

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010

Summary of the Guidelines Update

**National Comprehensive Cancer Network
Version 3.2010.**

Treatments Placed in New Categories:

Primary Induction Therapy for Transplant Candidates

Regimen (supporting trial)	Current category*	Previous category*
Bortezomib/dexamethasone <i>(Harousseau et al. ASCO 2008)</i>	1	2B
Bortezomib/doxorubicin/dexamethasone <i>(Sonneveld et al. ASH 2008)</i>	1	2B
Bortezomib/thalidomide/dexamethasone <i>(Cavo et al. ASH 2008)</i>	1	2B
Lenalidomide/dexamethasone <i>(Zonder et al. ASH 2007)</i>	1	2B

* Category 1 = uniform consensus, high evidence quality;
2B = nonuniform consensus, lower evidence quality

Primary Induction Therapy for Transplant Candidates (continued)

Regimen (supporting trial)	Current category*	Previous category*
Dexamethasone (<i>Rajkumar et al. JCO 2006</i>)	2B	2A
Thalidomide/dexamethasone (<i>Rajkumar et al. JCO 2006</i>)	2B	2A
Liposomal doxorubicin/vincristine/ dexamethasone (<i>Rifkin et al. Cancer 2006</i>)	2B	2A

* Category 2A = uniform consensus, lower evidence quality;
2B = nonuniform consensus, lower evidence quality

Treatments Placed in New Categories:

Primary Induction Therapy for Nontransplant Candidates

Regimen (supporting trial)	Current category	Previous category
Melphalan/prednisone/thalidomide (MPT) <i>(Multiple randomized trials compared MPT to MP)</i>	1	2A
Melphalan/prednisone/bortezomib (MPB) <i>(San Miguel et al. NEJM 2008 VISTA trial)</i>	1	2A
Lenalidomide/low-dose dexamethasone (Rd) <i>(Rajkumar et al. Lancet 2010)</i>	1	2B
Melphalan/prednisone (MP) <i>(Multiple trials compared MP to either MPT or MPB)</i>	2A	1

Primary Induction Therapy for Nontransplant Candidates (continued)

Regimen (supporting trial)	Current category	Previous category
Thalidomide/dexamethasone <i>(Rajkumar et al. JCO 2006)</i>	2B	2A
Dexamethasone <i>(Rajkumar et al. JCO 2006)</i>	2B	2A
Vincristine/doxorubicin/dexamethasone (VAD) ¹	2B	2A

Category 2A: Uniform consensus, lower evidence quality

¹ VAD is now category 2B; no specific reference has been cited for the change.

Maintenance Therapy

- Three independent trials with lenalidomide maintenance have recently reported improvement in disease progression.
 - CALGB-100104: 58% reduction in disease progression (ASH 2009; Abstract 3416.)
 - IFM 2005-02: Improved PFS and sCR/CR (ASH 2009; Abstract 529.)
 - MM-015: 75% reduction in disease progression (ASH 2009; Abstract 613.)
- Lenalidomide maintenance added (Category 2A).
- Thalidomide alone or with prednisone (Category 1 and 2B respectively).

Faculty Comments

DR GIRALT: NCCN guidelines have incorporated the results of multiple Phase III studies for transplant-eligible and transplant-ineligible patients, and the recommendations for initial therapy include regimens containing bortezomib or lenalidomide.

Lenalidomide maintenance studies were presented at ASH 2009. Although not yet published in peer-reviewed journals, these studies are important and should influence practice, and NCCN now acknowledges lenalidomide maintenance therapy in myeloma as an evidence-based option.

Faculty Comments (Continued)

DR ORLOWSKI: NCCN updates have been made because of the maturation of the major Phase III studies that incorporated novel agents such as bortezomib or lenalidomide in the initial treatment of myeloma.

A number of induction regimens incorporating novel agents have been upgraded in their level of recommendation from IIB to I. NCCN also added lenalidomide maintenance as a category IIA recommendation in view of results presented at ASH from the multitude of studies.

International Myeloma Working Group Guidelines for the Management of Multiple Myeloma Patients Ineligible for Standard High-Dose Chemotherapy with Autologous Stem Cell Transplantation

Palumbo A et al.

Leukemia 2009; 23(10):1716-30.

Introduction

- Prior guidelines were published in 2005.
- Current update conducted by a panel of clinical and statistical experts who reviewed articles from 2004-2008 and abstracts from 2006-2008.
- No changes to guidances on diagnosis, indications to start therapy or monitoring of myeloma.
- Changes in specific areas of multiple myeloma are summarized.

Update on Prognostic Factors and Response Criteria

- Cytogenetics and/or FISH should be performed in all patients at diagnosis and at the time of relapse.
- IMWG criteria should be used to assess response (*Leukemia* 2006; 20: 1467).
 - Response criteria of stringent CR and VGPR have been added.
 - Serum free light chain assay is used to determine stringent CR.

Front-Line Therapy

- IMWG considers MPT and VMP as standard treatment for initial induction therapy in patients ineligible for transplantation and Rd for patients who wish to postpone transplantation.
- Major trials reviewed:
 - RD vs Rd (Rajkumar et al. ASCO 2008)
 - MPT vs MP (Palumbo et al. *Blood* 2008)
 - MPT vs MP (Facon et al. *Lancet* 2007)
 - MPT vs MP (Hulin et al. ASH 2007)
 - VMP vs MP (San Miguel et al. *NEJM* 2008)

Therapy for Relapsed Myeloma

- In the relapsed setting, IMWG recommends:
 - Bortezomib with or without dexamethasone or in combination with liposomal doxorubicin
 - Lenalidomide in combination with dexamethasone
- Choice of salvage therapy depends on earlier exposure to a particular drug and concomitant comorbidities.

Supportive Care In Myeloma

- Bisphosphonates are recommended in patients with osteolytic lesions.
 - Comprehensive dental examination should be done before starting bisphosphonate therapy.
 - Continue bisphosphonates for two years. However, one year is sufficient for patients in CR/nCR.
- Vertebral fracture:
 - Balloon kyphoplasty has shown a marked reduction in back disability and pain in a randomized Phase III trial and should be considered as a standard approach if appropriate (*Clinical Lymphoma Myeloma* 2009; Abstract 204).

Faculty Comments

DR RICHARDSON: The updated guidelines from IMWG recommend a cytogenetic and/or FISH assay for all patients at diagnosis and at relapse. An additional update was in the determination of the CR quality by use of a serum free light chain assay and the identification of stringent CR.

This update also included incorporating novel agents such as bortezomib, lenalidomide or thalidomide in the initial therapy for transplant-ineligible patients.

Faculty Comments (Continued)

DR ORLOWSKI: I don't agree with the panel recommendation to perform cytogenetic and/or FISH testing at the time of relapse in transplant-ineligible patients.

I can understand it better for patients who have undergone transplants, because high-dose melphalan can result in chromosomal changes, especially the appearance of 17p abnormalities, but I am not sure that this happens in patients who have not undergone transplants.

Supportive care updates include the use of monthly bisphosphonates for a shorter period than two years for patients who achieve a CR.

International Myeloma Working Group Molecular Classification of Multiple Myeloma: Spotlight Review

Fonseca R et al.

Leukemia 2009; 23(12):2210-21.

Introduction

- Multiple myeloma (MM) is a clonal B-cell disorder with heterogeneity in outcome among different patients.
- Several subtypes have been identified at the genetic and molecular level.
- Genetic and molecular subtypes are associated with unique clinicopathologic features and have prognostic implications.

Genetic Classification

Hyperdiploid (h) MM	Nonhyperdiploid (nh) MM
<ul style="list-style-type: none">● 45% of all MM● Numerous chromosome trisomies● More favorable outcome● Slightly more common in males● More common in elderly	<ul style="list-style-type: none">● 40% of all MM● Highly enriched for IgH translocations● Overall less favorable outcome● Examples include t(11;14), t(4;14), t(14;16), del(17p)

Remaining 15% of MM is either with overlap or unclassified in the two major genetic categories.

Molecular Subtypes of MM

- t(11;14)
 - 15% of all MM
 - Hyposecretory disease
 - Associated with IgM myeloma
 - Prognosis neutral
- t(14;16)
 - 5-7% of all MM
 - High prevalence of concomitant chromosome 13 deletion
 - Higher frequency of IgA isotype
 - Aggressive clinical course

Molecular Subtypes of MM

- del(17p13)
 - Most aggressive disease
 - Higher prevalence of extramedullary disease
 - Short duration of response after transplant
- t(4;14)
 - 15% of all MM
 - High prevalence of concomitant chromosome 13 abnormalities
 - Poor outcome
 - Bortezomib may overcome the poor prognosis of this subgroup

Molecular Subtypes of MM

- Chromosome 13 abnormalities
 - Present in 50% of MM and 90% of t(4;14) and t(14;16)
 - Significance is considered as of surrogate association with nh MM
- Chromosome 1 abnormalities
 - Emerging marker
 - Negative prognostic association in some reports

Gene Expression Profiling

- University of Arkansas and IFM (Intergroupe Francophone du Myélome) have identified gene signatures that can provide prognostic discrimination.
- There is minimal overlap between these two signatures, and both will need validation.
- It is conceivable that gene signatures may become predictive markers in the future.

Summary and Recommendations

- Baseline genetic information should be obtained in all MM cases.
- FISH testing must be done on purified plasma cells and not on unsorted samples.
- Minimal panel required for prognostication should include t(4;14), t(14;16) and del(17p13).
- A more comprehensive panel should include testing for t(11;14), chromosome 13 deletion, ploidy category and chromosome 1 abnormalities.
- Gene expression signatures should be incorporated in all clinical trials.

Faculty Comments

DR GIRALT: The classification of myeloma using a variety of cytogenetic abnormalities as documented by conventional cytogenetics or FISH is becoming an accepted practice.

It is important to note that although no specific treatments have been devised for myeloma in patients with specific cytogenetic abnormalities, more and more data suggest that these abnormalities could be amenable to specific targeted therapies in the future.

This review article describes various myeloma-associated specific molecular abnormalities as distinct entities and divides them into two major subtypes. None of the clinical features described are specific enough to make the diagnosis clinically.

Faculty Comments (Continued)

Currently they have prognostic significance, and some of them may become predictive markers for specific therapies in the future.

The panel recommends that all patients with newly diagnosed multiple myeloma should undergo cytogenetic analysis and FISH analysis for t(4;14), t(14;16), t(11;14) and del 17p.

International Myeloma Working Group Guidelines for Serum-Free Light Chain Analysis in Multiple Myeloma and Related Disorders

Dispenzieri A et al.

Leukemia 2009; 23(2):215-24.

Introduction

- Serum free light chain (FLC) assay was developed in early 2000s.
- Assay consists of quantitating circulating free κ and λ light chain immunoglobulin as well as providing κ/λ FLC ratio (rFLC).
- This review describes uses in which FLC has proven its utility and areas in which it is still investigational.

Screening for Plasma Cell Disorders

Gold standard for plasma cell disorders screening is immunofixation electrophoresis (IFE) of serum and urine. A prior study identified 428 patients in the Mayo Clinic database who had positive urinary IFE (u IFE) and also had serum IFE (sIFE), serum protein electrophoresis (SPEP) and serum rFLC done (*Mayo Clin Proc* 2006;81:1575).

Laboratory test	% Abnormal	% Missed if urinary IFE was not done
sIFE or SPEP	93.5	6.5
sIFE or rFLC	99.5	0.5

Prognostic Value of Serum FLC Assay

- MGUS/Smoldering Myeloma/Solitary Plasmacytoma: Abnormal rFCL is an independent predictor for higher rate of progression.
- Multiple Myeloma: Highly abnormal rFLC (<0.03 or >32) predicts inferior outcomes when compared to those with less severe abnormality (*Leukemia* 2008;22:1933).
- Amyloidosis: Baseline FLC correlates with the risk of death (*Blood* 2006;107:3378).

Monitoring and Response Assessment with Serum FLC Assay

- Amyloidosis:
 - FLC response has been shown to correlate with survival (*BJH* 2003; 122: 78).
- Oligosecretory myeloma/light chain deposition disease:
 - No data suggest that FLC changes correlate with disease status or outcome.
 - However, anecdotal reports exist in the literature to support a role of FLC in this population, and authors confirm their personal experience of use in follow-up of such patients.

Monitoring and Response Assessment with Serum FLC Assay (continued)

- Active Multiple Myeloma:
 - There is no data to suggest routine use except to document stringent CR in a patient who has already attained CR.
 - FLC half-life is 2 to 4 hours, while that of IgG is 8 to 21 days.
 - FLC may detect an early response or an early relapse.
 - No data is currently available to show that early detection of response or relapse may change the patient's outcome.

Summary and Recommendations

- Serum FLC assay in combination with serum IFE is sufficient for screening plasma cell disorders.
- Serum FLC assay should be measured at diagnosis for prognostic purposes for all plasma cell disorders.
- Serum FLC assay should be conducted in the follow-up of patients with amyloidosis, oligosecretory myeloma and light chain-only myeloma and should also be conducted in patients with active multiple myeloma who have achieved a CR to determine a stringent CR.

Faculty Comments

DR RICHARDSON: This is a useful article that provides guidance on the use of free light chain (FLC) assays. In combination with serum immunofixation, FLC is highly sensitive and can replace 24-hour urine studies in screening for plasma cell disorders.

Baseline FLC has major prognostic value in virtually every plasma cell disorder, and finally, it allows monitoring of patients with oligosecretory myeloma or monitoring to determine the quality of CR in patients with myeloma.

Faculty Comments (Continued)

DR JAGANNATH: The assay quantitates the serum light chains that are circulating independent of the heavy chains. It could be used in various clinical scenarios and, most importantly, it has prognostic value for all plasma cell disorders.

Currently FLC has no value in the routine monitoring of active multiple myeloma. However, it makes it easier to follow patients with oligosecretory myeloma, amyloidosis or light chain disease, and it should be used in those settings.

The Use of Bisphosphonates in Multiple Myeloma: Recommendations of an Expert Panel on Behalf of the European Myeloma Network

Terpos E et al.

Ann Oncol 2009; 20(8): 1303-17.

Introduction

- Bone destruction occurs in 90% of patients with MM (*Oncologist* 2007;12:62).
- Bisphosphonates have become the standard of care in MM to reduce and delay the skeletal morbidity.
- Recommendations developed by an expert panel after multiple rounds of review of associated evidence are summarized.

Major Double Blind Trials of Bisphosphonates in MM

Bisphosphonate/ Control	Manuscript	N	Reduction of pain	Reduction of skeletal related events (SRE)
Pamidronate (IV) vs Placebo	<i>JCO</i> 1998;16:593	392	Yes	Yes
Zoledronic Acid (IV) vs Pamidronate (IV)	<i>Cancer</i> 2001;91:1191	108	Yes	Yes
Zoledronic Acid (IV) vs Pamidronate (IV)	<i>Cancer</i> 2003;98:1735	513	Yes	Yes

Renal Impairment with Bisphosphonates

- Serum creatinine should be monitored before each dose.
- Patients with renal impairment should have creatinine clearance rates, serum electrolytes and albuminuria also monitored.
 - Moderate renal impairment (creatinine clearance 30-60 mL/min):
 - Lower doses and longer infusions of pamidronate
 - Lower doses with no changes in infusion time with zoledronic acid
 - Severe renal impairment (creatinine clearance < 30 mL/minute): Should not receive bisphosphonates

Osteonecrosis of Jaw (ONJ) with Bisphosphonates

- Preventive dentistry with ongoing dental evaluation has shown a 75% reduction in ONJ (*Annals of Oncology* 2009; 20: 137).
- A comprehensive dental examination should be done before initiating bisphosphonates.
- Existing/high-risk dental conditions should be treated before starting bisphosphonates.
- Bisphosphonates should be stopped if a patient develops ONJ.

Summary

- Bisphosphonates should be administered to patients with MM with osteolytic lesions or osteopenia.
 - Bisphosphonates should be continued for 2 years, and administration beyond 2 years is not recommended.
- After 2 years, bisphosphonates should be reinitiated in patients with pain or documented progression in bone involvement.
- Patients with MGUS, asymptomatic multiple myeloma or solitary plasmacytoma should not receive bisphosphonates.

Faculty Comments

DR GIRALT: The European Myeloma Network convened an expert panel to discuss the use of bisphosphonates for patients with multiple myeloma. The panel recommends continuing bisphosphonates for two years for most patients with myeloma and emphasizes the need for initial and ongoing renal and dental evaluation in patients receiving bisphosphonates.

Faculty Comments (Continued)

DR JAGANNATH: Not all experts will agree that administration of bisphosphonates beyond two years is not to be recommended.

Evidence for benefit beyond two years may be difficult to generate in this setting, and a less frequent bisphosphonate administration might be considered.

In contrast, if a patient has attained CR after therapy with novel agents or transplant, he or she has no need to continue monthly therapy for two years.

My opinion, and that endorsed by the IMWG, is that frequency of administration could be reduced after less than two years for patients attaining CR.