Risk Factors for Progression in MGUS and SMM

S. Vincent Rajkumar
Professor of Medicine
Mayo Clinic
No conflicts to disclose
Progression in MGUS and SMM

## 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 Factors for Progression of MGUS: 
Size of M spike and Absolute Risk of Progression to Malignancy

Risk of Progression at 20 years

Risk of Progression at 20 years

Kyle RA and Rajkumar SV. Immunol Rev. 2003;194:112-139
Risk Factors for Progression of MGUS:
Size of M spike and Absolute Risk of Progression to Malignancy

Cumulative incidence (%)

Years

IgM 29%
IgA 25%
IgG 19%

7%
13%
18%

P < 0.001

Risk Factors for Progression of MGUS: Abnormal FLC Ratio and Absolute Risk of Progression to Malignancy

Effect of increasingly abnormal FLC ratio on the relative risk of progression of monoclonal gammopathy of undetermined significance to multiple myeloma or related disorder
Prognosis of MGUS: Risk Stratification using M spike size, 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

Rajkumar SV. Blood 2005;106:812-817
## Risk Stratification of MGUS

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>No. of patients</th>
<th>Relative risk</th>
<th>Absolute risk of progression (ARP) at 20 years with death as a competing risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk (No risk factor)</td>
<td>449</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>Low-Intermediate-risk (Any 1 factor)</td>
<td>420</td>
<td>5.4</td>
<td>21%</td>
</tr>
<tr>
<td>High-Intermediate-risk (Any 2 factors)</td>
<td>226</td>
<td>10.1</td>
<td>37%</td>
</tr>
<tr>
<td>High-risk (All 3 factors)</td>
<td>53</td>
<td>20.8</td>
<td>58%</td>
</tr>
</tbody>
</table>

CIRCULATING PLASMA CELLS IN MGUS


Cumulative Survival

No circulating plasma cells

Circulating plasma cells

Time (months)

P = .028
Risk of Progression of MGUS

MGUS

Cancers
- Myeloma
- Macroglobulinemia
- Plasmacytoma

Paraprotein
- AL Amyloidosis
- LCDD
- Cryoglobulinemia

Associations
- Neuropathy
- Proliferative GN
- Skin Disorders
- Fractures
SMM
Smoldering Multiple Myeloma

Robert A. Kyle, M.D., and Philip R. Greipp, M.D.

SMM Paradigm Shift

MGUS

Myeloma
International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Bladé, Giampiero Merlini, Maria Vitoria Marques, Shaji Kumar, Jens Hilgenhaus, Esteban Gázitúa, Paul Richardson, Ola Landgren, Bruno Pulci, Angelo Dispensa, Brendan Weksner, Xavier Lata, Sjoerd Zwerver, Sagar Lonial, Laura Rosinò, Elena Zucconi, Suresh Jagannath, Orhan Serer, Syed Velidi, Niall Connolly, Joo-Caen, SaadZ. Ullahmanj, Juan José Laheru, Hans Erik Johansen, Monal Gokas, Michele Cava, Hartmut Goldschmidt, Evangelos Papadopoulos, Robert A Kyle, Kenneth C Anderson, Brian J M Durie, Jesús F Sánchez-Migé

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
Smoldering Multiple Myeloma

Low-risk SMM:

High-Risk SMM

MM

- >60% BMPC
- FLCr >100
- >1 MRI focal lesions
High Risk Smoldering Multiple Myeloma

≥10% PCs plus:
  • M protein ≥3 gm/dL
  • Absence (<5%) of normal PCs by immunophenotyping plus Immunoparesis
  • Abnormal FLC ratio 8-100
  • Del(17p), t4;14, gain(1q21)
  • IgA type
  • Evolving pattern
  • Increased circulating plasma cells

25%/year risk of MM

Rajkumar SV, Landgren O, Mateos MV. Blood 2015
Mayo 2018 Risk Stratification (2-20-20)

Factors
- M Spike >2g/dL
- BMPC >20%
- FLC ratio >20

Stratification
- Low-risk: 0
- Intermediate-risk: 1
- High-risk: >=2

Lakshman et al, BCJ, 2018
### IMWG 2019 Risk Stratification of SMM (n=1151)

#### Risk Stratification Groups

<table>
<thead>
<tr>
<th>Risk Stratification Groups</th>
<th>Number of risk factors</th>
<th>Hazard Ratio (95% CI) Versus Low-risk group</th>
<th>Risk of Progression at 2 years</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group</td>
<td>0</td>
<td>Reference</td>
<td>5%</td>
<td>424 (37%)</td>
</tr>
<tr>
<td>Intermediate-risk group</td>
<td>1</td>
<td>2.25 (1.68 to 3.01)</td>
<td>17%</td>
<td>312 (27%)</td>
</tr>
<tr>
<td>High-risk group</td>
<td>2-3</td>
<td>5.63 (4.34 to 7.29)</td>
<td>46%</td>
<td>415 (36%)</td>
</tr>
</tbody>
</table>

**M Spike:** >2g/dL  
**FLC Ratio:** > 20  
**BMPC:** > 20%

## IMWG 2019 Risk Stratification of SMM

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLC Ratio</td>
<td></td>
</tr>
<tr>
<td>0-10 (ref)</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 10-25</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 25-40</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>5</td>
</tr>
<tr>
<td>M protein (g/dL)</td>
<td></td>
</tr>
<tr>
<td>0-1.5 (ref)</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 1.5-3</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>4</td>
</tr>
<tr>
<td>BMPC%</td>
<td></td>
</tr>
<tr>
<td>0-15 (ref)</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 15-20</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 20-30</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 30-40</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>6</td>
</tr>
<tr>
<td>FISH abnormality</td>
<td>2</td>
</tr>
</tbody>
</table>

Evolving SMM

Risk factors: eMP, eHb and BMPC $\geq$ 20%

Evolving MRI findings

Merz et al, Leukemia 2014
Future Directions
