MULTIPLE MYELOMA AFTER AGE OF 80 YEARS

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Epidemiology

• SEER Program between 1990-2004: 17 330 MM cases, 51% ≥ 70 y and 20% ≥ 80 y. 
  Brenner et al; Blood 2007 (on line)


• Thames Cancer Registry (99-2000): 855 MM cases, Median age 73 y, 4.82 cases per 100 000 for all, 38.35 cases per 100 000 by age 85+y. 
  Phekoo et al; BJH 2004; 127: 299-304
Age- and sex-specific incidence rates per 100 000 inhabitants per year for MM in the South Thames area between 1999 and 2000.

Presenting Features and Prognostic factors

• French retrospective series of 130 unselected MM pts 75+ y at diagnosis (1985-96, 7 centers): Identical presenting features to those reported in younger patients. Median Overall Survival 22 m. Pc Factors: age ≥85+y, PS ≥2, Creat ≥120 µm/l. 

• Greek myeloma study group data base (87-04): 1162 pts in all, 357 >70y (31%). Clinical, laboratory features similar except for advanced ISS. 
Survival

- SEER Program between 1990-2004:
  stronger increases for pts <50 y, and 50-59 y.
  No improvement among older pts.
  5 y survival 15%, 10 y survival 6% for pts 80+ y.
  *Brenner et al; Blood 2007 (on line)*

- National cohort in Sweden between 1994 - 2003:
  5 y survival: 27% pts 71-80 y, 19% pts 81+ y.
  *Kristinsson et al; J Clin oncol 2007; 25: 1993-99*

- Thames Cancer Registry (99-2000):
  Median survival 42m pts <65y, 18m pts >65y.
  *Phekoo et al; BJH 2004; 127: 299-304*
Period estimates of 10-year survival of patients with MM by major age groups in defined calendar periods from 1984-1986 to 2002-2004.

Brenner et al; Blood 2007 (on line)
Treatment

• The MP-T combination has become the standard treatment for newly diagnosed MM patients aged 65 to 75 years.

• However, no specific recommendation exists for pts >75 years regarding the benefit of adding thalidomide to MP.

• Patients older than 75 years have frequently been excluded from large clinical trials, although they represent more than 20% of MM pts.

Facon et al; Lancet 2007; 370: 1209-1218
Primary treatment with Melphalan, Dexamethasone and Thalidomide

- Opened Greek trial, 50 pts ≥ 75 years
- Melphalan 8 mg/m² + DXM 12 mg/m² + Thalidomide 300 mg/d (D 1-4) 12 cycles
- 62% PR > 50% + 10% CR (IF-)
- TTP = 21.2 months, OS = 28.2 months
- Toxicities (grade ¾): neutropenia 22%, thrombopenia 10%, TVP 9%
- Neuropathy (grade ½): 9%

Dimopoulos MA., the hematology journal 2006;91:252-254
IFM 01/01 Study Protocol:
In Newly Diagnosed Pts >75 yrs with MM

12 cycles MP, every 6 weeks

- Melphalan 0.2 mg/kg/d Day 1-4
- Prednisone 2 mg/kg/d Day 1-4

Double Blind

Placebo
2 caps 50 mg/d
72 weeks, continuously

Thalidomide
2 caps 50 mg/d
72 weeks, continuously

Clodronate was given to all pts;
No anti-coagulant prophylaxis was planned.
IFM 01/01 Study Protocol: In Newly Diagnosed Pts >75 yrs with MM

- The primary end-point was overall survival (OS).
- Secondary end-points were progression-free survival (PFS), response, and toxicity.
- The first central randomization was performed in April 2002.
- An interim analysis was planned after 200 pts were enrolled (April 2007).
- The trial was stopped after enrollment of 232 pts.

*Hulin et al. J Clin Oncol 2007; 441s (abstr 8001)*
### Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MP (n=100)</th>
<th>MP-T (n=100)</th>
<th>All Pts (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50%</td>
<td>39%</td>
<td>45%</td>
</tr>
<tr>
<td>Median age, yrs</td>
<td>77.9</td>
<td>79.2</td>
<td>78.9</td>
</tr>
<tr>
<td>&gt; 80 yrs</td>
<td>29%</td>
<td>38%</td>
<td>33.5%</td>
</tr>
<tr>
<td>Significant Comorbidity</td>
<td>60%</td>
<td>64%</td>
<td>62%</td>
</tr>
<tr>
<td>ISS Stage III</td>
<td>28%</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td>M-Component, IgG</td>
<td>60%</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td>B2 M ≥ 3.5 mg/l</td>
<td>66%</td>
<td>67%</td>
<td>67%</td>
</tr>
</tbody>
</table>
### Toxicity (1)

<table>
<thead>
<tr>
<th>Condition</th>
<th>MP (n=100)</th>
<th>MP-T (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>Grade 1: 18%</td>
<td>19%</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Grade 2: 4%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3: 2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3-4: 9%</td>
<td>21%</td>
<td>.01</td>
</tr>
<tr>
<td>Depression</td>
<td>Grade 2-4: 2%</td>
<td>8%</td>
<td>.04</td>
</tr>
</tbody>
</table>
## Toxicity (2)

<table>
<thead>
<tr>
<th></th>
<th>MP (n=100)</th>
<th>MP-T (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombosis</strong></td>
<td>Grade 3-4</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>Grade 2-4</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Somnolence</strong></td>
<td>Grade 2-4</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Nausea/Vomiting</strong></td>
<td>Grade 2-4</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Oedema</strong></td>
<td>Grade 2-4</td>
<td>8%</td>
</tr>
</tbody>
</table>
### Response to Treatment: Best Response at 12 months

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>MP-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least PR (50%)</td>
<td>31%</td>
<td>61%</td>
</tr>
<tr>
<td>At least VGPR (90%)</td>
<td>8%</td>
<td>23%</td>
</tr>
<tr>
<td>Complete Remission</td>
<td>1%</td>
<td>7%</td>
</tr>
</tbody>
</table>

$\text{p} < 0.0001$
PFS by Treatment: ITT, n=200 Pts

**Survival Distribution Function**

- **MP Thalidomide**
  - **PFS** = 24.1 months
  - [19.8 – 29]   Y/N=61/39

- **MP Placebo**
  - **PFS** = 19 months
  - [14.1 – 21.3]   Y/N=79/21

**Log-Rank test p=0.001**

**Graph Details:**
- **X-axis:** Time from randomization (months)
- **Y-axis:** Survival distribution

**Graph Legend:**
- Red line: MP Thalidomide
- Black line: MP Placebo
OS by Treatment: ITT, n=200 Pts

Survival Distribution Function

Log-Rank test $p=0.05$
Median follow-up time = 24 months

MP Thalidomide
Median OS = 45.3 m
[33.3 – Unreached] Y/N=39/61

MP Placebo
Median OS = 27.7 m
[24.6 – 34.9] Y/N=54/46
Treatment : Near future

- Spanish Phase ½ study (PETHEMA) :
  MP + Bortezomib 60 pts ≥ 65y, median age 75y.
  At least PR > 50% = 88%, PFS = 83% at 16m,
  Neutropenia 43%, Neuropathy 18% (grade ¾)

- Italian Phase ½ study (GIMEMA) :
  MP + Lenalidomide 53 pts ≥ 65y.
  At least PR > 50% = 81%, PFS = 92% at 12m,
  Neutropenia (grade ¾) = 68%
Conclusions (1)

- MP-T is effective for pts >75 years with newly diagnosed MM and showed clear superiority vs. MP in prolonging PFS and OS.

- The toxicity associated with MP-T in pts > 75 years was acceptable.
  - Shortened thalidomide treatment duration could reduce neurotoxicity.
  - LMWH or Aspirine prophylaxis could reduce thrombosis.

- MP-T could be the reference treatment for all patients older than 65 years with newly diagnosed Multiple Myeloma.
Conclusions (2)

• Within the past decade survival increased for young patients but no progress have been done for older patients although patients ≥ 80 years represent more than 20% MM patients.

• All the new agents effective in MM (Thalidomide, Bortezomib, Lenalidomide) could be prescribed to older patients. Toxicities are acceptable and manageable.

• A new era of progress is opened for these very elderly patients.
Back up Slides
Treatment after Progression

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MP (n=72)</th>
<th>MP-T (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts treated with Thalidomide after Progression</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>Pts treated with Bortezomib after Progression</td>
<td>32%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Survival Time after Progression

Survival Distribution Function

Time from progression (months)

MP-Thalidomide
Median 9.3 months
[4.2-Unknown]  O/N=26/48

MP Placebo
Median 9.8 months
[6.9-17.4]  O/N=39/64