From myeloma precursor diseases to Multiple Myeloma

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University Hospital of Salamanca
Salamanca. Spain
1. Diagnosis
   • Diagnostic criteria
   • Differential diagnosis

2. Pronostic factors

3. Therapeutic approaches
### Myeloma precursor diseases: diagnostic criteria

<table>
<thead>
<tr>
<th>Monoclonal Gammopathy of uncertain significance (MGUS)</th>
<th>Smouldering Multiple Myeloma (SMM)</th>
<th>Symptomatic Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal component</td>
<td></td>
<td>Present (serum/urine)</td>
</tr>
<tr>
<td>&lt; 3 g/dL serum</td>
<td>≥3 g/dL serum</td>
<td>AND</td>
</tr>
<tr>
<td>AND</td>
<td>AND/OR</td>
<td>AND</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>≥ 10%</td>
<td>AND</td>
</tr>
<tr>
<td>AND</td>
<td>AND</td>
<td>AND</td>
</tr>
<tr>
<td>Bone Marrow Plasma Cells (%)</td>
<td>End Organ Damage a</td>
<td>Present</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>End Organ Damage a</td>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Present/urine</td>
<td>Present/urine</td>
<td></td>
</tr>
</tbody>
</table>

**a)** Myeloma Related Organ or Tissue Impairment (end organ damage) related to Plasma cell proliferative process: anemia with 2 g/dL below the normal level or <10 g/dL, or serum calcium level >10 mg/L (0.25 mmol/L) above normal or >110 mg/dL (2.75 mmol/L), or lytic bone lesions or osteoporosis with compressive fractures, or renal insufficiency (creatinine >2 mg/dL or 173 mmol/L), [CRAB: Calcium increase, Renal impairment, Anemia and Bone lesion] or symptomatic hyperviscosity, amyloidosis or recurrent bacterial infections (>2 episodes in 12 m).

**b)** For symptomatic multiple myeloma, a minimum level of M-component or BM plasma cell infiltration (although usually it is >10%, is not required, provided that this two features coexists with the presence of end organ damage.

International Working Group (BJH 2003; 121:749)
Myeloma precursor diseases: diagnostic criteria

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</tr>
<tr>
<td>End Organ Damage</td>
<td>Absent</td>
<td>Absent</td>
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**Concomitant diseases that can mimic MM:**
- Increase of serum Cr due to diabetes or hypertension
- Anemia due to deficiency, chronic disease,..
- Diffuse osteoporosis
- Hyperparatiroidism
- Single asymptomatic bone lesion
Are there any risk factors predicting progression to active disease?

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Abnormal sFLC ratio
- Evolving MM
- Abnormal MR Imaging studies (MRI)

* After IMWG consensus criteria

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Smouldering Multiple Myeloma: PCs BM infiltration and Serum M-component level

Group 1: \( \text{PCBM} \geq 10\% + \MC \geq 3\text{g/dl} \)
Group 2: \( \text{PCBM} \geq 10\% + \MC < 3\text{g/dl} \)
Group 3: \( \text{PCBM} < 10\% + \MC \geq 3\text{g/dl} \)

TTP:
- Group 1: 2 y
- Group 2: 8 y
- Group 3: 19 y

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
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Smouldering Multiple Myeloma: serum immunoglobulin free-light chain (FLC) ratio (n:273)

Serum FLC ratio >0.125 or < 8
Smouldering Multiple Myeloma: serum immunoglobulin free-light chain (FLC) ratio (n=273)

- Serum FLC ratio >0.125 or < 8
- PCsBM Infiltration ≥ 10%
- Serum M protein ≥ 3 g/dL
- Serum FLC ratio <1/8 or >8

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

Dispenzieri A. Blood 2008; 111:785-9
Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Abnormal sFLC ratio
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
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* After IMWG consensus criteria

Smouldering Multiple Myeloma: Aberrant PCs by immunophenotype plus immunoparesis

- >95% aPC/BMPC + paresis
  - n= 39 (28 progr.)
  - Median 23 months

- >95% aPC/BMPC or paresis
  - n= 22 (10 progr.)
  - Median 73 months

- No adverse factors
  - n= 28 (1 progr.)
  - Median not reached

5 years p= 0.003

82%

42%

8%

% Time to progression

Months

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Abnormal sFLC ratio
- Evolving MM
- Abnormal MR Imaging studies (MRI)

* After IMWG consensus criteria

Smouldering Multiple Myeloma: evolution pattern: evolving vs nonevolving (n:48)

Evolving SMM (22): Previous history of MGUS; progressive increase of M-protein

Non-evolving (26): Stable serum M-protein until progression occurs

Evolving SMM TTP: 1.3 years

Non-evolving SMM TTP: 3.9 years

p < 0.007

Smouldering Multiple Myeloma: prognostic factors

- Serum level of Monoclonal Component (>3g/dl)
- Plasma Cells Bone Marrow infiltration (PCs>10%)
- Aberrant Plasma Cells by immunophenotype (≥ 95%)
- Reduction in uninvolved immunoglobulins
- Abnormal sFLC ratio
- Evolving MM
- Abnormal MR Imaging studies (MRI)

*After IMWG consensus criteria*

Smouldering Multiple Myeloma: MRI

43 pts with asymptomatic MM

**Spinal MRI:** 50% of pts: marrow involv
Patterns: Diffuse, variegated and **focal**

55 pts with stage I MM

**Spinal MRI:** 31% of pts: marrow involv
Patterns: Diffuse, variegated and **focal**

**Mariette et al. Br J Hematol 1998; 104:723-9**

Smouldering Multiple Myeloma: Whole MRI

149 patients with asymptomatic MM

**Whole MRI:** 28% of pts: Focal lesions

> 1 Focal lesion plus diffuse pattern → adverse prognosis

Recent data regarding prognostic factors in SMM

- New prognostic factors to identify high risk SMM patients
- Identification of ultra high risk SMM patients
Del(17p), t(4;14), and +1q21 predict progression from smoldering to symptomatic MM (n=248)

- del(17p13), t(4;14), +1q21 showed significant impact on TTP
- Presence of t(11;14) and del(13q14) of no statistical significance

<table>
<thead>
<tr>
<th></th>
<th>TTP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>4.9 years</td>
<td></td>
</tr>
<tr>
<td>+1q21 versus no gain of 1q21</td>
<td>3.7 years 5.3 years</td>
<td>0.013</td>
</tr>
<tr>
<td>del(17p13) versus no del(17p13)</td>
<td>2.7 versus 4.9 years</td>
<td>0.019</td>
</tr>
<tr>
<td>t(4;14) versus no t(4;14)</td>
<td>2.9 versus 5.2 years</td>
<td>0.021</td>
</tr>
<tr>
<td>HD versus NHD</td>
<td>3.9 versus 5.7 years</td>
<td>0.036</td>
</tr>
</tbody>
</table>

- Multivariate analysis: t(4;14), +1q21, HD, reduction of uninvolved immunoglobulins and risk score defined by Kyle et al. as independent factors for adverse outcome
- Conclusion: specific chromosomal aberrations drive transition from asymptomatic to symptomatic disease

Neben et al. ASH 2012 (Abstract 1806), poster presentation
Prognostic significance of whole MRI for patients with SMM

- **Retrospective study:** whole body MRI
  - 157 pts with SMM, 138 pts with MGUS, 249 pts MM

- **Results**

<table>
<thead>
<tr>
<th></th>
<th>MGUS patients</th>
<th>SMM patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal lesions</strong></td>
<td>23.9%</td>
<td>34.4%</td>
</tr>
<tr>
<td><strong>Diffuse infiltration</strong></td>
<td>53%</td>
<td>45.9%</td>
</tr>
<tr>
<td><strong>Adverse prognostic factors for PFS</strong></td>
<td>Presence and no. of focal lesions, severe diffuse infiltration Multivariate analysis: number of focal lesions (p=0.0005)</td>
<td>Plasma cell percentage, moderate diffuse infiltration (but not focal lesions), beta2-microglobulin</td>
</tr>
</tbody>
</table>

*Hillengass et al. ASH 2012 (Abstract 2911), poster presentation*
Ultra-high risk SMM: Serum involved/uninvolved free-light chain (FLC) Ratio

N = 586 patients

Median TTP: 15 m
Median TTP: 55 m

Larsen JT et al. Leukemia 2012; published online on October 16
Ultra-high risk SMM: peripheral blood plasma cell circulating (>5x10^6/L and/or 5% per 100 cytoplasmic Ig-positive PB mononuclear cells)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Median TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High circ PC</td>
<td>14 pts (15%)</td>
<td>12</td>
</tr>
<tr>
<td>Low circ PC</td>
<td>77 pts (85%)</td>
<td>57</td>
</tr>
</tbody>
</table>

P value: <0.001

Ultra-high risk SMM: Plasma Cells in the Bone Marrow at baseline

N= 655 patients

Should myeloma precursors diseases definitions revisited?

Definition of SMM should be revisited
Smoldering MM: Definition should be revisited


- Early MM: Median 23 months
- Median not reached

- MGUS: Median 73 months
- 82%
- 42%
- 8%
The standard of care is **no treatment** until disease progression occurs.

**Smouldering multiple myeloma**: management.


![Graph showing the progression of smouldering multiple myeloma and MGUS over years since diagnosis](chart.png)
Smoldering Multiple Myeloma: Management

## Conventional Chemotherapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>n</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS (mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>55</td>
<td>12 m</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>55</td>
<td>–</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

Abandon: No differences in survival and potential risk of secondary leukemias
## Bisphosphonates

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate vs** observation</td>
<td>88</td>
<td>–</td>
<td>48 m</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Zolendronic acid vs** observation</td>
<td>82</td>
<td>–</td>
<td>59 m</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

* Increase of bone density and decrease of bone resorption markers.

** Skeletal related events lower in the bisphosphonate groups (39% vs 73% and 55% vs 78%).

No anti-tumor effect
# Smoldering Multiple Myeloma: Management

## Thalidomide

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>ORR (%)</th>
<th>TTP</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Thalidomide*              | 29 | 34      | 63% at 2 yrs | 96% at 2 yrs | Rajkumar SV, et al. Leukemia 2003; 17: 775-779.
| Thal+Zol vs Zol           | 68 | 37-0%   | 4.3 -3.3y  | 74-73% at 5y | Witzig TE, et al. Leukemia 2013; 27: 220-5   |

* Low ORR plus Grade 3/4 AEs in 21%; dose reduction in 100%.

**Dose reduction in 86%; 50% discontinued. Patients in ≥ PR had a shorter time to treatment (< 2 years).
All these trials don’t support the early treatment in smoldering MM patients.

But…none of these trials discriminate the low risk patients (that probably will not benefit from intervention) from the high risk group, that may be the target for therapy.
QuiRedex: early treatment in high-risk SMM

Time elapsed from diagnosis to inclusion not superior to 5 years
No CRAB (hypercalcemia, anemia, bone lesions, renal impairment) or symptoms

Group 1: PCBM ≥ 10% + MC ≥ 3g/dl or
PCs BM ≥ 10% or M-protein ≥ 30 g/L
but BM aPC/nPC ≥ 95% plus immunoparesis

TTP: 2 y
TTP: 8 y
TTP: 19 y

% Time to progression

5 years

p = 0.003

Median 23 months

46%
Median 73 months

72%
Median not reached

4%

Months

QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial

**Induction**
- 9 x 28-day cycles
- **Lenalidomide** 25 mg/day on Days 1-21 +
- **Dexamethasone** 20 mg/day on Days 1-4, 12-15

**Maintenance**
- 28-day cycles
- **Lenalidomide** 10 mg/day on Days 1-21
  (Low-dose dexamethasone added at time of biologic progression)

Patients with high-risk smoldering MM
(N = 125)

No Treatment

No Treatment

2 yrs

In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

**Amendment in August 2011: Stop treatment after 2 years**

Lenalidomide + Dex: response rate

On ITT (n = 57) Median number of induction cycles: 9 (range 1–9)

ORR: 80%; sCR: 7%, CR: 7%; VGPR: 11%; PR: 65%; SD: 21%

After 9 induction cycles (n = 51)

After a median of 15 maintenance cycles (2-41) (n=50)

Len-dex vs no treatment: TTP to active disease (n = 119)

ITT analysis

Median follow-up: 40 months (range 27–57)

Lenalidomide + dex

Median TTP: NR

13 Progressions (22%)

No treatment

Median TTP: 21m

46 Progressions (74%)

HR: 5.59; 95% IC (2.9–11); p < 0.0001

<table>
<thead>
<tr>
<th>Condition</th>
<th>G1-2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>15 (28%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (20%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (13%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (20%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (18%)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (24%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Rash</td>
<td>18 (33%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Infection*</td>
<td>25 (46%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>DVT**</td>
<td>3 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

* One infection was Grade 4

**DVT prophylaxis with Aspirin (100mg) in 1 pt, oral anticoagulation in 1 pt with low INR levels and no px in the other one

## QuiRedex: toxicity profile during induction (n:62)

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<tr>
<th>Condition</th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
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<td>4 (7%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (6%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>6 (11%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (11%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (7%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (17%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (23%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Infection*</td>
<td>19 (35%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>DVT**</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
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*Mateos MV, et al. ASH 2011. Abstract 991*
## QuiRedex: toxicity profile during induction (n:125)

<table>
<thead>
<tr>
<th></th>
<th>Len-dex arm (n:62)</th>
<th>Abstention arm (n:63)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G1</td>
<td>G2</td>
</tr>
<tr>
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<td>8 (14%)</td>
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<tr>
<td>Thrombopenia</td>
<td>6 (11%)</td>
<td>1 (2%)</td>
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<tr>
<td>Asthenia</td>
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<td>5 (9%)</td>
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<tr>
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</tr>
<tr>
<td>DVT**</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>SPM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Hematologic</td>
<td>1 patient (PV)</td>
<td>1 patient (MDS)</td>
</tr>
<tr>
<td>-Non hematolog</td>
<td>3 patients*</td>
<td></td>
</tr>
</tbody>
</table>

*2 prostate cancers, 1 breast cancer

Len-dex vs no treatment: OS from inclusion
(n = 119)

Median follow-up: 40 months (range 27–57)

Lenalidomide + Dex: 94% at 3 years
No treatment: 80% at 3 years

HR: 3.24; 95% IC (1.05–9.9); p = 0.02

Len-dex vs no treatment: OS from diagnosis (n = 119)

Median follow-up: 47 months (range 27–104)

Lenalidomide + Dex: 94% at 5 yrs
No treatment: 78% at 5 yrs

HR: 3.5; 95% IC (1–10.8); p=0.01

**Len-dex vs no treatment: OS from diagnosis**

*(n = 119)*

**Median follow-up: 47 months (range 27–104)***

**Len + Dex**
- Proportion of patients alive: 94% at 5 yrs
- HR: 3.5; 95% IC (1–10.8); *p* = 0.01

**No treatment**
- Proportion of patients alive: 78% at 5 yrs

**Deaths:**
- 4 pts
  - Progression disease: 2 pts
  - Treatment-related tox: 1 pts
  - Other: 1 pt

**Deaths:**
- 13 pts
  - Progression disease: 9 pts
  - Treatment-related tox: 3 pts
  - Sudden death at home: 1 pt

---

### Abstention arm: outcome after progression to symptomatic disease

<table>
<thead>
<tr>
<th>Abstention arm</th>
<th>(n=46 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age:</strong></td>
<td>74 yrs</td>
</tr>
<tr>
<td><strong>Treatments received:</strong></td>
<td></td>
</tr>
<tr>
<td>58% bz-based comb (VMP)</td>
<td></td>
</tr>
<tr>
<td>28% ASCT</td>
<td></td>
</tr>
<tr>
<td>13% len-based comb</td>
<td></td>
</tr>
<tr>
<td>8% MP or conventional QT</td>
<td></td>
</tr>
<tr>
<td><strong>60% of pts alive at 3 yrs after progression</strong></td>
<td></td>
</tr>
</tbody>
</table>

**VISTA trial: 3 yr-OS: 69%**

Myeloma precursor diseases: Conclusions

- High-risk SMM patients should be called early Multiple Myeloma
- Len-dex is effective as early treatment, with benefit in TTP to active disease and also in OS
- Numerous clinical trials with several drugs are currently ongoing in this group of patients
Current Studies in High-Risk Smoldering MM

- **Lenalidomide** or observation (phase III)[1]
- Biomarker study of **elotuzumab** (phase II)[2]
- **Siltuximab** (anti IL6) or no treatment (phase II)[3]
- Biomarker study of **BHQ880 (anti DKK1)** (phase II)[4]:
  *Data presented at ASH2012: no antitumor effect but anabolic activity*
- **MLN9708 and dexamethasone** (phase II)[5]
- **Carfilzomib, lenalidomide, and dexamethasone** (phase II)[6]:
  *Very promising efficacy results were presented in Kyoto: 83% nCR/sCR*

2. ClinicalTrials.gov. NCT01441973.
5. ClinicalTrials.gov. NCT016609973.
Myeloma precursor diseases

- High-risk SMM patients should be called *early Multiple Myeloma*

- Len-dex is effective as early treatment, with benefit in TTP to active disease and also in OS

- Numerous clinical trials are currently ongoing in this group of patients

> These results support to change the current treatment paradigm for this patient population

*Early treatment in Early MM patients*