Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM)

BHS training
08/05/2015

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CHU Liège
Multiple myeloma precursor disease

- Monoclonal gammopathy of undetermined significance (MGUS): 3% of Caucasians (> 50 years)
  - Afro-american
  - Obesity
  - Family members

- Smoldering myeloma (SMM) accounts for approximately 15-34% of all newly diagnosed MM patients
Progression and clonal evolution in Myeloma

Initiation

Normal pre-germinal B cell ➔ MGUS ➔ Smoldering myeloma ➔ Myeloma ➔ EM-MM / PCL

Germinal centre ➔ Bone marrow ➔ Peripheral blood

Primary genetic events:
• IgH@ translocations
• Hyperdiploidy

Secondary genetic events:
• Copy number abnormalities
• DNA hypomethylation
• Acquired mutations

Tumor cell diversity

Clonal advantage

Competition selection for BM niche

Migration & founder effect

BM microenvironment changes
- Osteoclast activation ➔ increased angiogenesis
- Osteoblast inhibition ➔ altered expression of cytokines, growth factors and adhesion molecules
Criteria for diagnosis

**MGUS**
- M spike < 3g/dl
- Clonal BMPC < 10%

**Smoldering MM**
- M spike ≥ 3g/dl
- Clonal BMPC ≥ 10%

**Active MM**
- M spike ≥ 3g/dl
- Clonal BMPC ≥ 10%

Absence of anemia, bone lesions, normal calcium and kidney function

AND

Presence of anemia, bone lesions, high calcium or abnormal kidney function

Kyle, IMWG criteria, Leukemia 2010
The M Spike

Serum electrophoresis

Immunofixation
Hépatites chroniques virales
Hépatites médicamenteuses
Cirrhose alcoolique

Bloc bêta-gamma

Déficit immunitaire
Syndrome lymphoprolifératif
Immunosuppression acquise

Hypogammaglobulinémie
IT/IF recommandée

Maladies infectieuses
Maladies tumorales
Maladies traumatiques

Syndrome inflammatoire

Néphropathie diabétique
Néphrose lipoïdique
Lésion rénale

Syndrome néphrotique
Causes of monoclonal gammopathies

**Plasma cell disorders**
- MGUS
- Multiple myeloma
- Amyloid light chain amyloidosis
- Solitary plasmacytoma
- POEMS syndrome
- Castleman’s disease

**B-cell lymphoproliferative disorders**
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia
- Waldenström’s macroglobulinemia
- Post-transplant monoclonal gammopathies

**Infections**
- Bacterial
- Viral (hepatitis, EBV, CMV, HIV)

**Autoimmune disorders**
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjögren syndrome
- Scleroderma
- Psoriatic arthritis

**Skin disorders**

**Liver disorders**

**Glomerular nephropathies**

**Epithelial cancers**
(paraneoplastic syndromes)

**Other hematological disorders**
- Cryoglobulinaemia
- Myelodysplastic or myeloproliferative disorders
- Coagulation disorders

Incidence of MGUS
Advancing in the diagnosis

- Clinical history and examination
- Blood and urine analysis
- M-Protein level

## Alerting symptoms

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Diagnostic findings</th>
<th>Pathogenic mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone/back pain, cord compression, cauda equina</td>
<td>Lytic lesions, pathologic fractures, severe osteopenia</td>
<td>Myelophthisis, increased osteoclastogenesis, osteoblast inhibition, solitary plasmacytoma</td>
</tr>
<tr>
<td>Fatigue, malaise</td>
<td>Anemia</td>
<td>Myelophthisis, decreased EPO, hemolysis</td>
</tr>
<tr>
<td></td>
<td>Renal Failure</td>
<td>Light chain deposition, cast nephropathy, hypercalcemia-induced vasoconstriction, amyloidosis, urate nephropathy</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>Bone reabsorption secondary to myelophthisis and cytokine release</td>
</tr>
<tr>
<td></td>
<td>Hepatitis, liver failure</td>
<td>Amyloid infiltration, MM cell infiltration</td>
</tr>
<tr>
<td>Recurrent infections</td>
<td>Hypogammaglobulinemia, leukopenias</td>
<td>Myelophthisis</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>Polyradiculopathy, ischemic strokes, altered mental status</td>
<td>Amyloid deposition, cryoglobulinemia type I, hyperviscosity, hypercalcemia, uremia</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>Infiltrative cardiomyopathy, arrhythmias, pleural effusions, pulmonary edema</td>
<td>Cardiac or pulmonary amyloid, plasmacytoma, malignant pleural effusions, hyperviscosity</td>
</tr>
<tr>
<td>Purpura, petechiae, bleeding, acrocyanosis</td>
<td>Cryoglobulinemia type I, thrombocytopenia, hyperviscosity</td>
<td>M spike deposition, myelophthisis, hyperviscosity</td>
</tr>
</tbody>
</table>

Clinical history and examination

Blood and urine analysis

M-Protein level

Monoclonal Gammapathy of unknown significance

Further exploration for myeloma or lymphoproliferative disorder

Asymptomatic

Abnormal: presence of renal failure, anemia, hypercalcemia

Normal

Symptomatic

< 15 g/l

> 15 g/l

Further exploration for myeloma or lymphoproliferative disorder

Ig M

IgG, IgA, κ or λ

BM cytology/biopsy
CT scan thorax/abdomen

BM cytology/biopsy
Bone Survey
Blood and urine testing
Cytogenetics
Waldenström Disease
Monoclonal Gammapathy of unknown significance
Risk Stratification: Check for hemostatic, neuropathic, renal or bone complications

Further exploration for myeloma or lymphoproliferative disorder

Bone marrow cytology and biopsy
Bone survey by plain radiographs and/or MRI
β2-microglobulin,
Bence-Jones proteinuria
CT thorax/abdomen (in case of IgM)

β2-microglobulin ≤ 1.5 times normal

> 10% of clonal BMPC
Signs of organ damage

Presence of lympho-plasmocytic cells
Lymphadenopathy or organomegaly

Multiple Myeloma
Waldenström Disease

Caers J Ann Med 2013
Risk stratification

- Level of M-protein: 1.5 g/dl
- Isotype: IgG vs IgA, IgM
- BM plasmocytosis: 5%
- Reduced Ig levels
- Serum Free Light Chain ratio

Kyle, NEJM, 2002
### Risk Stratification for MGUS

#### Mayo Clinic (n= 1148)

<table>
<thead>
<tr>
<th>No of risk factors</th>
<th>No of patients, n(%)</th>
<th>Progression at 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>449 (38)</td>
<td>5%</td>
</tr>
<tr>
<td>1</td>
<td>420 (37)</td>
<td>21%</td>
</tr>
<tr>
<td>2</td>
<td>226 (20)</td>
<td>37%</td>
</tr>
<tr>
<td>3</td>
<td>53 (5)</td>
<td>58%</td>
</tr>
</tbody>
</table>

#### PETHEMA (n= 276)

<table>
<thead>
<tr>
<th>No of risk factors</th>
<th>No of patients, n(%)</th>
<th>Progression at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>127 (46)</td>
<td>2%</td>
</tr>
<tr>
<td>1</td>
<td>133 (48)</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>16 (6)</td>
<td>46%</td>
</tr>
</tbody>
</table>

### Risk Factors

- non IgG MGUS
- M protein > 1.5 g/dl
- FLC ratio < 0.26 or > 1.65

Rajkumar, Blood, 2005

### Risk Factors

- >= 95% of abnormal BMPC *
- DNA aneuploidy

* Decreased CD38 expression, expression of CD56, absence of CD19 and/or CD45

Perez-Persona, Blood, 2007
### Isotype IgG

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### M protein level

<table>
<thead>
<tr>
<th></th>
<th>&lt; 15 g/l</th>
<th>15 g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### FLC (kappa/lambda) ratio

<table>
<thead>
<tr>
<th></th>
<th>Normal ratio 0.26 ≤ x &lt; 1.65</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

### Total Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk of progression</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate-1 risk of progression</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate-2 risk of progression</td>
</tr>
<tr>
<td>3</td>
<td>High risk of progression</td>
</tr>
</tbody>
</table>

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Caers, Ann Med 2013
Rajkumar, Blood, 2005
Current IMWG recommendation

• **Low-risk MGUS**
  – Baseline BM cytology and skeletal survey not routinely indicated
  – Serum electrophoresis in 6 months and if stable, follow either every 2 years or if symptoms arise

• **Intermediate and high-risk MGUS**
  – Baseline BM cytology/biopsy and skeletal survey
  – Blood analysis (including serum electrophoresis) repeated in 6 months and than annually

Kyle, IMWG criteria, Leukemia 2010
Every MM is preceded by an MGUS

<table>
<thead>
<tr>
<th>Years prior to MM</th>
<th>M-spike</th>
<th>Abnormal FLC ratio</th>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>25/27</td>
<td>23/27</td>
<td>27/27</td>
</tr>
<tr>
<td>3</td>
<td>54/58</td>
<td>46/58</td>
<td>57/58</td>
</tr>
<tr>
<td>4</td>
<td>45/48</td>
<td>29/46</td>
<td>47/48</td>
</tr>
<tr>
<td>5</td>
<td>34/37</td>
<td>25/37</td>
<td>35/37</td>
</tr>
<tr>
<td>6</td>
<td>25/25</td>
<td>19/25</td>
<td>25/25</td>
</tr>
<tr>
<td>7</td>
<td>14/15</td>
<td>11/15</td>
<td>14/15</td>
</tr>
<tr>
<td>8 or more</td>
<td>13/17</td>
<td>8/17</td>
<td>14/17</td>
</tr>
</tbody>
</table>

Landgren, Blood 2009
MGUS, not that benign

- Increased risk of fractures
- Decreased bone densities
- Increased risk for venous and arterial thrombosis
- Neuropathy
  - IgM anti-MAG neuropathie
  - IgA, IgA CIPD
- Increased risk of infections
Smoldering Multiple Myeloma
Smoldering MM

- 276 SMM patients diagnosed 1970-1995
- 163 (59%) progressed
  - 158 MM
  - 5 amyloidosis
- Overall risk of progression (per year)
  - 10% in the first 5 years
  - 3% in the next 5 years
  - 1% in the next 5 years

Kyle, NEJM, 2007
Heterogenous entity

M-Protein > 30 g/l, PC > 10%

M-Protein < 30 g/l, PC > 10%

M-Protein > 30 g/l, PC < 10%

2 yr

8 yr

19 yr
Is it possible to identify high-risk patients?

Has an early treatment an additive value?

Cure?

Delay progression?

Limit complications?

Select an aggressive clone?
<table>
<thead>
<tr>
<th>Ultra-high risk (&gt; 80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow plasmocytosis &gt; 60%</td>
</tr>
<tr>
<td>Serum free light chain ratio &gt; 100</td>
</tr>
<tr>
<td>&gt; 1 focal lesion on axial MRI</td>
</tr>
</tbody>
</table>
Bone Marrow: plasmocytosis

Rajkumar, NEJM, 2011

Rago, Cancer, 2012
Serum: FLC > 100

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMPC, %</td>
<td>3.24</td>
</tr>
<tr>
<td>Serum M-spike</td>
<td>3.16</td>
</tr>
<tr>
<td>FLC ratio &gt; 100</td>
<td>3.23</td>
</tr>
</tbody>
</table>

Larsen, Leukemia 2013

Kastritis, Leukemia 2012
MRI

Axial MRI (n 96)

Whole body MRI (n 147)

Kastritis, Leukemia, 2013

Hillengass, JCO, 2010
Diagnosis of MM requires the presence of a clonal bone marrow plasmocytosis ≥10% or biopsy proven plasmacytoma and 1 or more of the following criteria

<table>
<thead>
<tr>
<th>Evidence of end organ damage, attributable to the underlying plasma cell proliferative disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Hypercalcemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarkers of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Clonal bone marrow plasma cells ≥60%</td>
</tr>
<tr>
<td>o Involved/uninvolved serum free light chain ratio ≥100</td>
</tr>
<tr>
<td>o &gt;1 focal lesions on magnetic resonance imaging studies</td>
</tr>
</tbody>
</table>

Rajkumar, Lancet Oncology, 2014
<table>
<thead>
<tr>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAYO CRITERIA (PC, M-protein, FLC)</strong></td>
</tr>
<tr>
<td><strong>PETHEMA CRITERIA (Flow cytometry and immunoparesis)</strong></td>
</tr>
<tr>
<td>Increase in paraprotein during follow-up</td>
</tr>
<tr>
<td>Diffuse bone marrow infiltration on MRI</td>
</tr>
<tr>
<td>Presence of circulating plasma cells</td>
</tr>
<tr>
<td>High-risk cytogenetics (del 17p, t(4;14), +1q21)</td>
</tr>
</tbody>
</table>
**Risk Stratification for SMM**

### Mayo Clinic (n = 273)

<table>
<thead>
<tr>
<th>No of risk factors</th>
<th>No of patients, n(%)</th>
<th>Progression at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76 (25)</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>115 (42)</td>
<td>51%</td>
</tr>
<tr>
<td>3</td>
<td>82 (30)</td>
<td>76%</td>
</tr>
</tbody>
</table>

**Risk Factors**
- BMPC > 10%
- M protein > 3 g/dl
- FLC ratio < 0.126 or > 8

Dispenzieri, Blood, 2008

### PETHAMA (n = 89)

<table>
<thead>
<tr>
<th>No of risk factors</th>
<th>No of patients, n(%)</th>
<th>Progression at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28 (31)</td>
<td>4%</td>
</tr>
<tr>
<td>1</td>
<td>22 (25)</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>39 (44)</td>
<td>72%</td>
</tr>
</tbody>
</table>

**Risk Factors**
- > 95% of abnormal BMPC *
- Immunoparesis

* Decreased CD38 expression, expression of CD56, absence of CD19 and/or CD45

Perez-Persona, Blood, 2007
PETHEMA

- > 95% of abnormal BMPC *
- Immunoparesis

p = 0.003

Median 23 months
n = 39 (28 progr.)

> 95% aPC/BMPC + paresis
n = 22 (10 progr.)

Median 73 months

No adverse factors
n = 28 (1 progr.)

Median not reached
Mayo Clinic Model

BMPC > 10%
M protein > 3 g/dl
FLC ratio < 0.126 or > 8

Gr 1: TTP 1.9 y
Gr 2: TTP 5 y
Gr 3: TTP 10 y

Dispenzieri, Blood, 2008
Progressive M-Component

Increase ≥ 10% in the M-protein level in each of the first two consecutive follow-up visits.

Rosinol, BJH 2003
## Cytogenetics

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>P</th>
<th>Median TTP (years)</th>
<th>TTP rate % at 3 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chromosomal aberrations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(17p13)</td>
<td>2.9</td>
<td>0.001</td>
<td>2.04 vs 5.62</td>
<td>56 vs 30</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>2.2</td>
<td>0.003</td>
<td>2.91 vs 5.71</td>
<td>55 vs 28</td>
</tr>
<tr>
<td>+1q21</td>
<td>1.66</td>
<td>0.02</td>
<td>3.86 vs NA</td>
<td>43 vs 27</td>
</tr>
<tr>
<td><strong>high risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperdiploidy</strong></td>
<td>1.67</td>
<td>0.016</td>
<td>3.92 vs NA</td>
<td>35 vs 29</td>
</tr>
<tr>
<td><strong>High tumor mass</strong></td>
<td>4.27</td>
<td>&lt; .001</td>
<td>1.23 vs 9.03</td>
<td>67 vs 23</td>
</tr>
<tr>
<td><strong>Bone marrow plasma cells (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>0.8</td>
<td>0.67</td>
<td>5.62</td>
<td></td>
</tr>
<tr>
<td>≥ 20</td>
<td>2</td>
<td>0.001</td>
<td>3.93</td>
<td>41</td>
</tr>
<tr>
<td>≥ 60</td>
<td>4.74</td>
<td>0.018</td>
<td>0.62</td>
<td>N/A</td>
</tr>
<tr>
<td>Abnormal sFLC</td>
<td>11.23</td>
<td>0.001</td>
<td>2.7 vs NA</td>
<td>50 vs 8</td>
</tr>
<tr>
<td>Aberrant plasma cells 95%</td>
<td>4.37</td>
<td>&lt; .001</td>
<td>1.23 vs 9.03</td>
<td>67 vs 23</td>
</tr>
</tbody>
</table>
Cytogenetics

Table 2. MCL outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>TTP rate at 3 years (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>T mass low, CA risk low</td>
<td>128</td>
<td>15</td>
<td>1 (1.0 to 1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T mass low, CA risk high</td>
<td>67</td>
<td>42</td>
<td>2.26 (1.16 to 4.40)</td>
<td>.016</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T mass high, CA risk low</td>
<td>29</td>
<td>64</td>
<td>4.13 (2.26 to 7.54)</td>
<td>&lt;.001</td>
<td>.53</td>
</tr>
<tr>
<td>T mass high, CA risk high</td>
<td>21</td>
<td>55</td>
<td>6.97 (3.98 to 12.22)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

N = 290

Progressing Patients (%) vs Time Since BM Assessment (years)
Cytogenetics

Initiation of PCD

Death

i

MGUS

SMM

Active MM

ii

MGUS

SMM

Active MM

iii

MGUS

SMM

Active MM

Dispenzieri, Blood 2013
Diffuse MRI pattern

Axial MRI (n 96)

Whole body MRI (n 96)

Table 3. Results of the Multivariate Analysis of All Variables and of Selected Variables for Progression-Free Survival

<table>
<thead>
<tr>
<th>Variable by Multivariate Analysis Type</th>
<th>Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI-FL above cutoff point of one FL</td>
<td>3.01</td>
<td>.002</td>
</tr>
<tr>
<td>Diffuse bone marrow infiltration in MRI</td>
<td>2.37</td>
<td>.03</td>
</tr>
<tr>
<td>M protein concentration ≥ 40 g/L</td>
<td>1.87</td>
<td>.44</td>
</tr>
<tr>
<td>Presence of IgA</td>
<td>0.84</td>
<td>.71</td>
</tr>
<tr>
<td>Reduction of uninvolved Ig</td>
<td>1.03</td>
<td>.95</td>
</tr>
<tr>
<td>Presence of urinary Bence Jones protein</td>
<td>0.94</td>
<td>.87</td>
</tr>
<tr>
<td>Plasma cell infiltration in bone marrow ≥ 20%</td>
<td>1.30</td>
<td>.53</td>
</tr>
<tr>
<td>Final model after backward selection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI-FL cutoff point</td>
<td>3.25</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diffuse bone marrow infiltration in MRI</td>
<td>2.64</td>
<td>.006</td>
</tr>
</tbody>
</table>

Kastritis, Leukemia, 2013

Hillengass, JCO, 2010
The Bologna group (n=73)
- Six out of 9 patients with a positive PET/CT progressed to symptomatic myeloma during their follow-up. The probability of progression within 3 years for patients with positive PET/CT was 65% vs 42% for PET/CT negative patients.

The Mayo Clinic (n=132)
- 19/33 patients (56%) with a positive PET-CT progressed to active myeloma within 2 years; in contrast to 28% with a negative PET/CT (22).
Circulating plasmocytes

More than 5% of plasmocytes based on an immunofluorescent assay performed on fixed peripheral blood mononucleated cells.

Bianchi, Leukemia 2013
IMWG considers that a prognostic factor that is able to identify

SMM cases with \(~80\%\) risk of progression at 2 years (median time of transformation 12 months)

justifies an early intervention
<table>
<thead>
<tr>
<th>Risk group</th>
<th>Probability of progression to myeloma or related disorder in first 2 years from initial diagnosis of SMM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow clonal plasma cells $\geq 60%$</td>
<td>90</td>
</tr>
<tr>
<td>Serum involved/uninvolved free light chain ratio $\geq 100$</td>
<td>80</td>
</tr>
<tr>
<td>Abnormalities on MRI ($&gt;1$ focal lesion)</td>
<td>70</td>
</tr>
<tr>
<td>Abnormal plasma cell immunophenotype $\geq 95%$</td>
<td>50</td>
</tr>
<tr>
<td>Evolving type of SMM*</td>
<td>65</td>
</tr>
<tr>
<td>$t(4;14)$ or del 17p</td>
<td>50</td>
</tr>
<tr>
<td>$M$ protein $\geq 30$ g/l and bone marrow clonal plasma cells $\geq 10%$</td>
<td>50</td>
</tr>
<tr>
<td>Serum involved/uninvolved free light chain ratio $\geq 8$ and $&lt;100$</td>
<td>40</td>
</tr>
<tr>
<td>No high-risk factors</td>
<td>10–20</td>
</tr>
</tbody>
</table>
International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, Maria-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstrathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Reksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel
Diagnosis of MM requires the presence of a clonal bone marrow plasmocytosis ≥10% or biopsy proven plasmacytoma and 1 or more of the following criteria

- **Evidence of end organ damage, attributable to the underlying plasma cell proliferative disorder**
  - Hypercalcemia
  - Renal insufficiency
  - Anemia
  - Bone lesions

- **Biomarkers of malignancy**
  - Clonal bone marrow plasma cells ≥60%
  - Involved/uninvolved serum free light chain ratio ≥100
  - >1 focal lesions on magnetic resonance imaging studies

Rajkumar, Lancet Oncology, 2014
### Should we treat SMM?

#### Conventional chemotherapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>N</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early MP vs deferred MP</td>
<td>25</td>
<td>52</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP vs observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early MP vs observation</td>
<td>75</td>
<td>40</td>
<td>79</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>55</td>
<td>48</td>
<td>71</td>
</tr>
</tbody>
</table>

- Early MP vs deferred MP
- MP vs observation

No differences in survival and potential risk of secondary leukemia

HJjorth, Eur J Haematol. 1993
Grignani, Br J Cancer 1996
Riccardi, Br J Cancer, 2000
## Should we treat SMM?

### Biphosphonates

<table>
<thead>
<tr>
<th>Agents</th>
<th>N</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolendronate vs Observation</td>
<td>81</td>
<td></td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>82</td>
<td></td>
<td>46</td>
<td>48</td>
</tr>
</tbody>
</table>

- Increase of bone density and decreased bone resorption markers
- SRE lower in the biphosphonates groups (39 vs 73%; 55 vs 78%)
- No anti-tumor effect

**References:**
- Martin, Br J Haematol, 2002
- D’arena, Leuk Lymphoma, 2011
- Musto, Cancer, 2008
Should we treat SMM?

<table>
<thead>
<tr>
<th>Thalidomide</th>
<th>ORR (%)</th>
<th>TTP (mo)</th>
<th>OS (mo) at 2y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>29</td>
<td>34</td>
<td>96%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thalidomide plus pamidronate</th>
<th>ORR (%)</th>
<th>TTP (mo)</th>
<th>OS (mo) at 4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide plus pamidronate</td>
<td>76</td>
<td>25</td>
<td>91%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thal-Zol vs Zol</th>
<th>ORR (%)</th>
<th>TTP (mo)</th>
<th>OS (mo) at 5y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thal-Zol vs Zol</td>
<td>35</td>
<td>33</td>
<td>74% at 5y</td>
</tr>
</tbody>
</table>

~ 30% ≥ PR; high toxicity; patients achieving PR had a shorter time to treatment

60% at 4y  91% at 4y

37%  0%
2.4 y  1.2 y
74% at 5y  73% at 5y

Rajkumar, Leukemia, 2003
Barlogie, Blood, 2008
Witzig, Leukemia, 2013
Should we treat SMM?

PETHEMA trial

Selection of high risk patients

PCs BM ≥ 10% plus M-protein ≥ 30 g/L

or

BM aPC/nPC > 95% plus immunoparesis
Should we treat SMM?

**Lenalidomide**

**Induction**
Nine 4-week cycles

**Treatment arm**
(n = 60)

- **Lenalidomide**
  25 mg/daily during 21d every 28 d

- **Dexamethasone**
  20 mg D1-D4 and D12-D15 every 28 d

**Maintenance**

- **Lenalidomide**
  10 mg/daily during 21 d every month*

**Control arm**
(n = 66)

- **Therapeutic abstention**

---

Mateos, ASH 2011
TTP to active disease

Lenalidomide maintenance
24 patients biological progressions
18 patients -- Dexa 20 mg d1-d4
3 PR
11 SD
4 MM

Median follow-up

No treatment
Median TTP: 23m
37 Progressions (59%)
20 patients: bone disease
7 patients: renal failure

Median TTP: NR
4 Progressions (7%)
4 pts: symptomatic PD

HR: 12.3; 95% IC (4.4–34.7); p < 0.0001
OS from inclusion

Median follow-up: 32 months (range 12–49)

Proportion of patients alive

Time from inclusion

Lenalidomide + Dex: 93% at 3 years
No treatment: 76% at 3 years

p=0.04

Mateos, ASH 2011
IMWG recommendations

• Ultra-risk patients are recommended to be treated
  – Potential harmful organ complications with significant long-term morbidity need to be avoided
  – Based patients’ health status and patients’ choice

• High risk patients should be followed regularly and might be candidates for early intervention clinical studies.

• Low risk patients: follow-up.
Conclusions

• MGUS and sMM are the most prevalent premalignant conditions in worldwide population

• Active myeloma for nearly all patients is preceded by MGUS/sMM.

• Prognostic categorization of MGUS and sMM is crucial to tailor their follow-up