Risk Stratification of Plasma Cell Disorders

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Risk Stratification of Plasma Cell Disorders

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Progression of MGUS to Myeloma

Primary Cytogenetic Abnormalities
- t(11;14)
- t(4;14)
- t(6;14)
- t(14;16)
- t(14;20)
- Trisomies

Secondary Cytogenetic Abnormalities
- 1q amp
- Del 17

Secondary Cytogenetic Abnormalities
- Myc translocations
- Del 17
- 1p del


Normal Plasma Cells → MGUS/SMM → Myeloma

Trisomies/IgH Translocations
Establishment of the clone
Secondary Cytogenetic Abnormalities
Del(17p), Gain(1q)
Secondary Cytogenetic Abnormalities
Occur with progression

- Relapsed Refractory MM
- Plasma Cell Leukemia
- Extra Medullary Disease
International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma


This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be
Revised IMWG Criteria for Myeloma

- **MGUS**
  - < 10% BMPC AND
  - < 3 g/dL M protein
  - No MDE

- **SMM**
  - 10-60% BMPC OR
  - \(\geq 3\) g/dL M protein
  - No MDE

- **MM**
  - Clonal plasma cell disorder AND
  - 1 or more MDE
    - CRAB
    - \(\geq 60\)% BMPC
    - \(\geq 100\) FLC ratio
    - \(>1\) MRI focal lesion

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**No MDE**

**MDE**

*MDE = Myeloma Defining Events
CRAB = Hypercalcemia, renal failure, anemia, or lytic bone lesions attributable to a clonal plasma cell disorder*

## Classification of MGUS

<table>
<thead>
<tr>
<th>Type of MGUS</th>
<th>Type of Progression</th>
<th>Risk of Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non IgM MGUS (IgG, IgA)</td>
<td>Myeloma, Plasmacytoma</td>
<td>1% per year</td>
</tr>
<tr>
<td>IgM MGUS</td>
<td>Waldenstrom Macroglobulinemia</td>
<td>1.5% per year</td>
</tr>
<tr>
<td>LC-MGUS</td>
<td>Light Chain Myeloma</td>
<td>Not known</td>
</tr>
</tbody>
</table>

All can progress to AL amyloidosis
Risk of Progression of MGUS

Years since Diagnosis of MGUS

Patients with Progression or Death (%)

Non-IgM MGUS, death without progression

IgM MGUS, death without progression

IgM MGUS, progression

Non-IgM MGUS, progression

MGUS Risk Stratification: M spike size, M spike type, and FLC ratio

- All 3 factors abnormal
- Any 2 factors abnormal
- Any 1 factor abnormal
- Serum M-spike <1.5 gm/dL, IgG Subtype and normal FLC ratio

Workup of Suspected MGUS

Suspected MGUS

- Low risk (< 1.5 g/dL, IgG type, normal FLC ratio), or
- IgM < 1.5 g/dL, or
- Light chain MGUS with FLC ratio < 8

Uncomplicated*

Bone marrow biopsy and skeletal survey may be deferred

Presence of unexplained symptoms or laboratory features of concern

Bone marrow biopsy required; skeletal survey (low dose whole body CT or conventional radiographs) required in non-IgM patients

*No unexplained symptoms or laboratory features concerning for serious plasma cell disorder.
Management of MGUS

All Patients with MGUS

Follow-up in 6 months

Stable

Risk stratification

Low risk

No MGUS follow-up; usual medical care

Intermediate or high risk

Annual MGUS follow-up: CBC, calcium, creatinine, SPEP, FLC

Possible progression

Workup for lymphoplasmacytic malignancy

No malignancy

Manage accordingly

Malignancy
Smoldering Multiple Myeloma

Robert A. Kyle, M.D., and Philip R. Greipp, M.D.
SMM vs MGUS

![Graph showing the comparison between Smoldering Multiple Myeloma (SMM) and Multiple Myeloma (MGUS) in terms of probability of progression over years since diagnosis.](image)
Smoldering Multiple Myeloma

Low-risk SMM:
- 5%/yr risk of MM

High-Risk SMM:
- 25% per year risk of MM
- >60% BMPC
- FLCr >100
- >1 MRI focal lesions

MM
Len/Dex versus Observation in High Risk SMM: TTP

Hazard ratio for progression, 0.18
P<0.001

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment group</td>
</tr>
<tr>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>50</td>
<td>14</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
</tr>
</tbody>
</table>

Len/Dex vs Observation in High-Risk SMM: OS

Hazard ratio for death, 0.31
P=0.03

No. at Risk
Treatment group 57 57 55 48 26 17 0
Observation group 62 60 57 46 27 17 0

High-Risk SMM: Median TTP ~ 2 Years

≥ 10% PCs plus:

• SMM with M protein ≥ 3 g/dL
• Absence (< 5%) of normal PCs by immunophenotyping plus Immunoparesis
• Abnormal FLC ratio 8-100
• Del(17p), t(4;14), gain(1q21)
• IgA SMM
• Evolving pattern
• Increased circulating plasma cells

Mayo 20-2-20 Risk Stratification of SMM

BMPC > 20%, M protein > 2 g/dL, and FLC ratio (FLCr) > 20

2 or more (High Risk)
Any 1
None

Management of SMM

Potential New Myeloma or Smoldering Myeloma

Any Myeloma-Defining Events?
- CRAB,
- > 60% PC,
- FLC > 100,
- MRI > 1 focal

Treat as myeloma

No Myeloma-Defining Events (SMM)

High-Risk SMM
(Median TTP ~2 years)

Evolving SMM or many high-risk factors

Consider treat as myeloma

Clinical trials

Low-Risk SMM
(~5% per year PD)

Observation

SMM Trial Strategy

Conceptual/Regulatory
- Len v Obs
- Rd vs Obs
- Dara vs Obs

- Necessary trials

Strategic: Delay Progression
- DRd vs Rd
- KRd

- Survival benefit with early therapy

Strategic: ? Cure
- CESAR
- ASCENT

- ? Cure possible with early therapy
### Molecular Classification of Myeloma

<table>
<thead>
<tr>
<th>Trisomic MM</th>
<th>IgH Translocations</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Trisomies*</td>
<td>▪ t(11;14) (CCND1)</td>
</tr>
<tr>
<td></td>
<td>▪ t(6;14) (CCND3)</td>
</tr>
<tr>
<td></td>
<td>▪ t(4;14) (FGFR3, MMSET)</td>
</tr>
<tr>
<td></td>
<td>▪ t(14;16) (C-MAF)</td>
</tr>
<tr>
<td></td>
<td>▪ t(14;20) (MAF-B)</td>
</tr>
</tbody>
</table>

*~10% have both trisomies and IgH translocations

The multiple myelomas — current concepts in cytogenetic classification and therapy

Shaji K. Kumar & S. Vincent Rajkumar
Cytogenetic Risk Stratification of Myeloma

- t(4;14) (FGFR3, MMSET)
- t(14;16) (C-MAF)
- t(14;20) (MAF-B)
- Trisomies*
- t(11;14) (CCND1)
- t(6;14) (CCND3)

Disease Aggressiveness

- del 17p, p53 mutations, gain 1q

- Double-Hit Myeloma = Any 2 high risk abnormalities
- Triple-Hit Myeloma = 3 or more high risk abnormalities

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Revised International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Frequency (% of patients)</th>
<th>5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum albumin &gt;3.5</td>
<td>28%</td>
<td>82%</td>
</tr>
<tr>
<td>• Serum beta-2-microglobulin &lt;3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No high risk cytogenetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal LDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>• Neither stage I or III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>• Serum beta-2-microglobulin &gt;5.5 and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated LDH</td>
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</tr>
</tbody>
</table>
Plasma Cell Leukemia
Plasma Cell Leukemia

PCL: ≥ 5% or more PCs on regular WBC differential

Summary

• New diagnostic criteria
• Molecular classification of MM
• Risk stratification systems for MGUS, SMM, MM are different
• New staging system for MM
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- **Downloadable slides** from this symposium (IMF link below)
- **Interactive Decision Support Tool** for myeloma, with personalized expert recommendations for your patients with myeloma
- **Online programs** on caring for your patients with myeloma

**myeloma.org/videos/new-strategies-multiple-myeloma-care-next-steps-future**

**clinicaloptions.com/MyelomaTool**

**clinicaloptions.com/oncology/topics/Multiple-Myeloma**