Management of Multiple Myeloma: The Changing Paradigm

Myeloma 101: Disease Overview

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Disclosures

• No Disclosures
“Mollities Ossium” Case #1

Sarah Newbury (1844)
- 1st Documented Myeloma Patient
- Treated with infusion of orange peel and rhubarb pill with opiates at night
- Autopsy revealed the cancellous part of her sternum was replaced by a “peculiar red matter”

“Mollities Ossium” Case #2

Thomas Alexander McBean (1850)
- Initially treated with bleeding and leeches, then steel and quinine
- Urine sample sent to Dr. Henry Bence Jones, who noted presence of large amounts of unusual protein
- Autopsy revealed soft, brittle bones, replaced by large, round, clear cells

Key Early Milestones

Plasma cells (1875)
Bone marrow biopsy (1929)
Serum Protein Electrophoresis (1930)
Melphalan (1958)
Monoclonal Protein (1961)
Prednisone (1962)
Evolution of Multiple Myeloma Treatment: 10 New Drugs Approved in ≤12 Years

Conventional Therapy

- High-dose melphalan
- Melphalan and prednisone
- High-dose dexamethasone
- VAD

Novel Therapy

- Revlimid
- Thalomid
- Velcade
- Doxil
- Kyprolis
- Ninlaro
- Pomalyst
- Farydak
- Empliciti
- Darzalex

Chemotherapy
- VAD, vincristine, doxorubicin, dexamethasone
- IMiD, immunomodulatory drug
- HDAC, histone deacetylase

Steroid
- High-dose dexamethasone

Transplant
- High-dose chemotherapy with autologous stem cell support
- High-dose chemotherapy with autologous bone marrow transplant

Proteasome inhibitor
- Bisphosphonates

Bone support
- Melphalan and prednisone

VAD, vincristine, doxorubicin, dexamethasone; IMiD, immunomodulatory drug; HDAC, histone deacetylase.
Multiple Myeloma Today

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


Agenda

• Historical Background
• Epidemiology
• **Pathobiology**
• Clinical Presentation
• Diagnostic Work-up
• Diagnostic Criteria
• Risk Stratification
• Treatment
What Is Multiple Myeloma?

Malignant Clonal Proliferation of Plasma Cells
Plasma Cell

Heavy Chain (IgG, IgM, IgA, IgD, IgE)

Light Chain (Lambda or Kappa)

Unique Antigen Binding Site

Initiating Genetic Event

Plasma Cell
Progression to Multiple Myeloma

Monoclonal Gammopathy Undetermined Significance (MGUS) → Smoldering Myeloma → Multiple Myeloma

Premalignant

Primary initiating events:

- IGH translocations
- Hyperdiploidy

Malignant

Secondary genetic events:

- Acquired mutations
- Copy number alterations

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Effects of Myeloma and Common Symptoms

Low Blood Counts
- Anemia is present in 60% of patients at diagnosis
- May lead to anemia and infection

Decreased Kidney Function
- Occurs in over half of myeloma patients

Bone Damage
- Affects 85% of patients
- Common sites include spine, pelvis, and ribs
- Leads to fractures

Bone Turnover
- Leads to high levels of calcium in blood (hypercalcemia)

About 10% to 20% of patients with newly diagnosed myeloma will not have any symptoms.
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Diagnosing Myeloma: Learn Your Labs!

Blood Tests

CBC
- Number of red blood cells, white blood cells, and platelets
- 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.

CMP
- Determine the level of a protein that indicates the presence/extent of MM and kidney function

B2M
- Detect the presence and level of M protein

SPEP
- Identify the type of abnormal antibody proteins

IFE
- Freelite® test measures light chains (kappa or lambda)

SFLC

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**
  - Detect Bence Jones proteins (otherwise known as myeloma light chains)

- **24-hr Urine Analysis**
  - Determine the presence and levels of M protein and Bence Jones protein

**UPEP**, urine protein electropheresis
Serum Protein Electrophoresis

Monoclonal protein

Myeloma Patient

Normal Patient
Diagnosing Myeloma: Know Your Imaging Tests!

Assess changes in the bone structure and determine the number and size of tumors in the bone.

**X-ray**

Conventional x-rays reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.

**MRI**

MRI & PET/CT appear to be more sensitive (85%) than skeletal x-rays for the detection of small lytic bone lesions.

**CT scan**

**PET scan**
Diagnosing Myeloma: Know Your Bone Marrow Tests!

- **Bone Marrow Aspiration and Biopsy**
  - Jamshidi needle

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

- **Bone Marrow**
- **Hip bone**
- **Skin**

- **Chromosome**

- **MM cell**
How Do We Match the Right Myeloma Medicines to Each Patient?

*Precision Medicine*

- Gene expression profiling (GEP)
- Whole-genome/whole-exome sequencing
- Next-generation sequencing

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
- Next-generation sequencing

Tailored treatment
Putting the Results Together

Diagnosis, Staging, and Prognosis

- Imaging results
- Bone marrow analysis
- Blood and urine test results
- Genomics
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Myeloma Diagnostic Criteria

- Monoclonal Gammopathy: Undetermined Significance (MGUS)
- Smoldering Myeloma
- Multiple Myeloma

Premalignant to Malignant
**2014 IMWG Myeloma Diagnostic Criteria**

<table>
<thead>
<tr>
<th>Multiple Myeloma</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma AND</td>
</tr>
<tr>
<td></td>
<td>● Evidence of end-organ damage attributed to a plasma cell disorder as defined by CRAB⁠¹ criteria</td>
</tr>
<tr>
<td></td>
<td>OR ≥ 1 biomarkers of malignancy which include bone marrow clonal plasmacytosis ≥ 60%, involved:uninvolved serum free light chains ≥ 100, or ≥ 1 focal lesion on MRI studies that is at least 5 mm in size.</td>
</tr>
</tbody>
</table>

**New in 2014**

**START TREATMENT!**

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⁠¹CRAB Criteria:
1) HyperCalcemia: Serum calcium > 1 mg/dL above the upper limit of normal or > 11 mg/dL
2) Renal insufficiency: creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL
3) Anemia: hemoglobin < 2 g/dL below the lower limit of normal or < 10 g/dL
4) Bone lesions: one more osteolytic lesions on skeletal survey, CT scan, or PET-CT

Myeloma Defining Events

SLiM CRAB

Sixty percent or greater clonal plasmacytosis
Light chain ratio ≥ 100
MRI changes
HyperCalcemia
Renal insufficiency
Anemia
Bone lesions
# 2014 IMWG Myeloma Diagnostic Criteria

<table>
<thead>
<tr>
<th>Definition</th>
<th>Myeloma Progression Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal gammopathy of undetermined significance (MGUS)</strong></td>
<td>1% per year</td>
</tr>
<tr>
<td>▪ Monoclonal protein &lt; 3 grams/dL</td>
<td></td>
</tr>
<tr>
<td>▪ Clonal bone marrow plasma cells &lt; 10%</td>
<td></td>
</tr>
<tr>
<td>▪ Absence of myeloma defining event or amyloidosis</td>
<td></td>
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**OBSERVATION**

| Smoldering Multiple Myeloma                                               |                          |
| ▪ Serum monoclonal protein ≥ 3 grams/dL or urinary monoclonal protein ≥ 500 mg/24 hrs and/or bone marrow plasmacytosis 10-60% |                          |
| ▪ Absence of myeloma defining event or amyloidosis                       |                          |

**OBSERVATION (OR TREATMENT ON CLINICAL PROTOCOL)**

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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
### Myeloma International Staging System (ISS)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Parameters</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Albumin $&gt; 3.5$ g/dL and $\beta$-2 microglobulin $&lt; 3.5$ mg/L</td>
<td>62 months</td>
</tr>
<tr>
<td>Stage II</td>
<td>Neither Stage I or Stage III</td>
<td>44 months</td>
</tr>
<tr>
<td>Stage III</td>
<td>$\beta$-2 microglobulin $&gt; 5.5$ mg/L</td>
<td>29 months</td>
</tr>
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</table>

*Applies only to newly diagnosed myeloma patients*
### Revised ISS (R-ISS) – NEW 2015

<table>
<thead>
<tr>
<th>R-ISS Stage</th>
<th>Parameters</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td>ISS Stage I AND 1) Standard risk cytogenetics AND 2) Normal LDH</td>
<td>Not reached</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>Not R-ISS Stage I or III</td>
<td>83 months</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>ISS Stage III AND 1) High-risk cytogenetics OR 2) Elevated LDH</td>
<td>43 months</td>
</tr>
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High-risk cytogenetics = del 17p, t(4;14), and/or t(14;16)  
Standard-risk cytogenetics = no high-risk cytogenetics


95% of patients received IMiDs or proteasome inhibitors

Greipp et al. *JCO*. 2005
How Aggressive Is My Myeloma?

Risk Level* (Degree of Aggressiveness)

- **High Risk**
  - Survival: 0-2 years
  - Patients affected (%): 60
  - FISH: del 17p, t(14;16), t(14;20)
  - GEP: High-risk signature

- **Intermediate Risk**
  - Survival: 3-4 years
  - Patients affected (%): 40
  - FISH: t(4;14)*

- **Standard Risk**
  - Survival: 4-5 years
  - Patients affected (%): 20
  - Cytogenetic: del 13 or hypodiploid, PCLI ≥3%
  - All others including:
    - Hyperdiploid
    - t(11;14)
    - t(6;14)

Currently cannot predict with great certainty all high-risk patients

Know Your Myeloma Genomics

Tissue banking (NDMM to RRMM)

What tests are available?

Is it available to me?

Interpreting results
MMRF CoMMpass<sup>SM</sup> 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.
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2016 Myeloma Standard of Care Treatment

MGUS

Close monitoring (observation)

SMM

Close monitoring (observation)
If high risk: possible myeloma drugs?

Active myeloma

If bone loss: bisphosphonates

Bone loss: bisphosphonates + other supportive treatments

Clinical trial participation should be considered.
Key Considerations for Optimal Disease Management

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

Multiple myeloma is a malignant clonal proliferation of plasma cells.

Myeloma can be preceded by the precursor stages MGUS and smoldering myeloma.

Myeloma classically presents with one or more CRAB signs/symptoms.

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!
MMRF Resources

Multiple Myeloma Disease Overview brochure

Multiple Myeloma Treatment Overview brochure

MMRF CoMMunity Gateway
www.mmrfcommunitygateway.org