OBJECTIVES

- To explain the incidence, risk factors and spectrum of monoclonal gammopathies
- To explain the clinical scenarios in which to suspect multiple myeloma
- Explain the diagnostic methods for myeloma
- To discuss the latest diagnostic criteria and staging system for myeloma
- Talk briefly about the management of myeloma
MULTIPLE MYELOMA

- Multiple myeloma is a clonal plasma cell malignancy characterized by infiltration of bone marrow and end organ damage with or without the secretion of monoclonal protein in the serum and/or urine.
- Second most common hematological malignancy comprising 10% of all such diagnoses.
- Two thirds of patients are older than 65 years at diagnosis.

Prevalence of monoclonal gammopathies at Mayo clinic

![Monoclonal Gammopathies Mayo Clinic 1960-2006](image)
Risk factors for monoclonal gammopathies

- Race: Higher risk (twice) in African Americans compared to Caucasians

- Chemical and radiation exposure
  - Increased risk among those with pesticide exposure.

- Familial risk
  - Increased risk among first degree relatives

Incidence of myeloma

New cases 2016: 30,330
% of all cancers: 1.8%
5-year survival 2006-2012: 48.5%

Normal Plasma Cell Development

Risk factors for monoclonal gammopathies

- Older age
- Immunosuppression
- Genetic predisposition
- Environmental exposures
- Secondary cytogenetic and marrow related changes
Pathogenesis of multiple myeloma

Multistep Pathogenesis of Multiple Myeloma

<table>
<thead>
<tr>
<th>Multistep progressive</th>
<th>Intramedullary multiple myeloma</th>
<th>Intramedullary multiple myeloma</th>
<th>Extramedullary multiple myeloma</th>
<th>Plasma-cell leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploidy (50% of patients)</td>
<td>Secondary translocations</td>
<td>Non-hyperdiploidy (50% of patients)</td>
<td>Increased expression of cyclin D1, D2, and D3</td>
<td>Oncogenic activation or mutation (RAS, FGFR3)</td>
</tr>
<tr>
<td>Bone marrow microenvironment</td>
<td>Bone resorption</td>
<td>Angiogenesis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key facts about myeloma

1. Diagnosis most often ages 65-70
2. Men 2:1
3. African-Americans ~ 2:1
4. Worst quality of life of any cancer
5. Survival has improved over last 10 years
6. But still virtually incurable for most patients
7. Universally evolves from “pre-malignant” state

Approach to Gammopathy

- Is it monoclonal? [No → Rheumatologic or hepatic diseases]
- Is there adenopathy? [Yes → Non-Hodgkin’s lymphoma?]
- Calcium, kidneys, and Hemoglobin normal? [Yes → MGUS or SMM]
- Are there CRAB criteria? [Yes → Myeloma ???]
**Precursor conditions**
- MGUS
- “Smoldering” myeloma

**CRAB CRITERIA**
- Calcium → High calcium
- Renal → Renal (kidney) failure
- Anemia → Reduced red blood cells
- Bone → Bone fractures

“normal marrow”

Marrow with multiple myeloma

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**Progression to symptomatic myeloma**

**Risk Factors:**
1. Type of M protein
2. Higher M spike
3. Higher plasma cell burden
4. Abnormal FLC ratio

DIAGNOSIS OF MYELOMA

• Clonal bone marrow PC >= 10%
• Serum and/or urine monoclonal protein
• End organ damage or CRAB features
  ➢ Hypercalcemia
  ➢ Renal failure
  ➢ Anemia
  ➢ Bone disease

When to suspect myeloma

• High serum protein with low albumin
• Unexplained hypercalcemia or renal failure
• Pathological fractures
• Bone pain, unusual in nature
• Anemia, unexplained by other medical conditions
Examples of lytic bone disease

Table 1. Newly Added Criteria To Diagnose MM

| Clonal bone marrow plasma cells >10% or plasmacytoma plus one of these: | 2-y Incidence of Organ Damage, % |
| Clonal marrow plasma cells ≥60% | 95 |
| Serum free light chain ratio >100 | 80a |
| ≥ 2 focal bone lesions >5 mm on MRI | 70-80 |

* 27% had acute renal failure as the myeloma-defining event. **MM**, multiple myeloma; **MRI**, magnetic resonance imaging

Source: myelomacrowd.org
## UPDATED IMWG CRITERIA FOR MM

<table>
<thead>
<tr>
<th>MGUS</th>
<th>SMOLDERING MYELOMA</th>
<th>MULTIPLE MYELOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• M protein&lt;3 g/dL and</td>
<td>• M protein&gt;=3 g/dL(serum) or &gt;=500 mg/24 hr(Urine) or • BM clonal plasma cells&gt;10% to 60% and • No myeloma defining events</td>
<td>• Underlying plasma cell proliferation • And 1 or more myeloma defining events • At least 1 CRAB feature • BM clonal PC&gt;=60% • At least one focal bone lesion on MRI • SFLC ratio&gt;=100</td>
</tr>
<tr>
<td>• BM clonal plasma cells&lt;10% and</td>
<td>• BM clonal plasma cells&gt;10% to 60% and • No myeloma defining events</td>
<td></td>
</tr>
<tr>
<td>• No myeloma defining events</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C: Serum calcium >11 mg/dL or >1 mg/dL than ULN  
R: Serum creatinine >2 mg/dL or crcl<40 ml/min  
A: Hemoglobin< 10 g/dL or >2 g lower than their baseline  
B: >1 lytic bone lesion >/= 5 mm in size

## OSU initial diagnostic studies

- **Laboratory studies**  
  - CBC, electrolytes, kidney function, calcium, liver function tests  
  - B₂Microglobulin, Albumin for ISS assessment  
  - M-protein assessment – SPEP/IFE, UPEP/IFE, serum immunoglobulins, serum free light chains
- **Bone marrow biopsy, Myeloma FISH panel**  
- **Skeletal survey**  
- **Consider baseline MRI T-spine, L-spine, pelvis without contrast (gadolinium)**  
- **Consider PET**
Detection of monoclonal protein

- Serum protein electrophoresis [SPEP] is a screening procedure to detect and quantify monoclonal protein.
- Serum immunofixation [IFE] is essential to label the heavy and light chains of the monoclonal protein [IgG, IgA, IgM; kappa and lambda].
- IFE helps differentiate monoclonal from polyclonal immunoglobulin and has more sensitivity compared with SPEP.

Target of serum free light chain assay; kappa or lambda

Can be IgG, IgA or IgM

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Serum free light chains

• About one fifth of patients with myeloma produce only free light chains in the serum (Bence Jones proteins), and can be missed by routine immunofixation.
• SFLC assay is an antibody based system that can be used to diagnose light chain myeloma, systemic AL amyloidosis, light chain deposition disease

NORMAL
• Serum free kappa LC: 3.3 to 19.4 mg/L
• Serum free Lambda LC: 5.7 to 26.3 mg/L
• Serum FLC ratio: 0.26 to 1.65
• Can be elevated in advanced renal failure
• Ratio >3 is less likely to be from renal failure alone

Uses of serum FLC assay

• Detection of light chain myeloma, systemic AL amyloidosis, LCDD
• Predicting the risk of progression of MGUS, SMM and solitary plasmacytoma to MM
• Documenting stringent complete response after achieving CR
• Can replace 24 hr UPEP at initial diagnosis when performed with SPEP/IFE
**International Staging System (ISS)**

<table>
<thead>
<tr>
<th>Better Response to Therapy</th>
<th>Stage I</th>
<th>Most Favorable Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors: beta-2 microglobulin &lt;3.5 mg/dL</td>
<td>Albumin &gt;3.5 g/dL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesser Response to Therapy</th>
<th>Stage II</th>
<th>Less Favorable Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors: beta-2 microglobulin &lt;3.5 mg/dL</td>
<td>Albumin &lt;3.5 g/dL or beta-2 microglobulin ≥ 3.5 – &lt; 5.5 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

**International Staging System for Symptomatic Myeloma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>ß₂-M &lt; 3.5 mg/L and serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td>Stage II</td>
<td>Not stage I or III</td>
</tr>
<tr>
<td>Stage III</td>
<td>ß₂-M ≥ 5.5 mg/L</td>
</tr>
</tbody>
</table>

**ISS**

<table>
<thead>
<tr>
<th>ISS</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62 (58-65)</td>
</tr>
<tr>
<td>2</td>
<td>44 (42-45)</td>
</tr>
<tr>
<td>3</td>
<td>29 (26-32)</td>
</tr>
</tbody>
</table>

**Risk stratification of myeloma**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Percentage of newly diagnosed patients with the abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Risk</td>
<td>75%</td>
</tr>
<tr>
<td>Trisomies</td>
<td></td>
</tr>
<tr>
<td>t(11;14)</td>
<td></td>
</tr>
<tr>
<td>t(6;14)</td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>10%</td>
</tr>
<tr>
<td>t(4;14)</td>
<td></td>
</tr>
<tr>
<td>Gain(1q)</td>
<td></td>
</tr>
<tr>
<td>t(11;14)</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>15%</td>
</tr>
<tr>
<td>t(14;16)</td>
<td></td>
</tr>
<tr>
<td>t(14;20)</td>
<td></td>
</tr>
<tr>
<td>del(17p)</td>
<td></td>
</tr>
</tbody>
</table>

**Revised ISS**

- Goal was to incorporate FISH and cytogenetic abnormalities to make the staging system comprehensive and better predictive of prognosis.
- Presence of del(17p), t(4;14), or t(14;16) were considered high risk.

<table>
<thead>
<tr>
<th>R-ISS</th>
<th>ISS</th>
<th>iFISH</th>
<th>LDH</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>β2M &lt; 3.5, Alb ≥ 3.5</td>
<td>Standard</td>
<td>Normal</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>83 mos.</td>
</tr>
<tr>
<td>3</td>
<td>β2M ≥ 5.5</td>
<td>High risk or high</td>
<td></td>
<td>43 mos.</td>
</tr>
</tbody>
</table>

Palumbo A et al. Revised International Staging System for Multiple Myeloma: A report from the international myeloma working group. JCO 33, 3-Aug-2015.
Overall survival (OS) in patients with MM stratified by revised International Staging System (R-ISS)

Fig 1. (A) Overall survival (OS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm. Median OS was not reached for patients included in R-ISS stage I, whereas it was 83 months for R-ISS stage II and 43 months for R-ISS stage III. (B) Univariable analysis of OS. CA, chromosomal abnormalities; F, female; HR, hazard ratio; LDH, lactate dehydrogenase; M, male; NR, not reached.

Published in: Antonio Palumbo; Hervé Avet-Loiseau; Stefania Oliva; Henk M. Lokhorst; Hartmut Goldschmidt; Laura Rotolo; Paul Richardson; Simona Caltagirone; Juan José Lahuerta; Thierry Facon; Sara Brighetti; Francesca Gay; Michel Attal; Roberto Passera; Andrew Spencer; Massimo Offidani; Shaji Kumar; Pellegrino Musto; Sagar Lonial; Maria T. Petrucci; Robert Z. Orlowski; Elena Zamagni; Gareth Morgan; Meletios A. Dimopoulos; Brian G.M. Durie; Kenneth C. Anderson; Pieter Sonneveld; Jesús San Miguel; Michele Cavo; S. Vincent Rajkumar; Philippe Moreau; Journal of Clinical Oncology 2015, 33, 2863-2869. DOI: 10.1200/JCO.2015.61.2267

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Response criteria in myeloma

<table>
<thead>
<tr>
<th></th>
<th>PR</th>
<th>VGPR</th>
<th>nCR</th>
<th>CR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Protein electrophoresis</td>
<td>&gt; 50%</td>
<td>&gt;90%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urine Protein electrophoresis</td>
<td>&gt;90%</td>
<td>&lt; 100 mg/24 hrs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serum/Urime Immunofixation</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow PC</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow immunoflorescence</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Free light chain ratio</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Duri et al, Leukemia. 2006 Sep;20(9):1467-73
Immunomodulators

• IMiDs bind to cereblon and inhibits cereblon E3 ligase activity, resulting in cell cycle arrest through impaired DNA repair, replication and transcription.
• May cause direct cytotoxicity by inducing free radical mediated damage
• Also have antiangiogenic and TNF alpha inhibitory properties

Proteasome inhibitors

• Proteasomes are multienzyme complexes that help maintain protein homeostasis through clearance of misfolded/unfolded and cytotoxic proteins
• Bortezomib, being a proteasome inhibitor, inhibits proliferation and induces apoptosis in MM cells resistant to conventional therapies
• In combination with dexamethasone, it overcomes resistance to apoptosis conferred by IL-6 or adhesion to bone marrow stromal cells
**Pharmacology in myeloma**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CLASS</th>
<th>ROUTE</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (Velcade)</td>
<td>PI</td>
<td>SC</td>
<td>*PN, *VZV reactivation, cardiac, cytopenias, diarrhea, local pain</td>
</tr>
<tr>
<td>Carfilzomib (Kyprolis)</td>
<td>PI</td>
<td>IV</td>
<td>*Cardiovascular, pulmonary, renal, GI, cytopenias</td>
</tr>
<tr>
<td>Ixazomib (Ninlaro)</td>
<td>PI</td>
<td>Oral</td>
<td>PN, VZV reactivation, edema, cytopenias, diarrhea, *eye disease</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>IMId</td>
<td>Oral</td>
<td>CNS, *PN, DVT/PE, skin</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid)</td>
<td>IMId</td>
<td>Oral</td>
<td>*Thrombocytopenia, *DVT/PE, skin, GI</td>
</tr>
<tr>
<td>Pomalidomide (Pomalytst)</td>
<td>IMId</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Panobinostat (Farydak)</td>
<td>HDACi</td>
<td>Oral</td>
<td>Cardiac, diarrhea</td>
</tr>
</tbody>
</table>

**Choice of induction regimen**

- Three drug regimen standard for patients who are fit and eligible for auto SCT
- The triplet should include a PI and Dexamethasone, as PI have activity in high risk disease

- **Patient related**
  1. Age
  2. Performance
  3. Comorbidities: Peripheral neuropathy
     DM, CHF
  4. Resources

- **Disease related**
  1. Prognostic features – risk
  2. Disease presentation
  3. Organ impairment due to disease

- **Non-medical**
  1. Patient preferences
  2. Financial resources
  3. Availability of drug
Induction regimen

- **VRd** is the standard induction regimen for both transplant eligible and ineligible patients with NDMM.
- If Lenalidomide is not available for use as initial therapy or in the presence of ARF, other Bortezomib containing regimens such as VTd or VCd can be used instead of VRd.
- **Rd** is recommended for patients who are unable to tolerate a triplet regimen due to advanced age, comorbidities or poor PS.

Standard treatment for “fit” patients

1. Treatment until end organ damage reverses and good disease response is obtained (usually 3-4 months)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Mode</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Steroid</td>
<td>Pill weekly</td>
<td>insomnia, weight gain</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>IMiDs (immune modulating)</td>
<td>Pill daily</td>
<td>blood clots, diarrhea</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome Inhibitors</td>
<td>Shot 2x / wk subcutaneous</td>
<td>tingling numbness in hands or feet</td>
</tr>
</tbody>
</table>

2. Autologous stem cell transplant = High dose IV melphalan 6 weeks of drug prep prior to transplant; 16 day hospital stay (Leads to 30 months of remission on average)

3. Lenalidomide (pill) maintenance (Adds 18 months of remission on average)
### Standard treatment for “unfit” patients

1. Treatment until damaged organs are as good as they are going to get (usually 3-4 months)

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2. Lenalidomide (pill) or bortezomib (SQ) maintenance

### Neuropathy - bortezomib

- Can occur abruptly and can be painful, debilitating.
- Greatly diminished by weekly once and subcutaneous administration, without losing efficacy.
- Duloxetine, effective in other chemo induced neuropathy, can be used in BIPN.
Bone disease

- Bone disease is an important cause of morbidity in MM
- Treatment and prevention of skeletal lesions is a vital part of management of MM
- Bone disease is mediated by IL-6 and osteoclast activating factor (OAF)
- Bisphosphonates are an integral part of treatment of MM

Bone disease

- Bisphosphonates inhibit bone resorption by suppressing osteoclast activity
- Also affect the microenvironment in which tumor cells grow and may have direct anti-tumor activity
- Prevent skeletal events, reduce bone pain, and potentially prolong survival (Zoledronic acid)
- Risk for bisphosphonate-related osteonecrosis of jaw (BRONJ)
- Denosumab – moab to RANKL – approved for patients with renal failure
RELAPSED/REFRACTORY DISEASE

Management

- Second gen PI – Carfilzomib
- Immunomodulators – Pomalidomide
- Monoclonal antibodies – Daratumumab (CD 38)
- Histone deacetylase inhibitor – Panabinostat
- Metabolism inhibitors
- Chimeric Antigen Receptor – T cell therapy
Oncological emergencies in myeloma

• Hypercalcemia:
  • Can be asymptomatic or present with nausea, vomiting, polyuria, polydipsia, constipation, abdominal pain, altered mentation or seizures
  • iv fluids, bisphosphonates [do not wait for dental clearance]
  • Calcitonin for rapid reduction
  • Hemodialysis for extremely high levels

Oncological emergencies in myeloma

• Cord compression
  • Suspect in patients with back pain, motor/sensory deficits, bowel/bladder dysfunction
  • Can be due to extramedullary plasmacytoma or bone fragments from fractures
  • Prompt administration of steroids immediately followed by imaging
  • Radiation and/or surgery as needed
Oncological emergencies in myeloma

- Febrile neutropenia
- Often a complication from chemotherapy
- Prompt initiation of broad-spectrum antibiotics after initial work up for infection [chest x ray, blood and urine cultures]
- Aggressive fluid resuscitation
- Vasopressor and ventilator support as needed

For questions or comments regarding this talk, please email me at srinivas.devarakonda@osumc.edu