Management of Multiple Myeloma: The Changing Paradigm

Myeloma 101: Disease Overview, Prognosis, and Risk

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Multiple Myeloma Today

10% of all cancers are blood cancers

By comparison, 224,000 new lung cancer cases/year; 249,000 new breast cancer cases/year

CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.


What Is Multiple Myeloma?

Proliferation of monoclonal plasma cells, associated with production of monoclonal protein (immunoglobulin), and end organ damage

*Updated diagnostic criteria (2014) also includes ≥ 60% plasma cells in bone marrow; abnormal free light chain ratio ≥ 100; or > 1 focal lesion on MRI

Spectrum of Plasma Cell Dyscrasias

Symptomatic

No symptoms

Multiple myeloma

Smoldering multiple myeloma

Defined by M protein ≥ 3 g/dL and/or 24-hour urine M protein ≥ 0.5 g/day and/or bone marrow ≥ 10% plasma cells
15% of myeloma cases
10% risk of progression/year to active myeloma

Monoclonal gammopathy of unknown significance

• Precursor condition to myeloma
• Present in 3% of individuals over age of 50
• 1% risk of progression/year to multiple myeloma or related conditions
Effects of Myeloma and Common Signs and Symptoms

- **Low blood counts**
  - Anemia is present in 73% of patients at diagnosis

- **Decreased kidney function**
  - Present in 19% of patients at diagnosis; sometimes requiring dialysis; affects 50% of patients over course of illness

- **Bone damage**
  - Affects 79% of patients
  - Common sites include spine, pelvis, and ribs
  - Leads to fractures

- **Bone turnover**
  - May lead to high levels of calcium in blood (hypercalcemia); 13%

*About 10% of patients with newly diagnosed myeloma will not have any symptoms (smoldering multiple myeloma).*

- **Weakness**
- **Fatigue**
- **Infection**
- **Weakness**
- **Bone pain**
- **Loss of appetite**
- **Weight loss**

Key Considerations for Optimal Disease Management

1. Laboratory and imaging tests, tissue banking, and diagnosis
2. Staging and prognosis
3. Consider a second opinion
4. Know the standard of care
5. Consider clinical trials


Accessed April 14, 2016.
**Types of Monoclonal Protein (M Protein) in Multiple Myeloma**

- **Intact immunoglobulin** (for example, IgGκ, IgAλ, etc)
  - 80% of myeloma cases
- **Light chain only**
  - Also known as Bence Jones protein
  - 20% of all myeloma cases
  - Renal failure more common in light chain multiple myeloma; creatinine >2 mg/dL in 1/3 of cases
- **No monoclonal protein present (non-secretory)**
  - 3% of cases of multiple myeloma

**Measurement of monoclonal protein: how to interpret laboratory results**
Serum protein electrophoresis

Example of a normal serum protein electrophoresis
No abnormal protein band is present

Serum protein electrophoresis

Bone marrow

Plasma cells
(a type of white blood cell)

Diverse range of antibodies or immunoglobulins (which are a type of protein)

Serum protein electrophoresis
Normal
In plasma cell dyscrasias...

**Monoclonal proliferation of plasma cells**
- Normal, polyclonal plasma cell
- Monoclonal plasma cell

**Monoclonal immunoglobulin present**

- Monoclonal spike on serum protein electrophoresis (SPEP)
- Normal SPEP

Measurement of monoclonal protein

**Serum protein electrophoresis**
- Shows an abnormal band in 82% of myeloma patients
- Sensitive to ~0.5 g/dL of M protein

IgG kappa monoclonal spike, 4.14 g/dL.

Adding **serum immunofixation** increases sensitivity to 93%
- Sensitivity 0.15 g/dL
- SPEP and immunofixation **not sensitive** for light chain myeloma

Adding **urine protein electrophoresis and immunofixation** increases sensitivity to 97% (e.g. identifying 20% of light chain multiple myeloma cases **not detected** by SPEP and immunofixation)
Serum Free Light Chain Assay

Nephelometric/turbidimetric latex assay

SPEP + immunofixation + SFLC sensitivity >99%

Diagnosing Myeloma: Learn Your Labs

Blood Tests

- CBC: Number of red blood cells, white blood cells, and platelets
- CMP: Measure levels of albumin, calcium, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and creatinine. Assess function of kidney, liver, and bone status and the extent of disease.
- B2M: Determine the level of a protein that indicates the presence/extent of MM and kidney function; part of ISS staging system
- SPEP: Detect the presence and level of M protein in serum
- IFE: Identify the type of M protein
- SFLC: Serum free light chain assay measures free light chains (kappa or lambda)

CBC, complete blood count; CMP, complete metabolic panel; B2M, beta-2 microglobulin; SPEP, serum protein electrophoresis; IFE, immunofixation electrophoresis; SFLC, serum free light chain assay
Diagnosing Myeloma: Learn Your Labs

Urine Tests

- **UPEP (Urine Protein Electrophoresis)**
  - Detect Bence Jones proteins (also known as myeloma light chains)
  - Determine the presence and levels of Bence Jones protein

24-hr Urine Analysis

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Diagnosing Myeloma: Know Your Imaging Tests

- **Conventional x-rays** reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.
- **MRI** is more sensitive for lesions.
- **CT and PET/CT** are also more sensitive than conventional x-rays.
Diagnosing Myeloma: Know Your Bone Marrow Tests

**Bone Marrow Aspiration and Biopsy**
- Jamshidi needle
- Bone marrow
- Hip bone
- Skin

**Conventional Cytogenetic Analysis**
- Karyotyping
- FISH (fluorescence in situ hybridization)

**Bone Marrow Aspiration and Biopsy**
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**Conventional Cytogenetic Analysis**
- Karyotyping
- FISH (fluorescence in situ hybridization)

How Do We Match the Right Myeloma Medicines to Each Patient? *Precision Medicine*

Personalizing medical care with DNA testing of many different genes (genomics) at the same time

**Bone marrow tissue samples**
- Newly diagnosed → relapse

**Genomic testing**
- Gene expression profiling (GEP)
- Whole-genome/whole-exome sequencing

**Tailored treatment**
MMRF CoMMpass Study: Advancing Personalized Medicine Research

- Landmark study focusing on the genomics of myeloma
- Goals:
  - Learn which patients respond best to which therapies
  - Achieve better treatments targeted to each patient's biological makeup
- 1,000 newly diagnosed patients will be followed for at least 8 years

For more information call the MMRF at 866-603-6628 or visit www.themmmrf.org.

Know Your Myeloma Genomics

- Tissue banking (New diagnosis to relapse)
- What tests are available?
- Is it available to me?
- Interpreting results
Putting the Results Together

Imaging results
Blood and urine test results
Bone marrow analysis
Genomics

Staging and Prognosis

Staging myeloma
Historically, Durie-Salmon staging system used (1975)

Utility of Durie-Salmon staging limited due to subjective assessment of bone lesions

International Staging System

Published in 2005

Relies on two laboratory results from blood:
1. Albumin
2. β2 microglobulin

Current Multiple Myeloma Staging: International Staging System (ISS)


Stage II

Neither stage I nor stage III

Stage I

Stage III

B2M = β2 microglobulin

B2M < 3.5 mg/dL

Albumin ≥3.5 g/dL

Stage I

Stage II

Stage III

B2M > 5.5

Revised ISS Incorporates High-Risk Chromosomal Abnormalities and Elevated LDH

Standard Risk Factors for MM and the R-ISS

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>ISS stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Serum β2-microglobulin &lt; 3.5 mg/L, serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td>II</td>
<td>Not ISS stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2-microglobulin ≥ 5.5 mg/L</td>
</tr>
<tr>
<td>CA by iFISH</td>
<td>Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)</td>
</tr>
<tr>
<td>High risk CA</td>
<td>No high-risk CA</td>
</tr>
<tr>
<td>Standard risk</td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>Serum LDH &lt; the upper limit of normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Serum LDH ≥ the upper limit of normal</td>
</tr>
<tr>
<td>High</td>
<td></td>
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<tr>
<td>A new model for risk stratification for MM R-ISS</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>ISS stage I and standard-risk CA by iFISH and normal LDH</td>
</tr>
<tr>
<td>II</td>
<td>Not R-ISS stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>ISS stage III and either high-risk CA by iFISH or high LDH</td>
</tr>
</tbody>
</table>

High risk chromosomal abnormalities (detected by FISH):
- del(17p)
- t(4;14)
- t(14;16)

CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, Revised International Staging System

Palumbo et al., J Clin Oncol 2015
How Aggressive Is My Myeloma?

Risk Level* (Degree of Aggressiveness)

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
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<tr>
<td>Patients affected (%)</td>
<td>80</td>
<td>60</td>
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</table>

**High Risk**
- FISH: del 17p
- FISH: t(14;16)
- FISH: t(14;20)
- GEP: High-risk signature

**Intermediate Risk**
- FISH: t(4;14)*

**Standard Risk**
- Cytogenetic: del 13 or hypodiploid
- PCLI ≥ 3%
- All others including:
  - Hyperdiploid
  - t(11;14)
  - i(16)

Currently cannot predict with great certainty all high-risk patients

*Based on the Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013

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After Establishing a MM Diagnosis, Find Out From Your Doctor...

- What type of myeloma do I have?
- What is my myeloma stage?
- Do I have any cytogenetic abnormalities?
- What is my long-term prognosis?
- Can I bank my bone marrow tissue for future analysis and precision medicine?*
- What treatment options should I consider?

*Tissue banking may not be an option at some oncology offices
Question

ISS staging (2005) requires results from which of the following studies?
1. Blood
2. Urine
3. X-rays (skeletal survey), CT scans, and/or MRI
4. Bone marrow biopsy

Answer Options
A. 1 only
B. 1 and 2
C. 1, 2, and 4
D. 3 and 4
E. All of the above

Treatment Overview
Overview of Treatment Approach

MGUS
Close monitoring (observation)

Smoldering myeloma
Close monitoring (observation)
If high risk: possible myeloma drugs (as part of a clinical trial)

Active myeloma
Initial therapy
• Myeloma drugs
• High-dose chemotherapy/ stem cell transplantation (option, if eligible)
Maintenance option
Therapies for relapsed/ refractory myeloma

If bone loss: bisphosphonates
Bone loss: bisphosphonates + other supportive treatments

Clinical trial participation should be considered

Evolution of Multiple Myeloma Treatment: 10 New Drugs Approved in ≤12 Years

Conventional Therapy
High-dose chemotherapy (melphalan) with autologous bone marrow transplant
High-dose chemotherapy (melphalan) with autologous stem cell support

“Novel” Therapies
Bortezomib
Lenalidomide
Carfilzomib
Pomalidomide
VAD
Melphalan and prednisone
High-dose dexamethasone
Bisphosphonates

Chemotherapy Steroid
IRAK Proteasome inhibitor
HDAC inhibitor Transplant
Monoclonal Antibody Bone support

VAD, vincristine, doxorubicin, dexamethasone; IMD, immunomodulatory drug; HDAC, histone deacetylase.
**Currently Available Therapies Targeting Myeloma Cells**

**Targeted Therapies**
- Bortezomib (Velcade)
- Carfilzomib (Kyprolis)
- Panobinostat (Farydak)
- Ixazomib (Ninlaro)

**Immunotherapies**
- Thalidomide (Thalomid)
- Lenalidomide (Revlimid)
- Pomalidomide (Pomalyst)
- Daratumumab (Darzalex)
- Elotuzumab (Empliciti)

**Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets**

Novel Therapies and Immunotherapy

PLD, pegylated liposomal doxorubicin; IMiD, immunomodulatory drug; HDAC, histone deacetylase; CDK, Cyclin D kinase; SINE, selective inhibitor of nuclear export; BCMA, B cell maturation antigen

*Not yet FDA-approved; only available in clinical trials
†Treatments studied in MMRC trials
‡FDA-approved for a non-MM indication
Summary

- Multiple myeloma can have numerous effects on the body
- Genomics is growing and may lead to personalized treatments
- Survival improving because of new drugs and new combinations of drugs
- Treatment paradigm will continue to change with the approval of additional novel agents

Be an informed and empowered patient!

Thank you for your time!

MMRF Resources

- Multiple Myeloma Disease Overview brochure
- Multiple Myeloma Treatment Overview brochure
- MMRF CoMMunity Gateway www.mmrfcommunitygateway.org