Multiple Myeloma

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The first case of myeloma was described in 1844 by Dr. Samuel Solly

Dr. Solly thought that the disease was an inflammatory process that began with a “morbid action” of the blood vessels in which the “earthy matter of the bone is absorbed and thrown out by the kidneys in the urine.”

Images of the first patient, a 39-year-old woman
Myeloma is the 24th most common cause of cancer-related mortality in Uganda

The global incident of myeloma has increased 42% in the past decade.
The incidence of myeloma is higher in more developed countries.
The median age at diagnosis is 69 years in the U.S.
The disease is more common in black men in the U.S.

<table>
<thead>
<tr>
<th>Race</th>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>8.2</td>
<td>5.2</td>
</tr>
<tr>
<td>White</td>
<td>7.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Black</td>
<td>15.7</td>
<td>11.5</td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>4.7</td>
<td>3.0</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>5.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>8.3</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Symptoms of myeloma

- Fatigue
- Bone pain
- Fractures
- Neuropathy
- Frequent infections
- Unexplained weight loss
- Spinal cord compression
Myeloma is a malignancy of terminally differentiated plasma cells.
Plasma cell secrete immunoglobulin

Types of light chains
- Kappa
- Lambda

Types of heavy chains
- IgG
- IgM
- IgA
- IgD
- IgE
Plasma cell neoplasms

Multiple myeloma

Light chain amyloidosis
  • Deposition of an abnormally folded light chain protein in tissue

POEMS disease
  • Polyneuropathy (nerve damage)
  • Organomegaly (enlarged organs)
  • Endocrinopathy (disorders involving hormone production)
  • Monoclonal gammopathy (presence of an M-protein)
  • Skin rash

Lymphoplasmacytic lymphoma
  • Plasma cell disease involving the lymph nodes

Waldenström’s macroglobulinemia
  • A type of lymphoplasmacytic lymphoma that makes IgM M-protein

Solitary plasmacytoma

Plasma cell leukemia
  • Greater than 20% plasma cells in the blood
Diagnostic work-up for myeloma

Recommended in all patients
  ✓ Bone marrow biopsy and aspirate
    ✓ Flow cytometry and immunohistochemistry
    ✓ Cytogenetics
    ✓ FISH
  ✓ Serum protein electrophoresis
  ✓ Serum free light chains
  ✓ 24-hour urine protein electrophoresis
  ✓ X-rays

Recommended in certain patients
  ✓ MRI scan
  ✓ CT scan
  ✓ PET scan
## Myeloma immunophenotype

<table>
<thead>
<tr>
<th>Marker</th>
<th>Normal plasma cell</th>
<th>Myeloma cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD138</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD38</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD19</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD19</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD45</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD56</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Kappa:Lambda</td>
<td>2:1</td>
<td>&gt; 4:1 or &lt; 1:2</td>
</tr>
</tbody>
</table>

Myeloma cell markers are positive for CD138, CD38, and negative for CD19 and Kappa:Lambda. The ratio of Kappa:Lambda is either greater than 4:1 or less than 1:2.
Common chromosomal abnormalities in myeloma

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion 13q</td>
<td>45-50%</td>
<td>Neutral</td>
</tr>
<tr>
<td>Gain 1q</td>
<td>35-40%</td>
<td>Poor</td>
</tr>
<tr>
<td>Deletion 1p</td>
<td>30%</td>
<td>Poor</td>
</tr>
<tr>
<td>Translocation (11;14)</td>
<td>15-20%</td>
<td>Neutral</td>
</tr>
<tr>
<td>Translocation (4;14)</td>
<td>15%</td>
<td>Poor</td>
</tr>
<tr>
<td>Deletion 17p</td>
<td>10%</td>
<td>Poor</td>
</tr>
<tr>
<td>Translocation (14;16)</td>
<td>5-10%</td>
<td>Poor</td>
</tr>
<tr>
<td>Translocation (6;14)</td>
<td>2%</td>
<td>Neutral</td>
</tr>
<tr>
<td>Translocation (14;20)</td>
<td>1%</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

p = short arm of chromosome; q = long arm of chromosome
Myeloma diagnostic criteria

**Pre-cancer**
- Monoclonal Gammopathy of Undetermined Significance (MGUS)
  - M-protein: < 3.0 g/dl
  - Light chain ratio: < 100
  - Bone marrow plasma cells: < 10%
  - End organ damage: No

**Cancer**
- Smoldering Myeloma
  - M-protein: > 3.0 g/dl
  - Light chain ratio: < 100
  - Bone marrow plasma cells: 10-59%
  - End organ damage: No

- Multiple Myeloma
  - M-protein: Any
  - Light chain ratio: > 100
  - Bone marrow plasma cells: > 60%
  - End organ damage: Yes

“CRAB criteria”
Myeloma end-organ damage

- Calcium level elevated
- Renal failure
- Anemia
- Bony lytic lesions
Revised International Staging System (ISS)

Stage I
- Beta-2 microglobulin < 3.5 mg/L and
- Albumin ≥ 3.5 g/dL and
- LDH normal and
- No high risk cytogenetics

Stage II
- Not stage I or II

Stage III
- Beta-2 microglobulin > 5.5 mg/L and
- High risk cytogenetics or
- Elevated LDH

High risk cytogenetics
- Deletion(17)p
- Translocation(4;14)
- Translocation(14;16)
Higher stage predicts more aggressive disease

NR = not reached (i.e. beyond the duration of the study)

Journal of Clinical Oncology (2015)
Treatment overview

- Induction: 3-4 months
- Autologous stem cell transplant: 3 months
- Maintenance: As long as tolerated
## International Myeloma Working Group Response Criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>M-protein</th>
<th>Immunofixation</th>
<th>Urine light chains</th>
<th>Bone marrow plasma cells</th>
<th>Light chain ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Normal</td>
</tr>
<tr>
<td>Complete</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>&lt; 5%</td>
<td>Any</td>
</tr>
<tr>
<td>Very good partial</td>
<td>90-100% ↓</td>
<td>Any</td>
<td>&lt; 100 mg</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Partial</td>
<td>50-89% ↓</td>
<td>Any</td>
<td>90-100% ↓</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Minimal</td>
<td>25-49% ↓</td>
<td>Any</td>
<td>50-89% ↓</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>25% ↑</td>
<td>Any</td>
<td>25% ↑</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>
Myeloma treatment algorithm

**Standard risk (t(11;14), t(6;14) and trisomies)**
- VRd or lenalidomide and dexamethasone* for 12 months
- Lenalidomide maintenance until disease progression for a minimum of 1 year
- Four cycles of VRd

**Intermediate risk (t(4;14))**
- VRd for ~12 months
- Bortezomib-based maintenance until disease progression or as tolerated
- Four cycles of VRd

**High risk (del(17p), t(14;16) and t(14;20))**
- VRd for ~12 months
- Bortezomib and lenalidomide, or bortezomib only, until disease progression as tolerated
- Four cycles of VRd or KRd (consider clinical trials)

**Transplant ineligible**
- ASCT
- Four cycles of VRd
- Collect stem cells
- Lenalidomide maintenance for at least 2 years
- Bortezomib maintenance for 2 years

**Transplant eligible**
- ASCT (preferred)
- Four cycles of VRd
- ASCT Discuss tandem ASCT
- Bortezomib and lenalidomide or carfilzomib and lenalidomide until disease progression (minimum bortezomib or carfilzomib)
VTD is superior to VCD as induction therapy

<table>
<thead>
<tr>
<th></th>
<th>VTD (n = 169)</th>
<th>VCD (n = 169)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intent to treat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥CR</td>
<td>13.0%</td>
<td>8.9%</td>
<td>.22</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>66.3%</td>
<td>56.2%</td>
<td>.05</td>
</tr>
<tr>
<td>≥PR</td>
<td>92.3%</td>
<td>83.4%</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Per protocol</strong></td>
<td>n = 157</td>
<td>n = 154</td>
<td></td>
</tr>
<tr>
<td>≥CR</td>
<td>14.0%</td>
<td>9.1%</td>
<td>.17</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>70.7%</td>
<td>60.4%</td>
<td>.05</td>
</tr>
<tr>
<td>≥PR</td>
<td>98.7%</td>
<td>90.3%</td>
<td>.001</td>
</tr>
</tbody>
</table>

Early autologous stem cell transplant is superior to RVD alone

Maintenance therapy improves PFS and OS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Regimen</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 2005-02²</td>
<td>614</td>
<td>ASCT→Rm vs. ASCT→placebo</td>
<td>Median PFS (Rm vs. placebo): 46 vs. 24 mo (HR, 0.52; P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median OS (Rm vs. placebo): NR vs. 90 mo (HR, 0.92; P = .52)</td>
</tr>
<tr>
<td>CALGB 100104⁶</td>
<td>460</td>
<td>ASCT→Rm vs. ASCT→placebo</td>
<td>Median TTP (Rm vs. placebo): 53 vs. 26 mo (HR, 0.54; P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median OS (Rm vs. placebo): NR vs. 76 mo (HR, 0.60; P &lt; .001)</td>
</tr>
<tr>
<td>RV-MM-PI-209⁹</td>
<td>402</td>
<td>MPR→Rm vs. MEL200→Rm vs. MPR vs. MEL200</td>
<td>Median PFS (Rm vs. no R): 41.9 vs. 21.6 mo (HR, 0.47; P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-y OS (Rm vs. no R): 88% vs. 80% (HR, 0.64; P = .14)</td>
</tr>
<tr>
<td>Gay et al¹⁰</td>
<td>389</td>
<td>CRD→Rm vs. MEL200→Rm vs. CRD→Rm + P vs. MEL200</td>
<td>Median PFS (Rm + P vs. Rm): 37.5 vs. 28.5 mo (HR, 0.84; P = .34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-y OS (Rm + P vs. Rm): 83% vs. 88% (HR, 1.51; P = .21)</td>
</tr>
<tr>
<td>IFM/DFCI¹³</td>
<td>700</td>
<td>RVD→ASCT→Rm vs. RVD→Rm→ASCT</td>
<td>Median PFS (ASCT→Rm vs. Rm): 43 vs. 34 mo (HR, 1.5; P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-y PFS (ASCT→Rm vs. Rm): 47% vs. 35% (HR 1.5, P &lt; .001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-y OS (ASCT→Rm vs. Rm): 83% vs. 81% (HR 1.2, P = NS)</td>
</tr>
</tbody>
</table>
| FIRST¹⁵       | 1623| Rd vs. Rd18 vs. MPT                       | Median PFS (Rd vs. Rd18 vs. MPT): 25.5 vs. 20.7 vs. 21.2 mos (HR, Rd vs. MPT, 0.72; P = .00006; Rd vs. Rd18, 0.70; P = .00001; Rd18 vs. MPT, 1.03; P = .7)
|               |    |                                          | 4-y OS (Rd vs. Rd18 vs. MPT): 59.4% vs. 55.7% vs. 51.4% (HR, Rd vs. MPT, 0.78; P = .017; Rd vs. Rd18, 0.90; P = .31; Rd18 vs. MPT, 0.88; P = .18) |
| MM-015¹⁶      | 460| MPR→Rm vs. MPR vs. MPR vs. MP           | Median PFS (MPR→Rm vs. MPR vs. MP): 31 vs. 14 vs. 13 mo (HR, MPR→Rm vs. MP, 0.49; P < .001; MPR→Rm vs. MP, 0.40; P < .001)
|               |    |                                          | Median OS (MPR→Rm vs. MPR vs. MP): 56 vs. 52 vs. 54 mo (HR, MPR→Rm vs. MP, 0.88; P < .43; MPR→Rm vs. MP, 0.95; P < .74) |

Abbreviations: ASCT = autologous stem cell transplant; Bm = bortezomib maintenance; CR = complete response; CRD = cyclophosphamide, dexamethasone, and lenalidomide; HR = hazards ratio; nCR = near complete response; OS = overall survival; P = prednisone; PAD = bortezomib, Adriamycin, and dexamethasone; PFS = progression-free survival; Rm = lenalidomide maintenance; RVDm = RVD maintenance; Tm = thalidomide maintenance; TTP = time to progression; VAD = vincristine, Adriamycin, and dexamethasone.