Flame cell - 1.

Peter Maslak, ASH Image Bank 2011; 2011-4174
Multiple Myeloma - 1.

Stanely Schrier, ASH Image Bank 2011; 2011-1814
Relapsed multiple myeloma - 1.

Peter Maslak, ASH Image Bank 2013; 2013-3990
Leukemic phase of multiple myeloma - 2.

John Lazarchick, ASH Image Bank 2011; 2011-4095
Multistep pathogenesis of multiple myeloma

**Multistep progressive disease**

- MGUS
  - Hyperdiploidy (50% of patients)
- Intramedullary multiple myeloma
  - Secondary translocations
- Extramedullary multiple myeloma
  - Oncogenic activation or mutation (RAS, FGFR3)
- Plasma-cell leukemia
  - MYC dysregulation, TP53 mutation

**Cytogenetic abnormalities**

- Non-hyperdiploidy (50% of patients)

**Other molecular alterations**

- Increased expression of cyclin D1, D2, and D3

**Bone marrow microenvironment**

- Bone resorption

**Angiogenesis**

Cellular interactions in marrow in multiple myeloma

**Table 1. Diagnostic Criteria, Diagnostic Evaluation, and Staging System for Multiple Myeloma.**

**Diagnostic criteria**
- **Diagnosis of myeloma**
  - At least 10% clonal bone marrow plasma cells
  - Serum or urinary monoclonal protein
- Myeloma-related organ dysfunction (CRAB criteria)
  - Hypercalcemia (serum calcium >11.5 mg/dl [2.88 mmol/liter])
  - Renal insufficiency (serum creatinine >2 mg/dl [177 µmol/liter])
  - Anemia (hemoglobin <10 g/dl or >2 g/dl below the lower limit of the normal range)
  - Bone disease (lytic lesions, severe osteopenia, or pathologic fracture)

**Diagnostic evaluation**
- **Diagnosis**
  - Medical history and physical examination
  - Routine testing: complete blood count, chemical analysis with calcium and creatinine, serum and urine protein electrophoresis with immunofixation, quantification of serum and urine monoclonal protein, measurement of free light chains
  - Bone marrow testing: trephine biopsy and aspirate of bone-marrow cells for morphologic features; cytogenetic analysis and fluorescence in situ hybridization for chromosomal abnormalities
  - Imaging: skeletal survey, magnetic resonance imaging if skeletal survey is negative

**Prognosis**
- Routine testing: serum albumin, β₂-microglobulin, lactate dehydrogenase

**Staging**
- **International Staging System**
  - **Stage I:** serum β₂-microglobulin <3.5 mg/liter, serum albumin ≥3.5 g/dl
  - **Stage II:** serum β₂-microglobulin, <3.5mg/liter plus serum albumin <3.5 g/dl; or serum β₂-microglobulin 3.5 to <5.5 mg/liter regardless of serum albumin level
  - **Stage III:** serum β₂-microglobulin ≥5.5 mg/liter

**Chromosomal abnormalities**
- High-risk: presence of t(4;14) or deletion 17p13 detected by fluorescence in situ hybridization
- Standard-risk: t(11;14) detected by fluorescence in situ hybridization

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Table 2. Commonly Used Therapy Regimens in Newly Diagnosed Multiple Myeloma.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Schedule</th>
<th>Complete Response Rate after Induction</th>
<th>Progression-free Survival</th>
<th>Overall Survival</th>
<th>Serious Toxic Effects Occurring in ≥10% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib–dexamethasone</strong></td>
<td>Bortezomib: 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk for a total of 4–8 cycles; dexamethasone: 40 mg/day given orally on days 1–4 and 9–12 every 3 wk for a total of 4–8 cycles.</td>
<td>21*</td>
<td>Median, 36 mo</td>
<td>At 3 yr, 81%</td>
<td>Infection (10%)</td>
</tr>
<tr>
<td><strong>Bortezomib–dexamethasone–cyclophosphamide</strong></td>
<td>Bortezomib: 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 4 wk for a total of 4–12 cycles; dexamethasone: 40 mg/day given orally on days 1–4, 9–12, and 17–20 or on days 1, 2, 4, 5, 8, 9, 11, 12 every 4 wk for a total of 4–12 cycles; cyclophosphamide: 300 mg/m² given orally on days 1, 8, 15, 22 every 4 wk for a total of 4–12 cycles.</td>
<td>46*</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Thrombocytopenia (25%), neutropenia (13%), anemia (12%), hyperglycemia (13%)</td>
</tr>
<tr>
<td><strong>Bortezomib–dexamethasone–lenalidomide</strong></td>
<td>Bortezomib: 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11 every 3 wk for a total of 4–8 cycles; dexamethasone: 20 mg/day given orally on days 1, 2, 4, 5, 8, 9, 11, 12 every 3 wk for a total of 4–8 cycles; lenalidomide: 25 mg/day given orally on days 1–14 every 3 wk for a total of 4–8 cycles.</td>
<td>29</td>
<td>At 18 mo, 75%</td>
<td>At 18 mo, 97%</td>
<td>Lymphopenia (14%)</td>
</tr>
<tr>
<td><strong>Lenalidomide–dexamethasone</strong></td>
<td>Lenalidomide: 25 mg/day given orally on days 1–21 every 4 wk for a total of 4 cycles or until progression or intolerance; dexamethasone: 40 mg/day given orally on days 1, 8, 15, 22 every 4 wk for a total of 4 cycles or until progression or intolerance.</td>
<td>24†</td>
<td>Median, 25 mo</td>
<td>At 1 yr, 96%</td>
<td>Neutropenia (20%), deep-vein thrombosis (12%)</td>
</tr>
<tr>
<td><strong>Melphalan–prednisone–thalidomide</strong></td>
<td>Melphalan: 0.15 mg/kg given orally on days 1–7 every 4 wk for a total of 6 cycles or 0.25 mg/kg on days 1–4 every 6 wk for a total of 12 cycles; prednisone: 1.5 mg/kg given orally on days 1–7 every 4 wk for a total of 6 cycles or 2 mg/kg on days 1–4 every 6 wk for a total of 12 cycles; thalidomide: 100 mg/day given orally continuously until progression or intolerance or 200 mg/day continuously for a total of 12 cycles of 6 wk.</td>
<td>13–16</td>
<td>Median, 22–28 mo</td>
<td>Median, 45–52 mo</td>
<td>Neutropenia (16–50%), deep-vein thrombosis (12%), peripheral neuropathy (6–10%), infection (10–13%)</td>
</tr>
<tr>
<td><strong>Melphalan–prednisone–bortezomib</strong></td>
<td>Melphalan: 9 mg/m² given orally on days 1–4 every 5–6 wk for a total of 9 cycles; prednisone: 60 mg/m² given orally on days 1–4 every 5–6 wk for a total of 9 cycles; bortezomib: 1.3 mg/m² given as bolus intravenous infusion on days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4) and on days 1, 8, 22, 29 (cycles 5–9) every 6 wk for a total of 9 cycles or 1.3 mg/m² on days 1, 8, 15, 22 every 5 wk for a total of 9 cycles.</td>
<td>24–30</td>
<td>Median, 22–27 mo</td>
<td>At 2 yr, 85–87%</td>
<td>Neutropenia (28–40%), thrombocytopenia (20–37%), anemia (10–19%), peripheral sensory neuropathy (5–14%)</td>
</tr>
<tr>
<td><strong>Melphalan–prednisone–lenalidomide</strong></td>
<td>Melphalan: 0.18 mg/kg given orally on days 1–4 every 4 wk for a total of 9 cycles; prednisone: 2 mg/kg given orally on days 1–4 every 4 wk for a total of 9 cycles; lenalidomide: 10 mg/day given orally on days 1–21 every 4 wk for a total of 9 cycles; by the 10th cycle, maintenance with lenalidomide at 10 mg/day on days 1–21 every 4 wk until progression or intolerance.</td>
<td>16</td>
<td>At 2 yr, 55%</td>
<td>At 2 yr, 82%</td>
<td>Neutropenia (71%), anemia (24%), thrombocytopenia (38%), infection (10%)</td>
</tr>
</tbody>
</table>

* In these trials, the response is reported as immunofixation-negative complete response plus immunofixation-positive complete response.
† In this trial, the response is reported as immunofixation-negative complete response plus very good partial response.