MULTIPLE MYELOMA 101

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What is multiple myeloma?

Multiple myeloma is a type of blood cancer that affects plasma cells, a type of white blood cell. In multiple myeloma, these cells become cancerous and start growing uncontrollably in the bone marrow, where they produce abnormal proteins called M proteins. These proteins can circulate in the blood and affect various organs and systems in the body.

Key points:
- Normal plasma cells
- Multiple myeloma cells
- Bone
- Bone marrow
- Light chain
- Heavy chains
- Antibodies
- M proteins
Myeloma in Mummies

Ancient affliction. A high-resolution CT scan of the lumbar spine region of a 2150-year-old Egyptian mummy revealed small, round lesions.
How common is multiple myeloma?

- 2nd most common cancer of the blood
- 30,280 new cases in 2017
- 103,463 living with, or in remission
- Myeloma represents 1.8% of all new cancer cases in the U.S.
- Myeloma is most frequently diagnosed among people aged 65-74
- Median age at diagnosis 69

MM: Epidemiology

- 30,280 new cases/year
- 11,240 deaths/year
- 104,000 patients alive with MM/year
- Median age 70 years
- Slowly increasing incidence
- Males > Females (57:43)
- 1.8% of all malignancies
  - 10% of all hematologic malignancies
  - 20% in African-Americans
Etiology: Risk Factors for MM

- Chronic exposure to low-dose ionizing radiation (? Radon)
- Occupational exposure (e.g. chemical)
- Genetic factors-increase MGUS risk in families
- Chronic antigenic stimulation (eg, recurrent infections and drug allergies)
- Agent orange, 9/11 exposure
- Ultimately, we do not know why patients develop MM
Small inherited risk

- Landgren et al First degree relatives of 4488 Swedish MGUS pts had increased relative risk of:
  - MGUS 2.84 (1.45-5.57)
  - WM 4.94 (1.32-18.46)
  - MM 2.87 (1.92-4.27)
  - CLL 2.05
- No increased risks of NHL, HD
- Incidence in African Americans 17.4
Monoclonal Gammopathy of Undetermined Significance (MGUS)

- 3.5% of all 50 year olds
- ~10% of 80 year olds
- Dysregulation of normal immune system
- BENIGN
Prevalence of Monoclonal Gammopathy of Undetermined Significance (MGUS) in Men and Women by Age (1A) and by race and ethnicity (1B)
ALL MGUS IS NOT CREATED EQUAL

Risk Factors for Potential Malignancy

- Type of paraprotein (e.g. IgG)
- Amount of paraprotein (> 1.5 g)
- Free light chain ratio (0.26 to 1.65)

Risk at 20 years ranges
- 5% (no risk factors)
- 27% (two risk factors)
- 58% (three risk factors)
Smoldering Myeloma
Smoldering Myeloma

• No symptoms; no related organ/tissue impairment
• New criteria for smoldering myeloma\(^1\)
• 10% to 20% of newly diagnosed myeloma\(^2\)
• Can remain indolent for yrs
• Progression rate: ~ 50% at 5 yrs\(^3\)
  – Progression rate in high-risk subgroup: 80% at 2 yrs\(^4\)

Smoldering Multiple Myeloma

Biomarkers to Predict Risk of Progression

FLC ratio ≥ 100 predicts risk ($P < .0001$)

Clonal plasma cells in BM predicts risk ($P < .001$)

**Updated IMWG Criteria for Diagnosis of Multiple Myeloma**

<table>
<thead>
<tr>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein &lt; 3 g/dL</td>
</tr>
<tr>
<td>Clonal plasma cells in BM &lt; 10%</td>
</tr>
<tr>
<td>No myeloma defining events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoldering Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein $\geq$ 3 g/dL (serum) or $\geq$ 500 mg/24 hrs (urine)</td>
</tr>
<tr>
<td>Clonal plasma cells in BM $\geq$ 10% to 60%</td>
</tr>
<tr>
<td>No myeloma defining events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple Myeloma</th>
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</thead>
<tbody>
<tr>
<td>Underlying plasma cell proliferative disorder</td>
</tr>
<tr>
<td>AND 1 or more myeloma defining events</td>
</tr>
<tr>
<td>$\geq$ 1 CRAB* feature</td>
</tr>
<tr>
<td>Clonal plasma cells in BM $\geq$ 60%</td>
</tr>
<tr>
<td>Serum free light chain ratio $\geq$ 100</td>
</tr>
<tr>
<td>$&gt;$ 1 MRI focal lesion</td>
</tr>
</tbody>
</table>

* C: Calcium elevation ($> 11$ mg/dL or $> 1$ mg/dL higher than ULN)
  R: Renal insufficiency (creatinine clearance $< 40$ mL/min or serum creatinine $> 2$ mg/dL)
  A: Anemia (Hb $< 10$ g/dL or 2 g/dL < normal)
  B: Bone disease ($\geq 1$ lytic lesions on skeletal radiography, CT, or PET-CT)

MM: Clinical Manifestations

Series of genetic mutations, translocations, normal cell turns malignant
Hallmarks of myeloma: CRAB (also known as myeloma defining events)

A = Anemia

C = Hypercalcemia

R = Renal Complications

B = Bone Disease

Recurrent infections*

* Not an MDE, yet relatively common

Effects of Myeloma and Common Symptoms

About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.

- Low blood counts
  - Weakness
  - Fatigue
  - Infection

- Decreased kidney function
  - Weakness

- Bone damage
  - Bone pain

- Bone turnover
  - Loss of appetite
  - Weight loss

Diagnostic Workup

**Lab tests:**
- Serum protein electrophoresis (SPEP)
- Urine protein electrophoresis (UPEP)
- Complete metabolic panel (CMP)
- CBC + differential
- Plasma ratio of free kappa/lamba light chains
- Monoclonal protein analysis (MPA)

**Bone marrow biopsy:**
- FISH, cytogenetics, and gene expression profiling (GEP)

**Imaging:**
- Skeletal survey
- MRI, CT
- PET scan ± MRI, CT

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)

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

- Detect Bence Jones proteins (otherwise known as myeloma light chains)
- Determine the presence and levels of M protein and Bence Jones protein

UPEP, urine protein electrophoresis
Types of Monoclonal Protein (M Protein) in Multiple Myeloma

**Intact immunoglobulin**
- For example:
  - IgG+kappa
  - IgG+lambda
  - IgA+kappa
  - IgA+lambda
  - 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

**Non-secretory**
- No monoclonal protein present
- 3% of cases of multiple myeloma
Monoclonal Protein—M Spike

- Amount/type of M protein varies among patients (IgG, IgA 80% of cases)
- Abnormal M protein (immunoglobulin [Ig]) loses immune function and adheres and binds to tissues
Immunofixation to Determine Type of Monoclonal Protein

IgG kappa M protein

Lambda Light Chains

Kyle RA and Rajkumar SV. Cecil Textbook of Medicine, 22nd Edition, 2004
Intact Immunoglobulin

Free Light Chain

FLC reference range:
κ 3.3 – 19.4 mg/L
λ 5.7 – 26.3 mg/L
κ/λ ratio 0.26 - 1.65
Myeloma Cells
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 and 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

Bone marrow
Hip bone
Skin

Chromosome

Conventional cytogenetic analysis
Karyotyping

FISH (fluorescence in situ hybridization)

Myeloma cell
### How aggressive is my myeloma?

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Standard Risk(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-risk genetic abnormalities(^{a,b})</td>
<td>• All others including:</td>
</tr>
<tr>
<td>- t(4;14)</td>
<td>- Trisomies</td>
</tr>
<tr>
<td>- t(14;16)</td>
<td>- t(11;14)</td>
</tr>
<tr>
<td>- t(14;20)</td>
<td>- t(6;14)</td>
</tr>
<tr>
<td>- Del 17p</td>
<td></td>
</tr>
<tr>
<td>- p53 mutation</td>
<td></td>
</tr>
<tr>
<td>- Gain 1q</td>
<td></td>
</tr>
<tr>
<td>• RISS Stage 3</td>
<td></td>
</tr>
<tr>
<td>• High plasma cell S-phase(^c)</td>
<td></td>
</tr>
<tr>
<td>• GEP: high-risk signature</td>
<td></td>
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</tbody>
</table>

- Double-hit myeloma: any two high-risk genetic abnormalities
- Triple-hit myeloma: three or more high-risk genetic abnormalities

**Currently cannot predict with great certainty all high-risk patients.**

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

\(^a\) Trisomies may ameliorate; \(^b\) By FISH or equivalent method; \(^c\) Cut-offs vary; \(^d\) t(11;14) may be associated with plasma cell leukemia

Technological advances in detecting biomarkers in multiple myeloma


G banding  FISH  Gene expression profiling  Global gene mapping  Next-generation sequencing

TC classification  Methylation miRNA

Hyperdiploid
Chromosome gain
3, 5, 7, 9, 11, 15, 19, 21

Translocations
\( t(14;16) \)
\( t(14;20) \)

Translocations
\( t(4;14) \)
\( t(11;14) \)
\( t(6;14) \)

Normal M/GUS MM
-30 -21 -13 -04 04 13 21 30

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CCR Reviews
# REVISED- International Staging System (ISS): Prognostic Groupings

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Stage I  | Serum $\beta_2$-microglobulin $<$ 3.5 mg/L  
Serum albumin $\geq$ 3.5 g/dL  
Standard risk cytogenetics  
Normal LDH |
| Stage II | Not R-ISS stage I or stage III                                           |
| Stage III| Serum $\beta_2$-microglobulin $\geq$ 5.5 mg/L and high risk cytogenetics by FISH or high LDH [t(4;14), t(14;16), 17p] |

Know the Diagnosis
Key Items That Define the Diagnosis

MGUS
- M protein <3 g/dL
- Clonal plasma cells in BM <10%
- No myeloma-defining events

1% risk of progression/year to multiple myeloma or related conditions

Smoldering Myeloma
- M protein ≥3 g/dL (serum) or ≥500 mg/24 hrs (urine)
- Clonal plasma cells in BM ≥10%–60%
- No myeloma-defining events

10% risk of progression/year to active myeloma

Multiple Myeloma
- Underlying plasma cell proliferative disorder
- AND ≥1 myeloma-defining events
- ≥1 CRAB* feature
- Clonal plasma cells in BM ≥60%
- Serum free light chain ratio ≥100
- >1 MRI focal lesion

*C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
A: Anemia (Hb <10 g/dL or 2 g/dL < normal)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

Putting the Results Together

- Imaging results
- Blood and urine test results
- Bone marrow analysis
- Genomics

Staging, and Prognosis
Multiple clones may be present at the time of diagnosis. The predominant clone may change over time, especially after treatment rounds. Hypothesis: effective treatment reduces or eliminates the dominant clone; however, other clones can still exist.

Relapse can occur when:

Existing clone no longer has to compete for space with the formerly dominant clone.

Acquires additional mutation(s) providing a growth and/or survival advantage.

Treatment Overview
Overview of Treatment Approach

MGUS
- Close monitoring (observation)

SMM
- 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 possible)
- Maintenance option
- Therapies for relapsed/refractory myeloma
- Bone loss: bisphosphonates + other supportive treatments

If bone loss: bisphosphonates

Clinical trial participation should be considered.
History of Treatment

• 1844: Rhubarb and infusions of orange peel for Sarah Newbury
• 1845: Phlebotomy, then leeches for maintenance therapy (William McBean)
• 1947: Urethane reported by Alwall
• 1958: Blohkin reports sarcolysin (melphalan) in 3 of 6 patients
• 1962: Bergsagel expands use of melphalan
• 1962: Maas report on prednisone
First Randomized Trial in MM

- A controlled trial of urethane treatment in multiple myeloma.
  
  Holland JR, Hosley H, Scharlau C, Carbone PR, Frei E 3rd, 
  Brindley CO, Hall TC, Shnider BI, 
  Gold GL, Lasagna L, Owens AH Jr, Miller SP.

- Randomized 83 patients with treated or untreated multiple myeloma to receive urethane or a placebo consisting of a cherry-and cola-flavoured syrup.

- No difference was seen in objective improvement or in survival in the two treatment groups. In fact, the urethane-treated patients died earlier.

Blood 1966; 27: 328-342
Fig. 1.—Survival from onset of treatment plotted by life table method in patients with multiple myeloma according to treatment category.

Table 7.—Median Survival from Onset of Treatment of Patients with Multiple as Influenced by Prior and Present Treatment

<table>
<thead>
<tr>
<th></th>
<th>Median Survival, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Urethane</td>
<td>8</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
</tr>
</tbody>
</table>

A = Prior urethane.
B = Other prior treatment.
C = No prior treatment.
Evolution of Multiple Myeloma Treatment: 11 New Drugs Approved in ≤15 Years

Conventional Therapy
- High-dose chemotherapy with autologous bone marrow transplant
- High-dose chemotherapy with autologous stem cell support
- VAD: vincristine, doxorubicin, dexamethasone
- IMiD, immunomodulatory drug
- HDAC, histone deacetylase
- High-dose dexamethasone
- Bisphosphonates
- High-dose melphalan
- Melphalan and prednisone

Novel Therapy
- Revlimid
- Thalomid
- Velcade
- Doxil
- Kyprolis
- Ninlaro
- Pomalyset
- Farydak
- Empliciti
- Darzalex
- Empliciti
- Darzalex
- Xgeva

VAD, vincristine, doxorubicin, dexamethasone; IMiD, immunomodulatory drug; HDAC, histone deacetylase.
Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets

**Novel Therapies and Immunotherapy**

- **2003**: Revlimid, Kyprolis, Thalomid
- **2006**: Velcade, Doxil
- **2007**: Pomalyst, Farydak
- **2010**: Ninlaro, Empliciti, Darzalex
- **2013**: Pomalyst, Farydak
- **2015**: Venetoclax, Isatuximab
- **2018**: Darzalex, Xgeva, Selinexor
- **2019+**: Anti-BCMA antibodies (GSK2857916, AMG 224)
- **2019**: Atezolizumab

**Key Classes and Targets**

- **IMiD**
- **Proteasome inhibitor**
- **HDAC inhibitor**
- **Chemotherapy**
- **Monoclonal antibody**
- **Adoptive T cell therapy**
- **Checkpoint inhibitors**
- **CDK inhibitor**
- **SINE**
- **Bone support**
- **Bcl-2 inhibitor**

**Abbreviations**

- PLD, pegylated liposomal doxorubicin; IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
- *Not yet FDA-approved; only available in clinical trials
- †Treatments studied in MMRC trials
- ‡FDA-approved for a non-MM indication
## Measuring Response to Therapy

A wide range of tests are used to measure response to therapy, including M-Protein Reduction and Immunofixation. The table below summarizes the tests used for different types of responses.

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Abbreviation</th>
<th>M-Protein Reduction</th>
<th>Immunofixation</th>
<th>Bone Marrow</th>
<th>Freelite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>sCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>VGR</td>
<td>&gt;90%</td>
<td>&lt;100 mg/24 hrs</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Partial response</td>
<td>PR</td>
<td>&gt;50%</td>
<td>&gt;90%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stable response</td>
<td>SD</td>
<td>Does not meet criteria for response or progressive disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>PD</td>
<td>An increase of 25% in M-protein; an increase of 10% in bone marrow plasma cells</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a complete response (CR).
Getting to Minimal Residual Disease (MRD): New Definitions for CR

S.S. Patient

Disease burden

- Newly diagnosed: $1 \times 10^{12}$
- $1 \times 10^8$
- $1 \times 10^4$
- 0.0

CR

Stringent CR

Molecular/Flow CR

?Cure?

Bortezomib
Lenalidomide Combinations
Minimal Residual Disease (MRD)

A

Progression-Free Survival (proportion)

Time Since MRD Assessment (months)

B

Overall Survival (proportion)

Time Since MRD Assessment (months)

\( \chi^2 = 68.4949 \)

\( P < .001 \)

\( \chi^2 = 40.1305 \)

\( P < .001 \)

No. at risk
Adverse; MRD+ 42
Adverse; MRD− 67
Favorable; MRD+ 53
Favorable; MRD− 79

No. at risk
Adverse; MRD+ 42
Adverse; MRD− 67
Favorable; MRD+ 53
Favorable; MRD− 79
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
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!