When does “Smoldering” become an Open Flame?
Evolving Diagnostic Criteria for Multiple Myeloma

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Disclosures

No conflicts to disclose
Smoldering Multiple Myeloma

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

To burn without flame…
• IgH translocations
• Trisomies
• Both
## Previous Disease Definitions

<table>
<thead>
<tr>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
</thead>
</table>
| • <10% BMPC AND  
• <3gm/dL M protein | • ≥10% BMPC OR  
• ≥3 gm/dL M protein |

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

Catch-22
The case for observation…

• No good treatments

• Some patients can go several years without progression

• Lack of evidence of benefit with early therapy

Active Drugs in Multiple Myeloma

Old Drugs
- Alkylators
- Steroids
- Interferon
- Anthracyclines

Older Drugs
- Bortezomib
- Thalidomide
- Lenalidomide

Recently Approved Drugs
- Carfilzomib
- Ixazomib
- Pomalidomide
- Daratumumab
- Panobinostat
- Elotuzumab

Future Drugs
- Ixazomib
- Marizomib
- Isatuximab
- Dinaciclib
- Filanesib
- LGH447
- ABT-199

Rajkumar SV. 2015
Len/Dex versus Observation in High Risk SMM: TTP

A

Freedom from Progression to Symptomatic Disease (%)

Hazard ratio for progression, 0.18
P<0.001

Months

No. at Risk
Treatment group 57 57 48 38 20 14 0
Observation group 62 49 32 21 11 3 0

Len/Dex versus Observation in High Risk SMM: OS

B

Overall Survival since Study Inclusion (%)

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

Months

SMM verus MGUS

SMM Paradigm Shift

MGUS

Myeloma
Bone Marrow Plasma Cell ≥60%

FLC Ratio $\geq 100$ and Risk of progression to myeloma

Larsen J, et al. *Leukemia* advance online publication 27 November 2012; doi: 10.1038/leu.2012.296
Whole body MRI

149 patients with asymptomatic MM

28% of patients with focal lesions and ≥1 focal lesion in 15%

 Median TTP: 13 mo.

Log-rank P<0.001

≤1 focal lesion
>1 focal lesion

<table>
<thead>
<tr>
<th>Time since MRI treatment (months)</th>
<th>≤1 FL</th>
<th>&gt;1 FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>126</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>106</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>81</td>
<td>10</td>
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<td>18</td>
<td>64</td>
<td>5</td>
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<tr>
<td>24</td>
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<td>30</td>
<td>36</td>
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<tr>
<td>36</td>
<td>20</td>
<td>0</td>
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<tr>
<td>42</td>
<td>11</td>
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</tr>
<tr>
<td>48</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>54</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

FL, focal lesion; NR, not reached.

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

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<tr>
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<td>• ≥10%-60% BMPC OR</td>
<td>• PCPD, AND</td>
</tr>
<tr>
<td>• &lt;3 gm/dL M protein AND</td>
<td>• ≥3 gm/dL S. M protein OR</td>
<td>• 1 or more MDE</td>
</tr>
<tr>
<td>• No MDE</td>
<td>• ≥500 mg/24h Ur. M protein AND</td>
<td>• CRAB</td>
</tr>
<tr>
<td></td>
<td>• No MDE</td>
<td>• ≥60% BMPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥100 FLC ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &gt;1 MRI focal lesion</td>
</tr>
</tbody>
</table>

**No MDE**

MDE, myeloma-defining events

**MDE**

Advanced Imaging

CT

PET-CT

Diagnosis of Myeloma

• Judgment
  • Hypercalcemia
  • Renal Failure
  • Anemia
  • Bone

• Judgment
  • Interpreting FLC ratio
  • Clinical course
  • Imaging studies

REVISED DEFINITION OF SMM
# Revised IMWG Criteria

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• ≥3 gm/dL S. M protein **OR**  
• ≥500 mg/24h Ur. M protein **AND**  
• No MDE | • PCPD, **AND**  
• 1 or more MDE  
• CRAB  
• ≥60% BMPC  
• ≥100 FLC ratio  
• >1 MRI focal lesion |

MDE, myeloma-defining events

Smoldering Multiple Myeloma

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

High-Risk SMM

25%/year risk of MM

MM
- >60% BMPC
- FLCr ≥100
- >1 MRI focal lesions
Smoldering Multiple Myeloma

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

High-Risk SMM

25%/year risk of MM
CRITERIA FOR HIGH RISK SMM
High Risk SMM: Median TTP ~2 years

≥10% PCs plus:

- SMM with 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)
- M protein ≥4 gm/dL
- IgA SMM
- Evolving pattern
- Increased circulating plasma cells

Rajkumar SV, Landgren O, Mateos MV. Blood 2015
Cytogenetically Defined, Risk-Based Classification of SMM

<table>
<thead>
<tr>
<th>High-Risk</th>
<th>High-Intermediate</th>
<th>Low-Intermediate</th>
<th>Low-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del 17p</td>
<td>Trisomies</td>
<td>All other</td>
<td>No cytogenetic abnormalities</td>
</tr>
<tr>
<td>t(4;14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain(1q)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Median TTP ~2 years

Median TTP ~3 years

Median TTP ~5 years

Median TTP ~10 years

Treatment of Smoldering Multiple Myeloma

Newly Diagnosed SMM

High Risk
- Evolving, or multiple high risk factors
  - Clinical Trials, or Observation Q3 months
  - Consider Rd, or MM therapy

Low Risk
- Observation

Rajkumar SV, Landgren O, Mateos MV. Blood 2015
E3A06: Phase III – High-Risk Smoldering Myeloma*

Lenalidomide vs. observation

PI: Sagar Lonial

- **Randomization**
  - Lenalidomide
  - Observation

- **CR/PR/ Stable**
  - Continue therapy till prog. or toxicity

- **Prog. anytime**
  - Off Rx

* Accruing