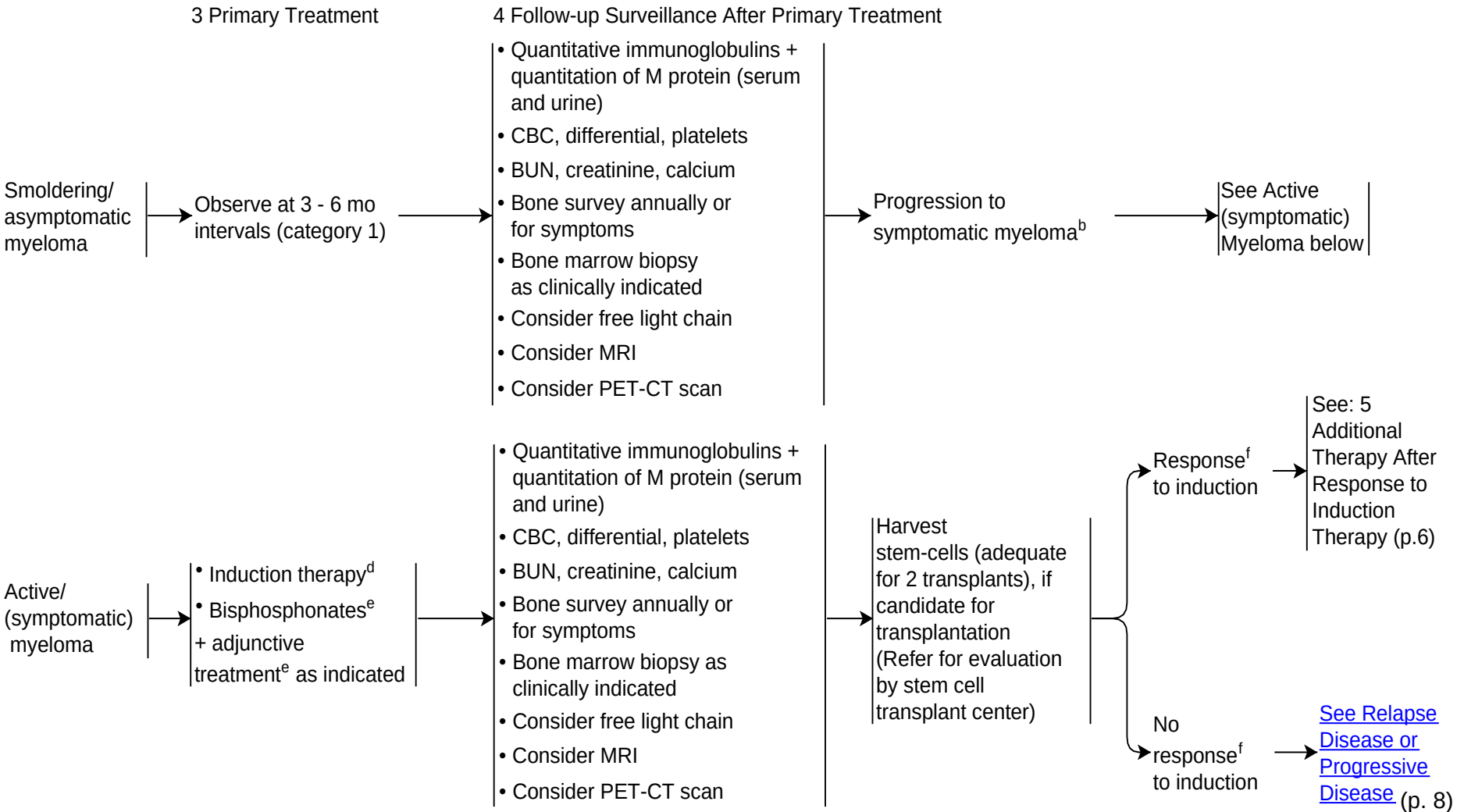
[a] See Staging Systems for Multiple Myeloma. (p. 9)
[b] See Definition of Multiple Myeloma (Smoldering and Active) (p. 10)
[c] Includes Durie-Salmon Stage I myeloma.

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.



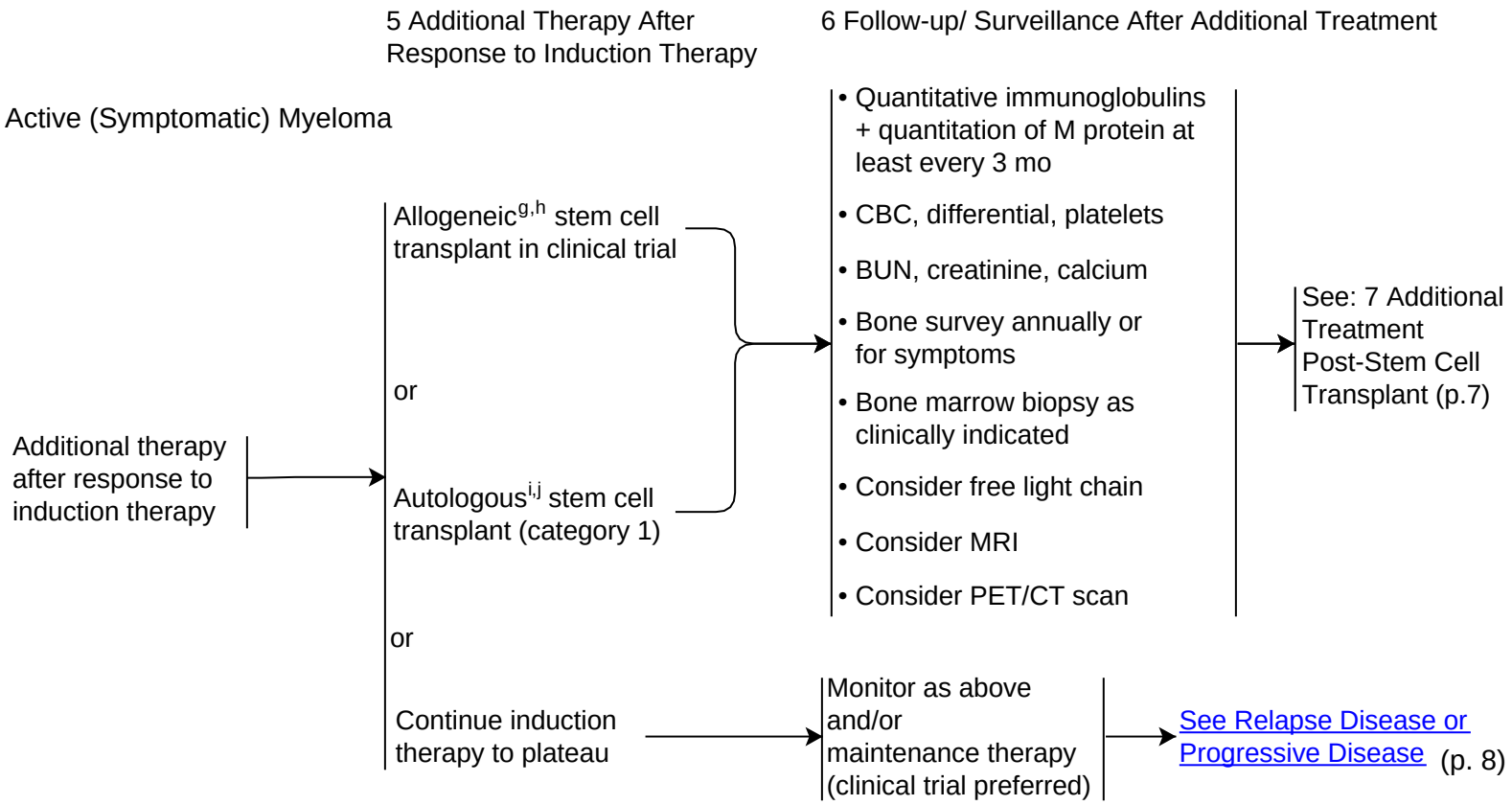
[f] See Response Criteria for Multiple Myeloma. (p. 11)

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.



[b] See Definition of Multiple Myeloma (Smoldering and Active) (p. 10)
[d] See Myeloma Therapy. (p. 15)
[e] See Adjunctive Treatment. (p. 17)
[f] See Response Criteria for Multiple Myeloma. (p. 11)

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.



g 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.

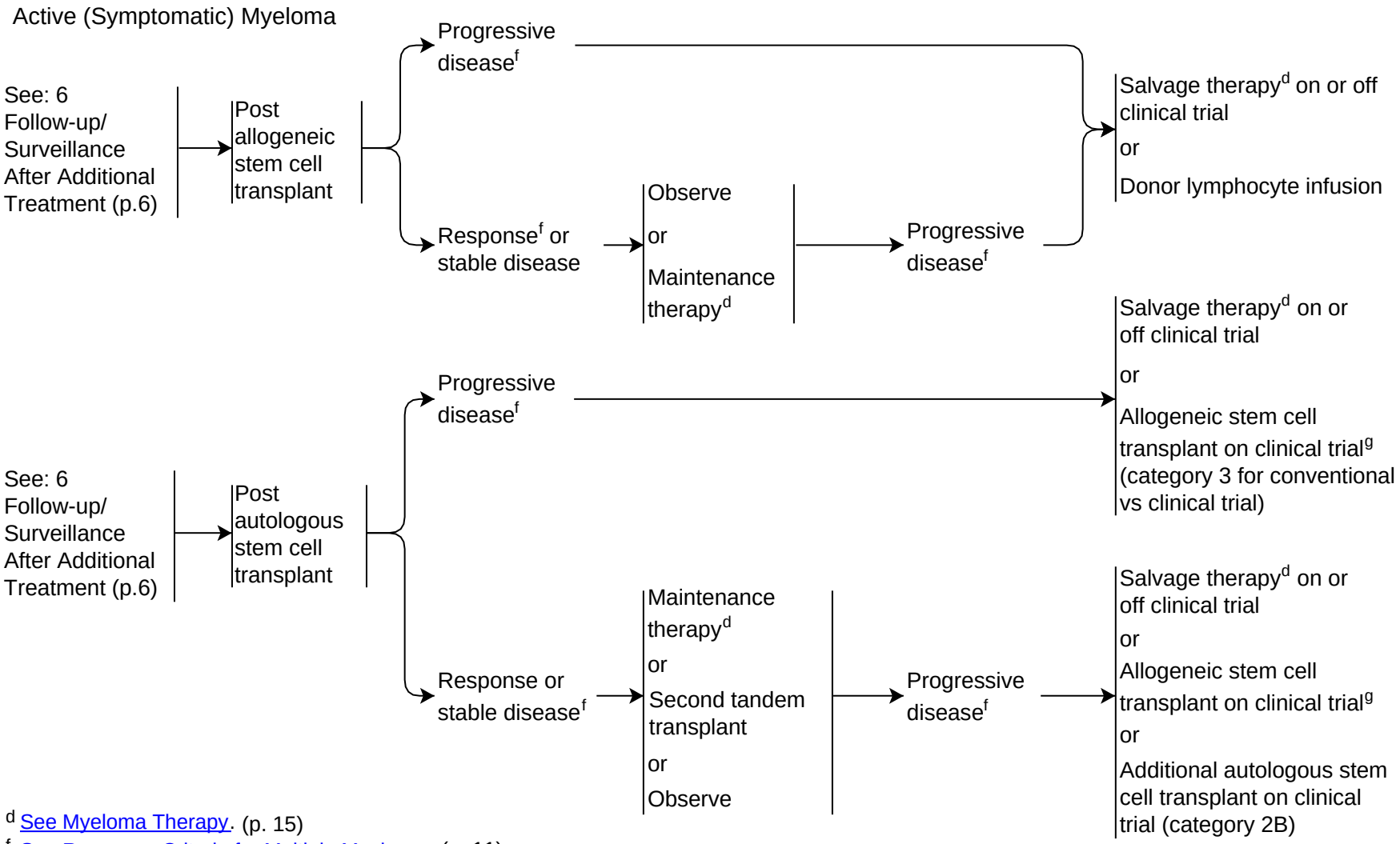
h A prospective trial by Bruno, et al. NEJM 2007;356:1110-1120, found improved survival for patients receiving an autologous transplant followed by non-myeloablative allograft compared to patients who received tandem autologous grafts. The IFM trial (99-03) by Garban et al, Blood 2006:107:3474, reported no overall survival or progression free survival with autologous transplant followed by mini allograft in high-risk myeloma patients.

i 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. J Clin Oncol 2005;23:9227-9233. Barlogie B, Kyle RA, Anderson KC, et al. J Clin Oncol. 2006;24:929-936.

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

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.

7 Additional Treatment Post-Stem Cell Transplant



[d] See Myeloma Therapy. (p. 15)

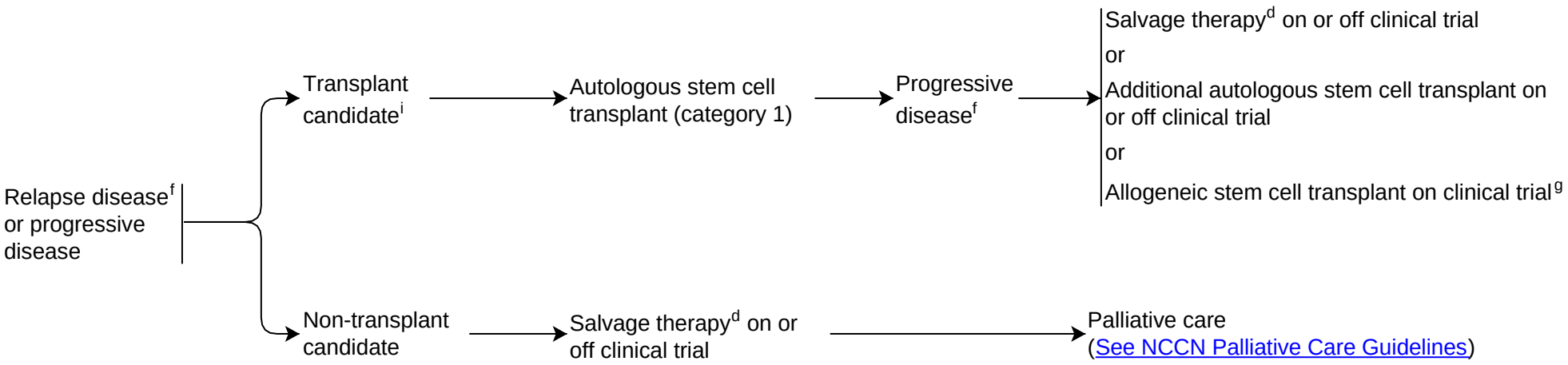
[f] See Response Criteria for Multiple Myeloma. (p. 11)

[g] 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.

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.

8 Relapse Disease or Progressive Disease

Active (Symptomatic) Myeloma



[d] See Myeloma Therapy. (p. 15)

[f] See Response Criteria for Multiple Myeloma. (p. 11)

[g] Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative on a clinical trial (off-trial category 3). Current data do not support miniallografting alone.

[i] 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. J Clin Oncol 2005;23:9227-9233. Barlogie B, Kyle RA, Anderson KC, et al. J Clin Oncol. 2006;24:929-936.

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.

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/24h	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 BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36:842-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1182674. Copyright © (1975) American Cancer Society. Reproduced with permission of John Wiley & Sons, Inc.
2. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412-3420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15809451

1 Definition of Multiple Myeloma (Smoldering and Active)

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

The International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: A report of the International Myeloma Working Group. Br J Haematol 2003;121:749-57.
International Uniform Response
Reprinted by permission from Macmillan Publishers Ltd. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.

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

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.

Response Criteria for Multiple Myeloma

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

Complete response (CR) requires all of the following:

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

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as partial response (PR), providing the remaining criteria satisfy the requirements for PR. This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

Partial response (PR) requires all of the following:

- ≥ 50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 wks.
- Reduction in 24 h urinary light chain excretion either by ≥ 90% or to 200 mg, maintained for a minimum of 6 wks.
- For patients with non-secretory myeloma only, ≥ 50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 wks.
- ≥ 50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response).

Patients in whom some, but not all, the criteria for PR are fulfilled are classified as MR, provided the remaining criteria satisfy the requirements for minimal response (MR).

MR requires all of the following:

- 25-49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 wks.
- 50-89% reduction in 24 h urinary light chain excretion, which still exceeds 200 mg/24 h, maintained for a minimum of 6 wks.
- For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 wks.
- 25-49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in size or number of lytic bone lesions (development of a compression fractures does not exclude response).

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.

Response Criteria for Multiple Myeloma

No change (NC) - Not meeting the criteria of either minimal response or progressive disease.

Plateau - Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 mo.

Time point for assessing response:

- Some responses can occur late post-transplant.
- Response to the transplant procedure will be assessed by comparison with results immediately prior to conditioning.
- If transplant is part of a treatment program response to the whole treatment program will be assessed by comparison with the results at the start of the program.

Relapse from CR requires at least one of the following:

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

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

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

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

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.

International Myeloma Working Group Uniform Response Criteria[1]

Response Category	Response Criteria[a]
sCR, stringent complete response	CR as defined below plus: Normal free light chain (FLC) ratio and absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR, complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
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

[a] 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.
[b] Confirmation with repeat bone marrow biopsy not needed.
[c] 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.

Relapse Subcategory	Relapse Criteria
Progressive disease[a] (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)[b] • Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL. • Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[c] • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).[b] It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice • 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) • Decrease in hemoglobin of ≥ 2 g/dL • Rise in serum creatinine by 2 mg/dL or more
Relapse from CR[a] (To be used only if the end point studied is DFS, disease free survival)[d]	Any one or more of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow[c] • Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, hypercalcemia)

[a] 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.
[b] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
[c] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

1. Reprinted by permission from Macmillan Publishers Ltd. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-1473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16855634.

1 Myeloma Therapy[a,b,c,d]

- 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 transplant.

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

- Primary induction therapy for non-transplant candidates:
  - → Bortezomib/dexamethasone
  - → Dexamethasone (category 2B)
  - → Lenalidomide/low-dose dexamethasone (category 1)
  - → Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)
  - → Melphalan/prednisone (MP)
  - → Melphalan/prednisone/bortezomib (MPB) (category 1)
  - → Melphalan/prednisone/thalidomide (MPT) (category 1)
  - → Melphalan/prednisone/lenalidomide (MPL)
  - → Thalidomide/dexamethasone (category 2B)
  - → Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)

[a] Selected, but not inclusive of all regimens.
[b] Treatments are listed alphabetically and do not imply preference.
[c] Recommend herpes zoster prophylaxis for patients treated with bortezomib.
[d] Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexmethasone.
[e] Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.

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.

1 Myeloma Therapy[a,b,c,d]

- Maintenance therapy:
  - → Interferon (category 2B)
  - → Lenalidomide[f]
  - → Steroids (category 2B)
  - → Thalidomide (category 1) ± prednisone (category 2B)

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

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

[b] Treatments are listed alphabetically and do not imply preference.

[c] Recommend herpes zoster prophylaxis for patients treated with bortezomib.

[d] Prophylactic anticoagulation recommended for patients receiving thalidomide-based therapy or lenalidomide with dexmethasone.

[f] Lenalidomide as maintenance has been evaluated in three independent randomized clinical trials. Results from each of these trials show improvements in TTP. The panel felt that this warranted inclusion; however, this recommendation remains Category 2A since these results have not undergone full peer review and safety/efficacy data are still preliminary.

[g] Bortezomib/liposomal doxorubicin is preferred to bortezomib single agent.

[h] These are representative regimens combining standard agents with novel agents.

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.

1 Adjunctive Treatment

Bone Disease

- Bisphosphonates (pamidronate and zoledronic acid)
  - → All patients with documented bone disease including osteopenia (category 1)
  - → Use of bisphosphonates in smoldering or stage I disease preferrably in the context of a clinical trial. These patients should have bone survey yearly
  - → Monitor for renal dysfunction with use of bisphosphonates
  - → Monitor for osteonecrosis of the jaw
- Radiation Therapy
  - → Low-dose radiation therapy (10–30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture or impending cord compression
  - → Limited involved fields should be used to limit the impact of irradiation on stem-cell harvest or impact on potential future treatments
- Orthopedic consultation should be sought for impending or actual long-bone fractures or bony compression of spinal cord or vertebral column instability
  - → Consider vertebroplasty or kyphoplasty for symptomatic vertebral compression fractures

Hypercalcemia

- Hydration/furosemide, bisphosphonates, steroids and/or calcitonin

Hyperviscosity

- Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity

Anemia (See NCCN Cancer -and Chemotherapy-Induced Anemia)

- 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
- Consider PCP, herpes, and antifungal prophylaxis if high-dose dexamethasone regimen
- Consider herpes zoster prophylaxis for patients treated with bortezomib

Renal Dysfunction

- Maintain hydration to avoid renal failure
- Avoid use of 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

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.

1 Initial Diagnostic Workup

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

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

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

Renal
- 24-hour urinary protein
- Creatinine clearance

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

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

Peripheral nervous system
- EMG (if clinically significant peripheral neuropathy)

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

2 Clinical Findings[1]

- Renal involvement only
- Cardiac involvement
- Multi-organ involvement

3 Primary Treatment

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

Options include:
- Best supportive care
- Bortezomib with or without dexamethasone[a]
- Dexamethasone and alpha-interferon
- Cyclophosphamide/thalidomide/dexamethasone
- Intermediate-dose or high-dose melphalan with stem cell transplant
- Lenalidomide and dexamethasone
- Oral melphalan and dexamethasone
- Thalidomide and dexamethasone

[a] Recommend herpes zoster prophylaxis for patients treated with bortezomib.

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.

Systemic Light Chain Amyloidosis References

[1] Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 2005;79:319-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16044444.

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Discussion

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 20,180 new cancer cases of MM in the United States in 2010, including 11,170 cases in men and 9,010 cases in women, with an estimated 10,650 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.

This guideline developed by the NCCN Multiple Myeloma panel addresses diagnosis, treatment and follow-up for multiple myeloma and systemic light chain amyloidosis.

Multiple Myeloma

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: 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); and beta-2 microglobulin. Increased BUN and creatinine indicate decreased kidney function, while LDH levels help assess tumor cell burden in lymphoma-like or plasmablastic myeloma. The level of beta-2 microglobulin reflects the tumor mass and is now considered a standard measure of the tumor burden. Serum analysis also includes quantitative immunoglobulins levels of different types of antibodies (IgG, IgA, and IgM); serum protein electrophoresis (SPEP); and serum immunofixation electrophoresis (SIFE) to obtain more specific information about the type of abnormal antibodies present. Assessing changes and proportions of various proteins, particularly the monoclonal protein (M protein), helps track 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. However, the FLC assay cannot replace the 24-h urine protein electrophoresis for monitoring myeloma patients with

measurable urinary M proteins. 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]

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).

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, and 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.

Other tests carried out as a part of initial diagnostic workup include skeletal survey, unilateral bone marrow aspirate and biopsy. Chromosomal analysis by conventional karyotyping (cytogenetics) and fluorescence *in situ* hybridization (FISH) may be performed in the plasma cells obtained from bone marrow aspiration. Cytogenetics and FISH may detect chromosomal abnormalities, frequently involving translocations of the immunoglobulin heavy chain genes. Specific chromosomal abnormalities that have been identified include a deletion in chromosome 13 [del(13)] and a translocation between chromosomes 4 and 14 [t(4;14)], both of which are associated with a poor prognosis. A translocation between 11 and 14 [t(11;14)] may be associated with an improved survival.[9, 10] Other chromosomal abnormalities include deletion in chromosome 17 [del(17)]; translocation between 14 and 16 [t(14;16)]; and amplification of 1q21. At the present time, there are inadequate data to determine how this prognostic information should be used to direct patient management. Also, the adverse impact of these cytogenetic abnormalities has been established in the context of conventional therapies and stem cell transplant but not with novel treatments.

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.

The NCCN Multiple Myeloma panel recommends additional tests that may be useful under some circumstances. These include magnetic resonance imaging (MRI) for suspected vertebral compression,[11] computed tomography (CT) or positron emission tomography (PET)/CT scan. Active myeloma is positive on PET scan.[12, 13] 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.[14] 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 multiple myeloma, physicians may use allogeneic (ie, from someone else) transplantation. In this approach, physicians administer non-myeloablative therapy and infuse stem cells (ie, 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.

Finally, since bisphosphonate therapy is a consideration in many patients with multiple myeloma, a baseline bone densitometry test may be recommended.

Diagnostic Categories

Based on the results of the clinical and laboratory evaluation previously discussed, patients are initially classified as either having smoldering

(asymptomatic) disease or active (symptomatic) disease. 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)[15]. 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 multiple myeloma.

Response Criteria

Assessing the response to treatment is a key determinant of myeloma treatment. Two different sets of response criteria, one developed by the European Group for Bone and Marrow Transplant (EBMT) and the other developed by the International Myeloma Working Group, are outlined in the NCCN treatment algorithms. The EBMT criteria categorize response as complete response, partial response, minimal response, relapse and progressive disease. In contrast the International Myeloma Working Group criteria categorize response as stringent complete response, complete response, very good partial response, partial response and stable disease. The International Myeloma Working Group criteria have been recently developed, but not yet validated. To date, the EBMT criteria have been more commonly used.

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.[16] However, the treatment and follow-up options for osseous and extraosseous plasmacytomas are similar.

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.[17, 18] Extraosseous plasmacytomas are treated initially with radiation therapy (45 Gy or more) to the involved field and/or surgery. Follow-up and surveillance for both solitary plasmacytoma and extra-osseous plasmacytoma consist of blood and urine tests done every 4 weeks initially to monitor response to the radiation therapy. If the patient achieves complete disappearance of the paraprotein, then the frequency could be reduced to every 3-6 months and as clinically indicated. If the protein persists, then the monitoring should continue every 4 weeks.

The blood tests include CBC; serum chemistry for creatine, albumin, LDH, calcium, beta-2 microglobulin; serum quantitative immunoglobulins, SPEP, and SIFE. Serum FLC assay may also be considered. The urine tests include 24 hour urine assay for total protein, UPEP, and UIFE.

Bone marrow biopsy should be considered as clinically indicated. Bone survey may be considered annually or as clinically indicated. MRI and/or CT and/or PET/CT may be considered every 6-12 months or as clinically indicated. PET imaging may detect early bone marrow involvement in patients with solitary plasmacytoma.[13, 19]

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

Smoldering (Asymptomatic) Myeloma

Patients with asymptomatic smoldering multiple myeloma have an indolent course for many years without therapy. These patients have 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, they do not have anemia, renal failure, hypercalcemia, or bone lesions. Patients with Durie-Salmon stage I myeloma also have low amounts of

M-protein without significant anemia, hypercalcemia, or bone disease. Patients with smoldering myeloma including Durie-Salmon Stage 1 do not need primary therapy because they can do well for many months to years before the disease progresses. These patients should initially be observed at 3-6 months intervals (category 1 recommendation).

The blood tests include CBC; serum chemistry for creatine, albumin, LDH, calcium, and beta-2 microglobulin; and serum quantitative immunoglobulins, SPEP, and SIFE. Serum FLC assay may also be considered. The urine tests include 24 hour urine assay for total protein, UPEP, and UIFE.

Bone marrow biopsy should be considered as clinically indicated. Bone survey may be considered annually or as clinically indicated. MRI and/or CT and/or PET/CT may be considered 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.[12] It can also assess the extent of active disease, detect extramedullary involvement or evaluate treatment response.[13, 20-22]

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

Active (Symptomatic) Multiple Myeloma

Induction Chemotherapy

Patients presenting with active (symptomatic) myeloma are initially treated with induction chemotherapy and in selected patients followed by high-dose chemotherapy and 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 transplant. 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 comorbidities. However, it should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant. It is also important to consider supportive care for all patients at 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).

Research into various induction regimens has focused on improving the complete response rates in both transplant and non-transplant candidates.

Primary Induction Therapy for Transplant Candidates

The present choices for induction therapy associated with high-response rates include bortezomib-, lenalidomide-, and thalidomide- containing regimens.

Bortezomib-based regimens

Bortezomib is a first-in-its-class proteasome inhibitor that not only directly targets the myeloma cell, but also targets the interaction between the tumor cell, and the bone marrow microenvironment. For example, apoptotic signaling of the myeloma cells can be triggered in a variety of ways. Bortezomib targets both intrinsic and extrinsic 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 (IFM 2005/01), 482 patients were randomized to either bortezomib and dexamethasone regimen or VAD (vincristine, doxorubicin, and dexamethasone) regimen as induction therapy prior to stem cell transplant.[23] The bortezomib and dexamethasone arm demonstrated a better complete response (CR) rate compared to VAD.[23] Updated results presented at the 2009 Annual Meeting of American Society of Hematology (ASH) confirmed significantly superior post-induction CR/near CR rates in the bortezomib plus dexamethasone arm versus the VAD arm (15% vs. 7%).[24] The rate of achieving very good partial response (VGPR) or better was also higher (39% vs. 16%).[24] Higher response rates post-induction translated to higher rates of progression-free survival (PFS) in bortezomib and dexamethasone arm following high-dose therapy and stem cell transplant. Updated data showed a trend towards prolonged PFS.[24] At a median follow-up of 32.2 months, median PFS was 36 months with bortezomib and dexamethasone versus 29.7 months for VAD.[24] Interestingly, within the bortezomib and dexamethasone group the results showed no significant difference in PFS between patients with ISS Stage III (β2M >5.5) versus Stage I/II (median 29.8 vs. 36.5 months, *P* = 0.1191), and between patients with versus those without adverse cytogenetics (median PFS of 33.5 vs. 36.5 months, *P*=0.1655).[24]

Another trial analyzed a large series of patients (younger 65 years) with newly diagnosed MM who were treated with induction therapy of bortezomib and dexamethasone versus VAD before treatment with high-dose melphalan.[25] The results demonstrate 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 induction therapy. Also, bortezomib and dexamethasone induction significantly improved the outcome of patients including those with t(4;14) compared with VAD.[25]

Based on the above data and the uniform consensus among the NCCN myeloma panel members, bortezomib plus dexamethasone is a category 1 option as induction therapy for transplant candidates.

The interim 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 (n = 300) demonstrated high response rates with the bortezomib, doxorubicin, and dexamethasone (PAD) versus VAD.[26] Post induction response rates with PAD were superior (79% vs. 57%, including CR /near CR of 7% vs. 2% and VGPR or better of 45% vs. 17%). This superior response rate was maintained even after transplant with significantly higher overall response rates (91% vs. 79%, and CR/near CR rates of 26% vs. 14%, and VGPR rates of 71% vs. 44%.)[26] No unexpected toxicities occurred, and deletion of chromosome 13q did not have a significant impact on response. Responses improved with bortezomib maintenance. Based on HOVON-65/ GMMG-HD4 trial interim data and the uniform consensus among the NCCN myeloma panel members, bortezomib, doxorubicin, and dexamethasone is a category 1 option for induction therapy for transplant candidates.

The GIMEMA Italian Multiple Myeloma Network reported updated results for a phase III trial investigating bortezomib, thalidomide, and dexamethasone versus thalidomide and dexamethasone induction therapy, followed by tandem autologous SCT with high-dose therapy (melphalan 200 mg/m^2), and consolidation therapy with the same induction regimen in 480 myeloma patients.[27] The addition of bortezomib to thalidomide and dexamethasone significantly improved overall response rates both following induction. The first analysis showed superior CR (19% vs. 5%), CR/near CR (26% vs. 9%), and ≥ VGPR (61%

vs. 28%) with bortezomib, thalidomide, and dexamethasone induction. This superiority was retained post-transplant, with higher CR (40% vs. 31%), CR/nCR (52% vs. 41%), and ≥ VGPR (79% vs. 64%) rates, and also post-consolidation.[28] Two-year PFS rates were significantly improved in the bortezomib, thalidomide, and dexamethasone arm (PFS 82% vs. 73%) and 30- month PFS rates were 76% vs. 58%.[28] The superior response with bortezomib, thalidomide, and dexamethasone induction was seen across poor prognostic sub-groups. Patients receiving this induction experienced grade 3/4 peripheral neuropathy; however, response rates remained high for those continuing treatment. A single institution's retrospective data has reported results similar to the interim data from the GIMEMA trial.[29] The findings of the retrospective analysis demonstrate that with bortezomib, thalidomide, and dexamethasone induction therapy overall response rate seen was 94% of the patients (32 patients out of 34 showed some response, including 56% VGPR or greater).[29] Based on GIMEMA trial data and the uniform consensus among the NCCN myeloma panel members, the addition of bortezomib to thalidomide and dexamethasone is a category 1 option for induction therapy for transplant candidates.

Data from three phase II studies involving 495 patients has demonstrated high response rates with bortezomib, cyclophosphamide, and dexamethasone.[30-32] The trial by Reeder et al carried out in the U.S. and Canada demonstrated ORR of 88% including a VGPR or greater of 61% and 39% CR/near CR with bortezomib, cyclophosphamide, and dexamethasone induction regimen. In patients who underwent transplantation, the depth of response was maintained post-transplant as well (70% CR/near CR; greater than or equal to VGPR 74%)[30] Analysis of the German DSMM XIa study also demonstrated high responses with bortezomib, cyclophosphamide, and dexamethasone induction regimen (ORR 84%; with 74% partial response (PR) and 10% CR). High response rates were also seen in patients with unfavorable cytogenetics.[31] In the EVOLUTION study, bortezomib, cyclophosphamide, and dexamethasone induction regimen demonstrated ORR of 87% (6% stringent CR; 35% near CR; and 45% PR).[32] Based on data from these three phase II studies, the NCCN panel has now included the combination of bortezomib, cyclophosphamide, and dexamethasone as a category 2A recommendation to the list of options of induction regimens available for transplant candidates.

Phase I/II study results have shown that lenalidomide, bortezomib and dexamethasone is very active and well tolerated in newly diagnosed MM patients.[33-35] This regimen is included as an induction therapy option for transplant candidates. It is a currently a category 2B recommendation as induction therapy for transplant candidates.

Bortezomib treatment has been associated with an incidence of herpes zoster.[36] The incidence of bortezomib-associated herpes zoster may be reduced with the use of prophylactic acyclovir.[37] The risk of deep vein thrombosis (DVT) is low with bortezomib; however, peripheral neuropathy and gastrointestinal disturbance can be higher. These adverse events are predictable and managed with patient monitoring and appropriate supportive care.[38] Bortezomib-based regimens may be of value in patients with renal failure and in those with adverse cytogenetic features.

Lenalidomide-based regimen

Lenalidomide, a potent analogue of thalidomide, received FDA approval for the treatment of relapsed/refractory MM in combination with dexamethasone (discussed further below under Salvage Therapy). However, lenalidomide and dexamethasone have been investigated as induction 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.[39] 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).[40, 41] At the time the SWOG trial was halted, lenalidomide plus dexamethasone arm showed improved CR rate compared to dexamethasone alone (22% vs. 4%).[39]

In a recent open-label trial, 445 patients newly diagnosed myeloma 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.[42] However, the high response rates did not result in superior time to progression, PFS, or overall survival (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 overall survival 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 = 0·0002); 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 induction with either dose followed by autologous stem cell transplantation was 92%, suggesting that lenalidomide plus dexamethasone is reasonable for induction therapy prior to stem cell transplant. Lenalidomide in combination with dexamethasone as induction regimen is a category 1 recommendation in the NCCN guidelines.

A retrospective analysis of 411 newly diagnosed patients treated with either lenalidomide plus dexamethasone (228) or thalidomide plus dexamethasone (183) was performed at the Mayo Clinic.[43] 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 partial response to lenalidomide and dexamethasone was 80.3% versus 61.2% with thalidomide and dexamethasone; very good partial response rates were 34.2% and 12.0%, respectively. Patients receiving lenalidomide and dexamethasone had longer time to progression (median, 27.4 vs. 17.2 months; P = 0.019), longer PFS (median, 26.7 vs. 17.1 months; P = 0.036), and better OS (median not reached vs. 57.2 months; P =0.018). 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 and dexamethasone were hematologic, mainly neutropenia (14.6% vs. 0.6%, P < 0.001); the most common toxicities in thalidomide and dexamethasone were venous thromboembolism (15.3% vs. 9.2%, P = 0.058) and peripheral neuropathy (10.4% vs. 0.9%, P < 0.001). Based on the results of this meta-analyses lenalidomide and dexamethasone appears well tolerated and more effective than thalidomide and dexamethasone. However, randomized prospective trials are needed to confirm these results.

A decrease in CD34-positive cells collected after prolonged lenalidomide treatment has been reported[44, 45] Guidelines by the International Myeloma Working Group (IMWG) suggest that patients on lenalidomide in combination with dexamethasone should have stem cells collected within the first 4 cycles of therapy.[46] The NCCN panel recommends harvesting peripheral blood early in the courses of induction with lenalidomide.

The incidence of deep vein thrombosis is low with single agent lenalidomide or lenalidomide plus low-dose dexamethasone, but rises when combined with high-dose dexamethasone. 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.[47] Prophylactic anticoagulation is also recommended when lenalidomide and dexamethasone is given.[38, 48]

Thalidomide-based regimen

Thalidomide attacks multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis and cytokine circuits, among others. Rajkumar et al reported the results of a study involving 207 patients with newly diagnosed multiple myeloma randomized to receive thalidomide and dexamethasone or dexamethasone alone.[49] 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.[48] Other side effects of thalidomide included rash, gastrointestinal disturbance, peripheral neuropathy, or somnolence.[38] The use of thalidomide requires individual patient consideration and the higher response rate of the thalidomide and dexamethasone combination must be weighed against the increased side effects.

Other regimens

Dexamethasone alone (category 2B recommendation) may be a reasonable option, as short-term induction therapy, for a highly selected group of patients, (eg, in those with renal failure, hypercalcemia, cord compromise requiring radiation therapy, cytopenia). Data from recent studies suggest that VAD no longer be recommended as most patients respond to induction regimen based on novel drug combinations. The other category 2B recommendation is liposomal doxorubicin, vincristine and dexamethasone (DVD) regimen.[50]

Primary Induction Therapy for Non-Transplant Candidates

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

Melphalan and prednisone (MP) has been a standard treatment of multiple myeloma 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.[51] 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.[52] Subsequently, a number of phase III trials have reported significant higher overall response rate with MPT versus MP (57%-76% vs. 31%-48%), including a higher CR or VGPR rate (7%-15.5%). The impact of MPT on survival is not clear as only the IFM studies[53, 54] have reported a survival advantage in patients on MPT. The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) carried out a phase III study to compare the standard MP versus MPT in 333 newly diagnosed elderly patients with MM.[55] 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 EFS was 13 months with MPT versus 9 months with MP and OS was 40 months with MPT versus 31 months with MP.[55] 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 overall response rates consistently seen in all these studies, MPT is a category 1 recommendation for patients not eligible for transplant. There is a significant risk of DVT with thalidomide;

therefore, use of prophylaxis in patients on MPT therapy is highly recommended.

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.[56] 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.[57] 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 were 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.[57]

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.[57] 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.[57] 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.

Advantages of MPB over MPT include more rapid response and higher rates of CR, which is associated with improved survival in the non-transplant setting.[58] 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.[59] 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 overall response rates 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.

Both MPT and MPB regimens have reported superior responses compared to MP; therefore, according to the NCCN myeloma panel, MP is a category 2A recommendation. Based on the results of the SWOG SO232 trial,[39] which included non-transplant candidates and the results of ECOG E4A03 trial[40] 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.[42] 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 OSl of 91% with lenalidomide and low-dose dexamethasone.[42] Therefore, lenalidomide in combination with low-dose dexamethasone considered a category 1 option by the NCCN panel for non-transplant candidates. The panel recommends appropriate

thromboprophylaxis for patients receiving this therapy.

Melphalan and prednisone in combination with lenalidomide (MPL) was studied in 54 patients with newly diagnosed MM.[60] 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 partial response, 47.6% achieved a very good partial response, and 24% achieved a complete immunofixation-negative response. One 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 hematologic toxicities are manageable, median PFS was 28.5 months, and 2-year OS was 91%.[61] 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. [62] The most common grade 3/4 toxicities were neutropenia (58% of patients) and thrombocytopenia (27%).[62]

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.[63] At a preplanned interim analysis the data monitoring committee detected a highly statistically significant improvement in PFS, the primary endpoint, for patients treated with MPL followed by lenalidomide maintenance compared with those who received MP.[63] The MPL regimen is now included as an option for patients ineligible for transplant in the updated NCCN Myeloma guidelines. It is a category 2A recommendation.

Among the bortezomib-based regimens, MPB has been investigated specifically in elderly patients in the phase III VISTA trial. 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. Bortezomib in combination with thalidomide and dexamethasone; bortezomib with dexamethasone; and MPB are being compared with each other in previously untreated elderly patients with MM ineligible SCT. The interim results demonstrate that all three regimens are active with good response rates with predictable and similar rates of toxicities reported for all arms.[64] The NCCN panel has now included bortezomib in combination with dexamethasone as an option for patients ineligible for transplant (category 2A). The older regimens like dexamethasone alone, thalidomide with dexamethasone, VAD, and DVD regimens are category 2B options.

Follow-Up after Induction Therapy

Following initial induction chemotherapy, patients are re-evaluated with the laboratory tests, bone survey and bone marrow 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 induction therapy to reach a treatment plateau. Treatment should be continued for, at most, two cycles beyond maximal response; continued treatment does not prolong the duration of the plateau phase.

Stem Cell Transplants

Introduction

High-dose chemotherapy and stem cell transplants (SCT) can be classified as a single autologous SCT, a tandem SCT, 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.[65, 66] An allogeneic SCT may also follow an autologous SCT. The NCCN 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, and TBI regimens have now been abandoned.[67]

Autologous Stem Cell Transplants

Autologous SCT results in high response rates and remains the standard of care following induction 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.[68] 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 overall survival (54 months in the high-dose group compared to 42 months for standard therapy).[69] 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.[70] 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.[68]

Another trial included 190 patients aged 55 to 65 randomized to standard or high-dose therapy.[71] 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 ($P = 0.7$). 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[27] also showed that a transplant performed at the time of relapse (as salvage therapy) has a similar OS compared to an early transplant.

It should be noted that all randomized studies of autologous SCT following induction 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 induction therapy with either bortezomib/dexamethasone versus VAD showed a marked improvement in overall response rate with bortezomib/dexamethasone over VAD (discussed in sections above).[23] After the first autologous SCT, CR/near CR rates were 40% in the bortezomib plus dexamethasone arm, compared with 22% in the VAD arm ($P = 0.0001$).[23] In the bortezomib plus dexamethasone arm 34% required a second SCT, compared with 47% of patients in the VAD arm.[23] With a median follow-up of 32.2 months, PFS after induction with bortezomib and dexamethasone versus VAD group was 36.0 and 29.7 months, respectively.[23] Responses were

evaluated post-induction 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 induction than in patients achieving a less than VGPR (median 41.1 vs. 29.0 months).[24]

In another study, bortezomib/dexamethasone with thalidomide was compared with thalidomide/dexamethasone for induction therapy prior to SCT in 450 patients.[27] The three drug yielded high response rates compared with the two drug regimen, with CR/near CR of 32% (vs. 12%) and VGPR of 62% (vs. 29%). After SCT, improved responses were still seen with bortezomib, dexamethasone, and thalidomide compared with thalidomide plus dexamethasone (CR/near CR 55% vs. 29%; VGPR, 76% vs. 53%). Taken together these studies suggest that improved responses with the new induction regimen result in improved outcomes after transplantation.[72] Studies have found that progressive disease emerging after initial induction chemotherapy does not preclude a good response to autologous SCT.[70, 73, 74] For example, Kumar and colleagues reported on a case series of 50 patients with primary progressive multiple myeloma receiving an autologous SCT.[74] 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 induction 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.[75] 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 stem cell transplant. 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.[76] 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.[71, 77-79] 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 Cavo trial[77] 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.[80] Also, post relapse survival was longer when event-free survival was sustained for at least 3.5 years after tandem transplantation.[80]

The NCCN 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 algorithms also identify two situations where a repeat salvage autologous SCT is recommended: 1) In patients initially treated with induction therapy alone, followed by an autologous SCT when the disease relapsed, who now have progressive disease following a first autologous SCT (category 2A); and 2) In patients with initial CR or near CR to an initial single autologous SCT who develop progressive disease. There are less data on this population of patients compared to autologous SCT for responsive or primary progressive disease, in part due to the age of the patients and extensive prior treatment. However, a systemic review sponsored by the American Society for Blood and Marrow Transplant (ASBMT) regarding this population reported that some of these patients can achieve durable complete or partial remission.[73] For this reason it is a category 2B recommendation and participation in a clinical trial is encouraged.

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, the lack of a suitable donor and the increased morbidity have 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 multiple myeloma. 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.[81] Other reviews have also reported increased morbidity without convincing proof of improved survival.[82,73] There are, however, intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.[70] 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 overall survival 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 SCT an accepted option in the setting of a clinical trial (category 2A) in patients with responsive or primary progressive disease, or as salvage therapy in patients with progressive disease following an initial autologous-SCT.

Another strategy that has been investigated is an initial autologous-SCT followed by a mini-allogeneic transplant. A prospective trial by Bruno et al[83] showed that, among patients (under 65 years) with a 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 contrast, in a comparison of tandem autologous-SCT versus those treated with an initial autologous-SCT followed by a mini-allogeneic transplant in high-risk patients in the IFM99-03 and IFM 99-04 studies[84] the OS and the event free survival were not significantly different for the two groups.

Mini- allogeneic transplants have also been investigated as salvage therapy. 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.[85] There was a 78% OS at a median 552 days after the mini-allogeneic transplant, with a 57% complete response rate and an overall response rate 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.[86] In this heterogeneous population of 229 patients, the 3-year overall and progression free survivals were 41% and 21%, respectively. Adverse overall survival was associated with chemoresistant disease, more than 1 prior transplant, and improved overall survival was associated with graft versus host disease, confirming the importance of a graft versus leukemia effect. This study concluded that mini-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.[87]

Maintenance Therapy Following Transplant

A variety of maintenance therapies, such as dexamethasone and interferon, have been investigated in patients whose disease responds to high-dose therapy with autologous or allogeneic SCT.[88] At the present time, the role of interferon[89] or steroid maintenance therapy[90] in general is uncertain, and for this reason these are category 2B recommendations as maintenance therapy.

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.[91] The median survival in the thalidomide group was 65.5 months compared to 44.5 months in the no treatment group (P = 0.9). Attal et al randomized 597 patients to one of three different strategies following tandem autologous stem cell transplantation, either no maintenance, pamidronate alone, or pamidronate combined with thalidomide.[92] There was a highly significant event free and overall survival 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. The results confirm that thalidomide added to maintenance is superior to prednisone alone.[93] In another randomized trial, thalidomide maintenance induced improvement in PFS in patients achieving less than a VGPR with no survival benefit.[94] Thalidomide has also been used before, during, and after tandem autologous SCT.[70, 95] 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 induction therapy, continued between the tandem autologous-SCTs, and was incorporated into consolidation therapy and continued as maintenance therapy.[95] The “no thalidomide” group received the same core therapy. After a median follow-up of 42 months, the thalidomide group 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 panel thalidomide alone is a category 1 recommendation and thalidomide with prednisone is a category 2A recommendation as maintenance therapy.

Lenalidomide as maintenance is being evaluated in three independent randomized phase III studies. The CALGB 100104 trial compared lenalidomide versus placebo as maintenance therapy after prior autologous stem cell transplant.[96] The preliminary results show that patients receiving lenalidomide maintenance following a autologous stem cell transplant had a 58% reduction in risk of their disease progressing.[97] These encouraging results have led to un-blinding of this trial.

Preliminary data from the international, randomized, double-blind phase III Intergroupe Francophone du Myelome (IFM) 2005-02 trial[98] show that following autologous stem cell transplant, patients treated with lenalidomide as consolidation therapy followed by lenalidomide as maintenance therapy had upgraded responses. The benefit of lenalidomide maintenance therapy was observed both among patients achieving or not a complete response after autologous SCT. Data from a pre-planned interim analysis show improved progression-free survival in patients receiving lenalidomide consolidation and maintenance compared to those who received placebo. [99]

Data from the Phase III MM-015 study shows that lenalidomide reduced the risk of disease progression by 47%. Analysis of PFS after cycle 9 of induction therapy shows that patients receiving lenalidomide as maintenance therapy had a 75% reduction in disease progression compared with those on placebo following induction.[63]

Based on the above evidence the NCCN Myeloma Panel recommends single agent lenalidomide as maintenance therapy. 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.

Bortezomib as maintenance therapy is currently under investigation[100, 101] and according to the NCCN Multiple Myeloma panel the currently available data are premature to recommend bortezomib in this setting.

Salvage Therapy

Conventional dose 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 stem cell transplant with progressive or relapsing disease after initial induction 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 induction therapy, patients may be retreated with the same induction regimen. Bortezomib is considered a category 1 recommendation for salvage therapy based on the results of a phase III trial (APEX trial) comparing bortezomib and high-dose dexamethasone as salvage therapy.[102] 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%). When combined with dexamethasone, bortezomib is considered a category 2A recommendation. In an updated efficacy analysis,[103] the response rate was 43% with bortezomib versus 18% for dexamethasone ($P < 0.0001$). 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. One-year survival rates were 80% and 67%, respectively ($P = 0.00002$). Patients with poor prognostic factors also benefited from bortezomib. Deletion of chromosome 13 did make a difference in patients treated with dexamethasone, as it was associated with worse survival, but it had no impact in bortezomib-treated patients.[104]

Regimen for combining bortezomib with pegylated liposomal doxorubicin (PLD) injection is a treatment option for multiple myeloma in patients who have not previously received bortezomib and have received at least 1 prior therapy. The FDA approval of this regimen was based on a priority review of data from an international phase III trial (n = 646), showing that use of the drug combination significantly extended the median time to disease progression compared with bortezomib alone (9.3 vs. 6.5 months).[105] Median duration of response was increased from 7.0 months to 10.2 months with the combination therapy. The most commonly reported grade 3 or 4 adverse reactions associated with use of doxorubicin liposome and bortezomib were neutropenia (32%), thrombocytopenia (24%), anemia (9%), fatigue (7%), asthenia (6%), diarrhea (7%), peripheral neuropathy (7%), and hand-foot syndrome (6%). Other commonly reported events (any grade) were pyrexia (31%), nausea (48%), vomiting (32%), constipation (31%), stomatitis (20%), and rash (22%). Based on these results, the NCCN Multiple Myeloma panel members consider this regimen as a category 1 recommendation for relapsed/refractory myeloma and consider it superior to bortezomib monotherapy.

Lenalidomide combined with dexamethasone has received FDA approval based on the results of two studies of 692 patients with multiple myeloma who had received at least one prior treatment and were 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. The updated clinical data from the pivotal North American Phase III trial (MM-009) in 353 previously treated multiple myeloma patients reported increased overall survival, as well as median time to disease progression in patients receiving lenalidomide plus dexamethasone compared to patients receiving dexamethasone plus placebo. Similar results were also shown in the trial from the international study MM-010. Patients in both these trials had been heavily treated prior to enrollment, many having failed three or more rounds of therapy with

other agents. In addition, more than 50 percent of patients in the study had undergone stem cell transplantation.[106, 107] Most adverse events and Grade 3/4 adverse events were more frequent in multiple myeloma 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 panel now considers this regimen as a category 1 recommendation.

Lenalidomide monotherapy has also been investigated[108] and is also a category 2A recommendation.

Thalidomide has also been investigated as a salvage therapy either as monotherapy[109, 110] or in combination with a variety of agents, including dexamethasone or in combination with dexamethasone, cisplatin, doxorubicin cyclophosphamide and etoposide (DT-PACE).[111] Thalidomide has been shown to induce responses in 30% of patients with progressive myeloma.[112] In another study of 65 patients with relapsed or progressive disease, 34% had minor (14%), partial (14%) or complete (6%) response; response was noted by 3 to 5 weeks of treatment.[113] Other salvage regimens, all considered category 2A, include, cyclophosphamide-VAD (C-VAD); high-dose (non-marrow ablative) cyclophosphamide, dexamethasone;- and DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin)

The addition of an alkylating agent (such as cyclophosphamide) to dexamethasone and a novel agent (such as lenalidomide or bortezomib) are being investigated. A retrospective analysis to assess the efficacy of lenalidomide in combination with cyclophoshamide and dexamethasone showed that this regimen is effective in heavily pre-treated patients with manageable side-effects.[114] A phase I/II study of cyclophosphamide and prednisone in combination with bortezomib in 37 relapsed/refractory MM patients demonstrated overall response rate of 95% with CR seen in over 50% of the patients.[115] The NCCN myeloma panel has added cyclophosphamide and dexamethasone in combination with either lenalidomide or bortezomib for relapsed/refractory myeloma.

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.[116] The overall response rate was 55% with a median progression-free survival of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90-100 mg/m^2). Toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients has suggests that bendamustine is effective and tolerable in patients with advanced progressive myeloma. The overall response rate seen in the analyses was 36%.[117] Bendamustine for treatment of relapsed/refractory myeloma is currently a NCCN category 2B recommendation.

Data from preclinical studies showed lenalidomide sensitizes myeloma cells to bortezomib and dexamethasone. The results of phase 1 and phase II studies show that this regimen is well tolerated and very active with durable responses seen in patients with heavily pretreated relapsed and/or refractory myeloma, including patients who have had prior lenalidomide, bortezomib, thalidomide and stem cell transplantation.[118, 119] Pending larger study data and peer reviewed publications, bortezomib in combination with lenalidomide/dexamethasone is a category 2B recommendation.

The NCCN myeloma panel members highly encourage enrolling patients in clinical trials.

Adjunctive Treatment

Important advances have been made in adjunctive treatment of patients with multiple myeloma. Additions include a recommendation for HSV prophylaxis in patients receiving bortezomib. In addition, anticoagulant

prophylaxis is recommended for patients receiving thalidomide or lenalidomide in combination with dexamethasone.[48, 120, 121]

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 multiple myeloma. 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.[122, 123] Zoledronic acid is more potent, can be administered more rapidly, and has equivalent benefits.[124] Based on published data and clinical experience, the guidelines recommend the use of bisphosphonates for all patients with multiple myeloma who have bone disease, including osteopenia (category 1).[125, 126] Results from the study conducted by Zervas et al[127] show a 9.5 fold greater risk for the development of osteonecrosis of the jaw with zoledronic acid compared to pamidronate. In light of these data, pamidronate may be preferred over zoledronic acid, until further published data on these adverse effects become available. In 10% to 20% of patients with earlier-stage disease who do not have bone disease, bisphosphonates may be considered but preferably in a clinical trial. An annual skeletal survey is recommended for follow-up of bone disease. Bone densitometry or other metabolic studies should be reserved for clinical trials. Patients who are chronic users of bisphosphonates should have their renal function monitored. They should be monitored for osteonecrosis of the jaw.

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

Other Complications

Hypercalcemia should be treated with hydration and furosemide, bisphosphonates, steroids, and/or calcitonin. Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity. [128]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[129, 130] (see NCCN Cancer- and Chemotherapy-Induced 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 should also be considered, if a high-dose dexamethasone regimen is used. Bortezomib treatment has been associated with an incidence of herpes zoster.[102, 131] Herpes prophylaxis should also be considered in patients receiving bortezomib[36] (see NCCN Prevention and Treatment of Cancer-Related Infections Guidelines). Hydration should be maintained and nonsteroidal anti-inflammatory agents (NSAIDs) should be avoided to decrease the chances of renal dysfunction; however, renal dysfunction is not a contraindication for transplant. The use of intravenous contrast media and NSAIDs should also be avoided in patients with renal impairment. Prophylactic anticoagulation should also be considered if a thalidomide-based, or lenalidomide/dexamethasone therapy is used.[48]

Systemic Light Chain Amyloidosis

Systemic light chain amyloidosis is characterized by decreased numbers of monoclonal plasma cells in the bone marrow; however, the protein produced by these plasma cells has an affinity for visceral organs (such as kidney, heart, liver, and spleen), and this protein causes related end-organ dysfunction.[132]

Workup

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

A majority of the patients present with one or more organ damage. Cardiac involvement is diagnosed by echocardiography (EKG), echocardiogram, chest x-ray, and high serum concentration of natriuretic peptide type-B (BNP) and troponin. Liver and gastrointestinal (GI) involvement is diagnosed by elevated serum alkaline phosphatase; performing stool guaiac tests to detect fecal occult blood; gastric emptying scan if gastroparesis is present; ultrasound or CT scan to determine craniocaudal liver span. An electromyogram (EMG) is a test is performed if the patient has significant peripheral neuropathy to confirm peripheral nervous system involvement. Endocrine tests and pulmonary tests may be performed if involvement of endocrine system or lungs is suspected.

Treatment

Treatment of systemic light chain amyloidosis should be in a clinical trial because data are insufficient to identify optimal treatment of the underlying plasma cell disorder. Most of the treatment strategies used in systemic light chain amyloidosis are derived from multiple myeloma regimens. Intermediate or high-dose melphalan followed by stem cell transplantation is one of the therapeutic options listed by the NCCN panel. However, this option may not be applicable to all. Patients have to be carefully selected as it is associated with significant treatment-related mortality.[133-135] The extent of organ involvement is considered as predictor of outcome.[136] In eligible patients, high-dose chemotherapy with peripheral blood stem cell transplantation has been associated with higher response rates higher OS than standard chemotherapy.[136] Complete response is defined as no evidence of an underlying plasma cell dyscrasia 1 year after treatment. The best outcomes following stem cell transplant have been reported in patients who achieve complete response to high-dose induction chemotherapy [137] including improvement of organ-related disease [138] The melphalan may be dosed according to risk and toxicity. The reported toxicity of reduced-dose of melphalan is substantially less than high dose.[139]

Melphalan and dexamethasone has also been used in the management of systemic light chain amyloidosis. Promising results have been shown in patients with primary amyloidosis who are ineligible for stem cell transplantation treated with combination of melphalan and high-dose dexamethasone. A hematologic response has been obtained in 67% patients and 33% of patients achieved complete remission.[140]

Improvement in organ function was seen in 48% of patients. The updated results reported that survival at 6 years was about 50% and progression free survival was 40%.[141]

Other treatment options include dexamethasone and alpha-interferon. In a multicenter, cooperative group trial (n = 93), complete hematologic response was seen in 24% and improvement of organ dysfunction in 45% of the evaluable patients; overall median survival was 31 months; and 2-year survival rate was 60%.[142]

Thalidomide in combination with dexamethasone was studied in a small group of patients.[143] Only 11 patients out of the 31 enrolled tolerated 400 mg/day of thalidomide for a median of 5.7 months; 20 patients experienced toxicity of grade 3 or more. Therefore, although this combination is active, the associated toxicity is substantial.

Phase II studies have shown lenalidomide in combination with dexamethasone is also active in the treatment of patients with systemic light chain amyloidosis, including those with relapsed/refractory disease.[144-146] The incidence of dermatologic adverse effects with combination was found to be higher in patients with amyloidosis compared to those with myeloma.[147] In addition, progressive azotemia has also been reported in patients with amyloidosis, warranting careful monitoring of patients on this regimen.[148]

Clinical studies have shown that bortezomib with or without dexamethasone is active in both untreated and relapsed amyloidosis.[149-153]

Wechalekar et al used oral regimen of cyclophosphamide, thalidomide, and dexamethasone (CTD) or a risk attenuated regimen CTDa in phase II study involving 75 patients with advanced AL amyloidosis, including 44 patients with clonal relapse after prior therapy. [154] Fifty-one (68%) patients received CTD and 24 (32%) received CTDa. The study reported overall hematologic response in 48 (74%) of 65 evaluable patients, including complete responses in 14 (21%) and partial responses in 34 (53%) cases. Median estimated OS from commencement of treatment was 41 months. Three-year estimated OS was 100% and 82% among patients with complete and partial hematologic response respectively. Treatment was discontinued in 8% of the patients due to toxicities. Grade 2 toxicities were seen in 52% of patients. Treatment related mortality was 4%.

Based on the evidence discussed above, the current NCCN guidelines list the following as therapeutic considerations for management of patients with systemic light chain amyloidosis (all category 2A recommendation): intermediate or high-dose melphalan followed by stem cell transplantation; oral melphalan and dexamethasone; dexamethasone in combination with alpha-interferon; thalidomide- , lenalidomide-, or bortezomib in combination with dexamethasone; single agent bortezomib; and CTD regimen.

The treatment options are listed alphabetically in the NCCN guidelines and do not indicate or imply preference. As the optimal therapy for systemic light chain amyloidosis still remains unknown, the NCCN panel members strongly encourage treatment in the context of clinical trial when possible.

References

1. Jemal A, Siegel R, Xu J and Ward E. Cancer Statistics, 2010. CA Cancer J Clin 2010. Available at http://www.ncbi.nlm.nih.gov/pubmed/20610543

2. Brenner H, Gondos A and Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 2008;111:2521-2526. Available at http://www.ncbi.nlm.nih.gov/pubmed/17901246

3. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516-2520. Available at http://www.ncbi.nlm.nih.gov/pubmed/17975015

4. Hideshima T and Anderson KC. Molecular mechanisms of novel therapeutic approaches for multiple myeloma. Nat Rev Cancer 2002;2:927-937. Available at http://www.ncbi.nlm.nih.gov/pubmed/12459731

5. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 2009;23:215-224. Available at http://www.ncbi.nlm.nih.gov/pubmed/19020545

6. Kuhnemund A, Liebisch P, Bauchmuller K, et al. 'Light-chain escape-multiple myeloma'-an escape phenomenon from plateau phase: report of the largest patient series using LC-monitoring. J Cancer Res Clin Oncol 2009;135:477-484. Available at http://www.ncbi.nlm.nih.gov/pubmed/18802723

7. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-1473. Available at http://www.ncbi.nlm.nih.gov/pubmed/16855634

8. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33. Available at http://www.ncbi.nlm.nih.gov/pubmed/12528874

9. Dewald GW, Therneau T, Larson D, et al. Relationship of patient survival and chromosome anomalies detected in metaphase and/or interphase cells at diagnosis of myeloma. Blood 2005;106:3553-3558. Available at http://www.ncbi.nlm.nih.gov/pubmed/16030187

10. Fonseca R, Barlogie B, Bataille R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. Cancer Res 2004;64:1546-1558. Available at http://www.ncbi.nlm.nih.gov/pubmed/14989251

11. Moulopoulos LA, Dimopoulos MA, Weber D, et al. Magnetic resonance imaging in the staging of solitary plasmacytoma of bone. J Clin Oncol 1993;11:1311-1315. Available at http://www.ncbi.nlm.nih.gov/pubmed/8315427

12. Durie BGM, Waxman AD, D'Agnolo A and Williams CM. Whole-body (18)F-FDG PET identifies high-risk myeloma. J Nucl Med 2002;43:1457-1463. Available at http://www.ncbi.nlm.nih.gov/pubmed/12411548

13. Schirrmeister H, Bommer M, Buck AK, et al. Initial results in the assessment of multiple myeloma using 18F-FDG PET. Eur J Nucl Med Mol Imaging 2002;29:361-366. Available at http://www.ncbi.nlm.nih.gov/pubmed/12002711

14. Greipp PR, Lust JA, O'Fallon WM, et al. Plasma cell labeling index and beta 2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. Blood 1993;81:3382-3387. Available at http://www.ncbi.nlm.nih.gov/pubmed/8507875

15. Greipp PR, San Miguel J, Durie BGM, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412-3420. Available at http://www.ncbi.nlm.nih.gov/pubmed/15809451

16. Knowling MA, Harwood AR and Bergsagel DE. Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. J Clin Oncol 1983;1:255-262. Available at

http://www.ncbi.nlm.nih.gov/pubmed/6668499

17. Dimopoulos MA, Goldstein J, Fuller L, et al. Curability of solitary bone plasmacytoma. J Clin Oncol 1992;10:587-590. Available at http://www.ncbi.nlm.nih.gov/pubmed/1548521

18. Hu K and Yahalom J. Radiotherapy in the management of plasma cell tumors. Oncology (Williston Park) 2000;14:101-108. Available at http://www.ncbi.nlm.nih.gov/pubmed/10680152

19. Kato T, Tsukamoto E, Nishioka T, et al. Early detection of bone marrow involvement in extramedullary plasmacytoma by whole-body F-18 FDG positron emission tomography. Clin Nucl Med 2000;25:870-873. Available at http://www.ncbi.nlm.nih.gov/pubmed/11079582

20. Bredella MA, Steinbach L, Caputo G, et al. Value of FDG PET in the assessment of patients with multiple myeloma. AJR Am J Roentgenol 2005;184:1199-1204. Available at http://www.ncbi.nlm.nih.gov/pubmed/15788594

21. Jadvar H and Conti PS. Diagnostic utility of FDG PET in multiple myeloma. Skeletal Radiol 2002;31:690-694. Available at http://www.ncbi.nlm.nih.gov/pubmed/12483429

22. Orchard K, Barrington S, Buscombe J, et al. Fluoro-deoxyglucose positron emission tomography imaging for the detection of occult disease in multiple myeloma. Br J Haematol 2002;117:133-135. Available at http://www.ncbi.nlm.nih.gov/pubmed/11918544

23. Harousseau JL, Mathiot C, Attal M, et al. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantion (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial. ASCO Meeting Abstracts 2008;26:Abstract 8505. Available at http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/8505

24. Harousseau J-L, Avet-Loiseau H, Attal M, et al. High complete and very good partial response rates with bortezomib--dexamethasone as induction prior to ASCT in newly diagnosed patients with high-risk myeloma: Results of the IFM2005-01 phase 3 trial. ASH Annual Meeting Abstracts 2009;114:Abstract 353. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/353

25. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients With t(4;14) myeloma but not outcome of patients with del(17p). J Clin Oncol 2010. Available at http://www.ncbi.nlm.nih.gov/pubmed/20644101

26. Sonneveld P, Van der Holt, B, Schmidt-Wolf, I, . First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing bortezomib, adriamycine, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with multiple myeloma (MM) Haematologica 2009;94:Abstract 191. Available at

27. Cavo M, Tacchetti P, Patriarca F, et al. Superior complete response rate and progression-free survival after autologous transplantation with up-front velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma. ASH Annual Meeting Abstracts 2008;112:Abstract 158. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;112/11/158

28. Cavo M, Tacchetti P, Patriarca F, et al. A phase III study of double autotransplantation incorporating bortezomib-thalidomide-dexamethasone (VTD) or thalidomide-dexamethasone (TD) for multiple myeloma: Superior clinical outcomes with VTD compared to TD. ASH Annual Meeting Abstracts 2009;114:Abstract 351. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/351

29. Kaufman JL, Nooka A, Vrana M, et al. Bortezomib, thalidomide, and dexamethasone as induction therapy for patients with symptomatic multiple myeloma: a retrospective study. Cancer 2010;116:3143-3151. Available at http://www.ncbi.nlm.nih.gov/sites/pubmed/20564642

30. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia

2009;23:1337-1341. Available at http://www.ncbi.nlm.nih.gov/pubmed/19225538

31. Einsele H, Liebisch P, Langer C, et al. Velcade, intravenous cyclophosphamide and dexamethasone (VCD) induction for previously untreated multiple myeloma (German DSMM XIa Trial). ASH Annual Meeting Abstracts 2009;114:Abstract 131. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/131

32. Kumar S, Flinn IW, Hari PN, et al. Novel three- and four-drug combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide, for newly diagnosed multiple myeloma: encouraging results from the multi-center, randomized, phase 2 EVOLUTION study. ASH Annual Meeting Abstracts 2009;114:Abstract 127. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/127

33. Richardson P, Jagannath S, Raje N, et al. Lenalidomide, bortezomib, and dexamethasone (Rev/Vel/Dex) as front-line therapy for patients with multiple myeloma (MM): preliminary results of a phase 1/2 study. ASH Annual Meeting Abstracts 2007;110:Abstract 187. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;110/11/187

34. Richardson P, Lonial S, Jakubowiak A, et al. Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: encouraging efficacy in high risk groups with updated results of a phase I/II study. ASH Annual Meeting Abstracts 2008;112:Abstract 92. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;112/11/92

35. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;116:679-686. Available at http://bloodjournal.hematologylibrary.org/cgi/content/abstract/bloodjournal;116/5/679

36. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 2008;26:4784-4790. Available at http://jco.ascopubs.org/cgi/content/abstract/26/29/4784

37. Vickrey E, Allen S, Mehta J and Singhal S. Acyclovir to prevent reactivation of varicella zoster virus (herpes zoster) in multiple myeloma patients receiving bortezomib therapy. Cancer 2009;115:229-232. Available at http://www.ncbi.nlm.nih.gov/pubmed/19090004

38. Mateos MV. Management of treatment-related adverse events in patients with multiple myeloma. Cancer Treat Rev 2010;36 Suppl 2:S24-32. Available at http://www.ncbi.nlm.nih.gov/pubmed/20472185

39. Zonder JA, Crowley J, Hussein MA, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): Results of the randomized, double-blinded, placebo-controlled SWOG Trial S0232. ASH Annual Meeting Abstracts 2007;110:Abstract 77. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;110/11/77

40. Rajkumar SV, Jacobus S, Callander N, et al. A randomized phase III trial of lenalidomide pus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the eastern Cooperative Oncology Group. ASH Annual Meeting Abstracts 2006;108:799. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;108/11/799

41. Rajkumar SV, Jacobus S, Callander N, et al. A randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. ASH Annual Meeting Abstracts 2007;110:74. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;110/11/74

42. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose

dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37. Available at http://www.ncbi.nlm.nih.gov/sites/entrez/19853510

43. Gay F, Hayman SR, Lacy MQ, et al. Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients. Blood 2010;115:1343-1350. Available at http://www.ncbi.nlm.nih.gov/pubmed/20008302

44. Kumar S, Dispenzieri A, Lacy MQ, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. Leukemia 2007;21:2035-2042. Available at http://www.ncbi.nlm.nih.gov/pubmed/17581613

45. Paripati H, Stewart AK, Cabou S, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. Leukemia 2008;22:1282-1284. Available at http://www.ncbi.nlm.nih.gov/pubmed/18216870

46. Kumar S, Giralt S, Stadtmauer EA, et al. Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens. Blood 2009;114:1729-1735. Available at http://www.ncbi.nlm.nih.gov/pubmed/19561323

47. Zangari M, Tricot G, Polavaram L, et al. Survival effect of venous thromboembolism in patients with multiple myeloma treated with lenalidomide and high-dose dexamethasone. J Clin Oncol 2010;28:132-135. Available at http://www.ncbi.nlm.nih.gov/sites/pubmed/19901114

48. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-423. Available at http://www.ncbi.nlm.nih.gov/pubmed/18094721

49. Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006;24:431-436. Available at http://www.ncbi.nlm.nih.gov/pubmed/16365178

50. Rifkin RM, Gregory SA, Mohrbacher A and Hussein MA. Pegylated liposomal doxorubicin, vincristine, and dexamethasone provide significant reduction in toxicity compared with doxorubicin, vincristine, and dexamethasone in patients with newly diagnosed multiple myeloma: a Phase III multicenter randomized trial. Cancer 2006;106:848-858. Available at http://www.ncbi.nlm.nih.gov/pubmed/16404741

51. Gregory WM, Richards MA and Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: an overview of published trials. J Clin Oncol 1992;10:334-342. Available at http://www.ncbi.nlm.nih.gov/pubmed/1531068

52. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet 2006;367:825-831. Available at http://www.ncbi.nlm.nih.gov/pubmed/16530576

53. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet 2007;370:1209-1218. Available at http://www.ncbi.nlm.nih.gov/pubmed/17920916

54. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. J Clin Oncol 2009;27:3664-3670. Available at http://www.ncbi.nlm.nih.gov/pubmed/19451428

55. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol 2010;28:3160-3166. Available at http://www.ncbi.nlm.nih.gov/pubmed/20516439

56. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus

melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906-917. Available at http://www.ncbi.nlm.nih.gov/pubmed/18753647

57. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 2010;28:2259-2266. Available at http://www.ncbi.nlm.nih.gov/pubmed/20368561

58. Harousseau J-L, Palumbo A, Richardson P, et al. Superior outcomes associated with complete response: analysis of the phase III VISTA study of bortezomib plus melphalan-mrednisone versus melphalan-prednisone. ASH Annual Meeting Abstracts 2008;112:Abstract 2778. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;112/11/2778

59. Yeh Y, Chambers J, Gaugris S and Jansen J. Indirect comparison of the efficacy of melphalan-prednisone-bortezomib Relative to melphalan-prednisone-thalidomide and melphalan-prednisone for the first line treatment of Multiple myeloma. ASH Annual Meeting Abstracts 2008;112:Abstract 2367. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;112/11/2367

60. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA--Italian Multiple Myeloma Network. J Clin Oncol 2007;25:4459-4465. Available at http://www.ncbi.nlm.nih.gov/pubmed/17785703

61. Palumbo A, Falco P, Falcone A, et al. Melphalan, prednisone, and lenalidomide for newly diagnosed myeloma: kinetics of neutropenia and thrombocytopenia and time-to-event results. Clin Lymphoma Myeloma 2009;9:145-150. Available at http://www.ncbi.nlm.nih.gov/pubmed/19406725

62. Roy V, Stewart AK, Bergsagel PL, et al. Phase II study of melphalan, prednisone and lenalidomide combination for newly diagnosed multiple myeloma patients who are not candidates for stem cell transplantation. ASH Annual Meeting Abstracts 2008;112:Abstract 2769. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;112/11/2769

63. Palumbo A, Dimopoulos MA, Delforge M, et al. A phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma. ASH Annual Meeting Abstracts 2009;114:Abstract 613. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/613

64. Niesvizky R, Reeves J, Flinn IW, et al. Phase 3b UPFRONT study: Interim results from a community practice-based prospective randomized trial evaluating three bortezomib-based regimens in elderly, newly diagnosed multiple myeloma patients. ASH Annual Meeting Abstracts 2009;114:Abstract 129. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/129

65. Badros A, Barlogie B, Morris C, et al. High response rate in refractory and poor-risk multiple myeloma after allotransplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions. Blood 2001;97:2574-2579. Available at http://www.ncbi.nlm.nih.gov/pubmed/11313244

66. Kroger N, Sayer HG, Schwerdtfeger R, et al. Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. Blood 2002;100:3919-3924. Available at http://www.ncbi.nlm.nih.gov/pubmed/12393448

67. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Blood 2002;99:731-735. Available at http://www.ncbi.nlm.nih.gov/pubmed/11806971

68. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 1996;335:91-97. Available at http://www.ncbi.nlm.nih.gov/pubmed/8649495

69. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348:1875-1883. Available at http://www.ncbi.nlm.nih.gov/pubmed/12736280

70. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/16432076

71. Fermand J-P, 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/16275936

72. Corradini P, Cavo M, Lokhorst H, et al. Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. Blood 2003;102:1927-1929. Available at http://www.ncbi.nlm.nih.gov/pubmed/12738666

73. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. Biol Blood Marrow Transplant 2003;9:4-37. Available at http://www.ncbi.nlm.nih.gov/pubmed/12533739

74. Kumar S, Lacy MQ, Dispenzieri A, et al. High-dose therapy and autologous stem cell transplantation for multiple myeloma poorly responsive to initial therapy. Bone Marrow Transplant 2004;34:161-167. Available at http://www.ncbi.nlm.nih.gov/pubmed/15133489

75. Attal M, Harousseau J-L, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349:2495-2502. Available at http://www.ncbi.nlm.nih.gov/pubmed/14695409

76. Stadtmauer EA. Multiple myeloma, 2004--one or two transplants? N Engl J Med 2003;349:2551-2553. Available at http://www.ncbi.nlm.nih.gov/pubmed/14695416

77. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol 2007;25:2434-2441. Available at http://www.ncbi.nlm.nih.gov/pubmed/17485707

78. Sonneveld P, van der Holt B, Segeren C, et al. Intensive versus double intensive therapy in untreated multiple myeloma: Updated analysis of the randomized phase III study HOVON 24 MM. ASH Annual Meeting Abstracts 2004;104:Abstract 948. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;104/11/948

79. Goldschmidt H. Single vs double high-dose therapy in multiple myeloma: second analysis of the GMMG-HD2 trial Haematologica 2005;90(s1):Abstract 38 Available at Not Available

80. Barlogie B, Attal M, Crowley J, et al. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. J Clin Oncol 2010;28:1209-1214. Available at http://www.ncbi.nlm.nih.gov/pubmed/20085933

81. Kyle RA. High-dose therapy in multiple myeloma and primary amyloidosis: an overview. Semin Oncol 1999;26:74-83. Available at http://www.ncbi.nlm.nih.gov/pubmed/10073564

82. Kumar A, Loughran T, Alsina M, et al. Management of multiple myeloma: a systematic review and critical appraisal of published studies. Lancet Oncol 2003;4:293-304. Available at

http://www.ncbi.nlm.nih.gov/pubmed/12732167

83. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/17360989

84. 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. Available at http://www.ncbi.nlm.nih.gov/pubmed/16397129

85. Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. Blood 2003;102:3447-3454. Available at http://www.ncbi.nlm.nih.gov/pubmed/12855572

86. Crawley C, Lalancette M, Szydlo R, et al. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. Blood 2005;105:4532-4539. Available at http://www.ncbi.nlm.nih.gov/pubmed/15731182

87. Zeiser R, Bertz H, Spyridonidis A, et al. Donor lymphocyte infusions for multiple myeloma: clinical results and novel perspectives. Bone Marrow Transplant 2004;34:923-928. Available at http://www.ncbi.nlm.nih.gov/pubmed/15361911

88. Browman GP, Bergsagel D, Sicheri D, et al. Randomized trial of interferon maintenance in multiple myeloma: a study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1995;13:2354-2360. Available at http://www.ncbi.nlm.nih.gov/pubmed/7666094

89. Fritz E and Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. Ann Oncol 2000;11:1427-1436. Available at http://www.ncbi.nlm.nih.gov/pubmed/11142483

90. Shustik C, Belch A, Robinson S, et al. A randomised comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7. Br J Haematol 2007;136:203-211. Available at http://www.ncbi.nlm.nih.gov/pubmed/17233817

91. Brinker BT, Waller EK, Leong T, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. Cancer 2006;106:2171-2180. Available at http://www.ncbi.nlm.nih.gov/pubmed/16598756

92. Attal M, Harousseau J-L, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006;108:3289-3294. Available at http://www.ncbi.nlm.nih.gov/pubmed/16873668?dopt=Abstract

93. Spencer A, Prince M, Roberts AW, et al. First Analysis of the Australasian Leukaemia and Lymphoma Group (ALLG) Trial of Thalidomide and Alternate Day Prednisolone Following Autologous Stem Cell Transplantation (ASCT) for Patients with Multiple Myeloma (ALLG MM6). ASH Annual Meeting Abstracts 2006;108:Abstract 58. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;108/11/58

94. Morgan GJ, Davies FE, Cavenagh JD and Jackson GH. Position statement on the use of bortezomib in multiple myeloma. Int J Lab Hematol 2008;30:1-10. Available at http://www.ncbi.nlm.nih.gov/pubmed/18190461

95. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med 2006;354:1021-1030. Available at http://www.ncbi.nlm.nih.gov/pubmed/16525139

96. McCarthy PL, Owzar K, Stadtmauer EA, et al. Phase III intergroup study of lenalidomide (CC-5013) versus placebo maintenance therapy following single autologous stem cell transplant for multiple myeloma (CALGB 100104): initial report of patient accrual and adverse events. ASH Annual Meeting Abstracts 2009;114:3416. Available at

http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/3416

97. McCarthy PL, Owzar K, Anderson KC, et al. Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104. ASCO Meeting Abstracts 2010;28:Abstract 8017. Available at http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/8017

98. Attal M, Harousseau JL, Marit G, et al. Lenalidomide after autologous transplantation for myeloma: first analysis of a prospective, randomized study of the Intergroupe Francophone Du Myelome (IFM 2005 02). ASH Annual Meeting Abstracts 2009;114:Abstract 529. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/529

99. Attal M, Cristini C, Marit G, et al. Lenalidomide maintenance after transplantation for myeloma. ASCO Meeting Abstracts 2010;28:Abstract 8018. Available at http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/8018

100. Mateos M-V, Oriol A, Martinez J, et al. A prospective, multicenter, randomized, trial of bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years. ASH Annual Meeting Abstracts 2009;114:3. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/3

101. Mellqvist U-H, Westin J, Gimsing P, et al. Improved response rate with bortezomib consolidation after high dose melphalan: first results of a Nordic myeloma study group randomized phase III trial. ASH Annual Meeting Abstracts 2009;114:530. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/530

102. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487-2498. Available at http://www.ncbi.nlm.nih.gov/pubmed/15958804

103. Richardson PG, Sonneveld P, Schuster M, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood 2007;110:3557-3560. Available at http://www.ncbi.nlm.nih.gov/pubmed/17690257

104. Jagannath S, Richardson PG, Sonneveld P, et al. Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. Leukemia 2007;21:151-157. Available at http://www.ncbi.nlm.nih.gov/pubmed/17096017

105. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol 2007;25:3892-3901. Available at http://www.ncbi.nlm.nih.gov/pubmed/17679727

106. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-2132. Available at http://www.ncbi.nlm.nih.gov/pubmed/18032762

107. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-2142. Available at http://www.ncbi.nlm.nih.gov/pubmed/18032763

108. Richardson P, Jagannath S, Hussein M, et al. A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma; prelininary Results. ASH Annual Meeting Abstracts 2005;106:1565. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;106/11/1565

109. Rajkumar SV, Fonseca R, Dispenzieri A, et al. Thalidomide in the

treatment of relapsed multiple myeloma. Mayo Clin Proc 2000;75:897-901. Available at http://www.ncbi.nlm.nih.gov/pubmed/10994824

110. Mohty M, Attal M, Marit G, et al. Thalidomide salvage therapy following allogeneic stem cell transplantation for multiple myeloma: a retrospective study from the Intergroupe Francophone du Myelome (IFM) and the Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC). Bone Marrow Transplant 2005;35:165-169. Available at http://www.ncbi.nlm.nih.gov/pubmed/15531895

111. Lee C-K, Barlogie B, Munshi N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol 2003;21:2732-2739. Available at http://www.ncbi.nlm.nih.gov/pubmed/12860952

112. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-1571. Available at http://www.ncbi.nlm.nih.gov/pubmed/10564685

113. Waage A, Gimsing P, Juliusson G, et al. Early response predicts thalidomide efficiency in patients with advanced multiple myeloma. Br J Haematol 2004;125:149-155. Available at http://www.ncbi.nlm.nih.gov/pubmed/15059136

114. Morgan GJ, Schey SA, Wu P, et al. Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients. Br J Haematol 2007;137:268-269. Available at http://www.ncbi.nlm.nih.gov/pubmed/17408469

115. Reece DE, Rodriguez GP, Chen C, et al. Phase I-II trial of bortezomib plus oral cyclophosphamide and prednisone in relapsed and refractory multiple myeloma. J Clin Oncol 2008;26:4777-4783. Available at http://www.ncbi.nlm.nih.gov/entrez/18645194

116. Knop S, Straka C, Haen M, et al. The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy. Haematologica 2005;90:1287-1288. Available at http://www.ncbi.nlm.nih.gov/pubmed/16154860

117. Michael M, Bruns I, Bolke E, et al. Bendamustine in patients with relapsed or refractory multiple myeloma. Eur J Med Res 2010;15:13-19. Available at http://www.ncbi.nlm.nih.gov/pubmed/20159666

118. Richardson PG, Jagannath S, Avigan DE, et al. Lenalidomide plus bortezomib (Rev-Vel) in relapsed and/or refractory multiple myeloma (MM): final results of a multicenter phase 1 trial. ASH Annual Meeting Abstracts 2006;108:405. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;108/11/405

119. Anderson KC, Jagannath S, Jakubowiak A, et al. Lenalidomide, bortezomib, and dexamethasone in relapsed/refractory multiple myeloma (MM): Encouraging outcomes and tolerability in a phase II study. ASCO Meeting Abstracts 2009;27:8536-. Available at http://meeting.ascopubs.org/cgi/content/abstract/27/15S/8536

120. Ikhlaque N, Seshadri V, Kathula S and Baumann MA. Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. Am J Hematol 2006;81:420-422. Available at http://www.ncbi.nlm.nih.gov/pubmed/16680743

121. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. Mayo Clin Proc 2005;80:1568-1574. Available at http://www.ncbi.nlm.nih.gov/pubmed/16342649

122. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. J Clin Oncol 1998;16:593-602. Available at http://www.ncbi.nlm.nih.gov/pubmed/9469347

123. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med 1996;334:488-493. Available at http://www.ncbi.nlm.nih.gov/pubmed/8559201

124. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled

analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19:558-567. Available at http://www.ncbi.nlm.nih.gov/pubmed/11208851

125. Bloomfield DJ, Krahn MD, Neogi T, et al. Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic hormone-resistant prostate cancer: based on a Canadian randomized trial with palliative end points. J Clin Oncol 1998;16:2272-2279. Available at http://www.ncbi.nlm.nih.gov/pubmed/9626231

126. Kyle RA, Yee GC, Somerfield MR, et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. J Clin Oncol 2007;25:2464-2472. Available at http://www.ncbi.nlm.nih.gov/pubmed/17515569

127. Zervas K, Verrou E, Teleioudis Z, et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. Br J Haematol 2006;134:620-623. Available at http://www.ncbi.nlm.nih.gov/pubmed/16889620

128. Lindsley H, Teller D, Noonan B, et al. Hyperviscosity syndrome in multiple myeloma. A reversible, concentration-dependent aggregation of the myeloma protein. Am J Med 1973;54:682-688. Available at http://www.ncbi.nlm.nih.gov/pubmed/4701949

129. Ludwig H, Fritz E, Kotzmann H, et al. Erythropoietin treatment of anemia associated with multiple myeloma. N Engl J Med 1990;322:1693-1699. Available at http://www.ncbi.nlm.nih.gov/pubmed/2342535

130. Osterborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma--a randomized multicenter study. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. Blood 1996;87:2675-2682. Available at http://www.ncbi.nlm.nih.gov/pubmed/8639883

131. Mateos M-V, Hernandez J-M, Hernandez M-T, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood 2006;108:2165-2172. Available at http://www.ncbi.nlm.nih.gov/pubmed/16772605

132. Falk RH, Comenzo RL and Skinner M. The systemic amyloidoses. N Engl J Med 1997;337:898-909. Available at http://www.ncbi.nlm.nih.gov/pubmed/9302305

133. Comenzo RL and Gertz MA. Autologous stem cell transplantation for primary systemic amyloidosis. Blood 2002;99:4276-4282. Available at http://www.ncbi.nlm.nih.gov/pubmed/12036853

134. Gertz MA, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for the management of primary systemic amyloidosis. Am J Med 2002;113:549-555. Available at http://www.ncbi.nlm.nih.gov/pubmed/12459400

135. Goodman HJ, Gillmore JD, Lachmann HJ, et al. Outcome of autologous stem cell transplantation for AL amyloidosis in the UK. Br J Haematol 2006;134:417-425. Available at http://www.ncbi.nlm.nih.gov/pubmed/16822290

136. Dispenzieri A, Kyle RA, Lacy MQ, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. Blood 2004;103:3960-3963. Available at http://www.ncbi.nlm.nih.gov/pubmed/14739213

137. Gertz MA, Lacy MQ, Dispenzieri A, et al. Effect of hematologic response on outcome of patients undergoing transplantation for primary amyloidosis: importance of achieving a complete response. Haematologica 2007;92:1415-1418. Available at http://www.ncbi.nlm.nih.gov/pubmed/17768110

138. Skinner M, Sanchorawala V, Seldin DC, et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. Ann Intern Med 2004;140:85-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/14734330

139. Gertz MA, Lacy MQ, Dispenzieri A, et al. Risk-adjusted manipulation of melphalan dose before stem cell transplantation in patients with amyloidosis is associated with a lower response rate. Bone Marrow

Transplant 2004;34:1025-1031. Available at http://www.ncbi.nlm.nih.gov/pubmed/15516945

140. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood 2004;103:2936-2938. Available at http://www.ncbi.nlm.nih.gov/pubmed/15070667

141. Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. Blood 2007;110:787-788. Available at http://www.ncbi.nlm.nih.gov/pubmed/17606766

142. Dhodapkar MV, Hussein MA, Rasmussen E, et al. Clinical efficacy of high-dose dexamethasone with maintenance dexamethasone/alpha interferon in patients with primary systemic amyloidosis: results of United States Intergroup Trial Southwest Oncology Group (SWOG) S9628. Blood 2004;104:3520-3526. Available at http://www.ncbi.nlm.nih.gov/pubmed/15308571

143. Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). Blood 2005;105:2949-2951. Available at http://www.ncbi.nlm.nih.gov/pubmed/15572585

144. Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood 2007;109:465-470. Available at http://www.ncbi.nlm.nih.gov/pubmed/17008538

145. Sanchorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. Blood 2007;109:492-496. Available at http://www.ncbi.nlm.nih.gov/pubmed/16960148

146. Dispenzieri A, Lacy M, Zeldenrust SR, et al. Long term follow-up of patients with immunoglobulin light chain amyloidosis treated with lenalidomide and dexamethasone. ASH Annual Meeting Abstracts 2008;112:Abstract 1737. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;112/11/1737

147. Sviggum HP, Davis MD, Rajkumar SV and Dispenzieri A. Dermatologic adverse effects of lenalidomide therapy for amyloidosis and multiple myeloma. Arch Dermatol 2006;142:1298-1302. Available at http://www.ncbi.nlm.nih.gov/pubmed/17043184

148. Batts ED, Sanchorawala V, Hegerfeldt Y and Lazarus HM. Azotemia associated with use of lenalidomide in plasma cell dyscrasias. Leuk Lymphoma 2008;49:1108-1115. Available at http://www.ncbi.nlm.nih.gov/pubmed/18452093

149. Kastritis E, Anagnostopoulos A, Roussou M, et al. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. Haematologica 2007;92:1351-1358. Available at http://www.ncbi.nlm.nih.gov/pubmed/18024372

150. Wechalekar AD, Lachmann HJ, Offer M, et al. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica 2008;93:295-298. Available at http://www.ncbi.nlm.nih.gov/pubmed/18245653

151. Kastritis E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light chain) amyloidosis. J Clin Oncol 2010;28:1031-1037. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20085941

152. Lamm W, Willenbacher W, Zojer N, et al. Efficacy of the combination of bortezomib and dexamethasone in systemic AL amyloidosis. ASH Annual Meeting Abstracts 2009;114:Abstract 2871. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/2871

153. Singh V, Saad A, Palmer J, et al. Response to bortezomib based induction therapy in newly diagnosed light chain (AL) amyloidosis. ASH Annual Meeting Abstracts 2009;114:Asbtract 1867. Available at http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;114/22/

1867

154. Wechalekar AD, Goodman HJ, Lachmann HJ, et al. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. Blood 2007;109:457-464. Available at http://www.ncbi.nlm.nih.gov/pubmed/16990593