Multiple Myeloma in 2012
transplant or not transplant?

Professor Philippe Moreau
University Hospital, Nantes, France
IFM90 trial

Tandem ASCT:

effective therapy in patients not achieving VGPR after the 1st high-dose therapy
IFM 94 single vs tandem: Overall survival

p < 0.01

< 65 years, de novo: 1990’s

Induction therapy

VAD

ASCT

Melphalan
200 mg/m²

(Melphalan)
200 mg/m²
Impact of CR + VGPR after HDT on outcome

How to improve the CR/VGPR rate?

How to prolonge the duration of response?

→ Incorporation novel agents
< 65 years, de novo

**Induction therapy**
- VAD
- Velcade-Dex (VD)
- Velcade-Thal-Dex (VTD)
- Vel-Rev-Dex (RVD)
- PAD

**ASCT**
- Melphalan 200 mg/m²
- (Melphalan) 200 mg/m²

**Consolidation and/or Maintenance**
- VTD
- Lenalidomide
- Bortezomib
# IFM 2005-01 Response To Induction Evaluatable Patients

<table>
<thead>
<tr>
<th></th>
<th>VAD N=218</th>
<th>Vel-Dex N=223</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1.4%</td>
<td>5.8%</td>
<td>0.012</td>
</tr>
<tr>
<td>CR+nCR</td>
<td>6.4%</td>
<td>14.8%</td>
<td>0.004</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>15.1%</td>
<td>37.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>62.8%</td>
<td>78.5%</td>
<td>.0003</td>
</tr>
<tr>
<td>MR+SD</td>
<td>26.6%</td>
<td>12.6%</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>4.1%</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.8%</td>
<td>0.5%</td>
<td></td>
</tr>
</tbody>
</table>

## Response to First ASCT
**Evaluable Patients**

<table>
<thead>
<tr>
<th></th>
<th>VAD N=218</th>
<th>Vel-Dex N=223</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>8.7%</td>
<td>16.1%</td>
<td>0.016</td>
</tr>
<tr>
<td>CR + nCR</td>
<td>18.4%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>37.2%</td>
<td>54.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>77.1%</td>
<td>80.3%</td>
<td>0.401</td>
</tr>
<tr>
<td>MR/SD/PD</td>
<td>3.7%</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>No ASCT</td>
<td>15.6%</td>
<td>11.7%</td>
<td></td>
</tr>
</tbody>
</table>
Protocol GIMEMA 26866138-MMY-3006
VTD vs TD incorporated into double ASCT for MM

RANDOMIZATION

INDUCTION
- VEL-THAL-DEX
- THAL-DEX

PBSC COLLECTION
- CTX

TRANSPLANTATION
- MEL 200
- MEL 200

CONSOLIDATION
- VEL-THAL-DEX
- THAL-DEX

MAINTENANCE
- DEX

Response to induction therapy

<table>
<thead>
<tr>
<th>% of patients</th>
<th>VTD (n=226)</th>
<th>TD (n=234)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+nCR</td>
<td>33</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VGPR</td>
<td>61</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Response to first ASCT (MEL 200 mg/m\(^2\))

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>VTD (n=226)</th>
<th>TD (n=234)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+nCR</td>
<td>55</td>
<td>32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>43</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VGPR</td>
<td>76</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
A) Time to best complete or near complete response

B) Time to progression or relapse

C) Progression free survival

VTD = bortezomib with thalidomide plus dexamethasone
TD = thalidomide plus dexamethasone

4 cycles
Disease response evaluation after 2 cycles & 4 cycles

**VD (IFM 2005/01)**
- Vel 1.3mg/m² d1,4,8,11
- Dex 40mg d1-4,9-12
- Cycles 1 & 2
d1-4, cycles 3 & 4

**vTD**
- Vel 1mg/m² d1,4,8,11
- Thal 100mg/d
- Dex idem

increased up to 1.3 & 200mg/day
if response < PR after 2 cycles
+ LMWH

03/2008 → 01/2009, 205 patients < 65 years
Aug 15th, 191 patients evaluable (95 VD, 96 vTD)

Investigator-based assessment

<table>
<thead>
<tr>
<th></th>
<th>VD</th>
<th>vTD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>%CR</td>
<td>12</td>
<td>14</td>
<td>0.68</td>
</tr>
<tr>
<td>% &gt; VGPR</td>
<td>36</td>
<td>50</td>
<td>0.047</td>
</tr>
<tr>
<td>% &gt; PR</td>
<td>81</td>
<td>91</td>
<td>0.06</td>
</tr>
<tr>
<td>Stable</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Prog</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Combinations in the Upfront Treatment of MM

Up to eight 21-day cycles

Phase II: Len 25, Btz 1.3, Dex : 20

Best response to treatment overall and in the phase II population

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>All pts (N=66)</th>
<th>Phase II (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>19 (29)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>nCR</td>
<td>7 (11)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>VGPR</td>
<td>18 (27)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>PR</td>
<td>22 (33)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>CR+nCR</td>
<td>26 (39)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>CR+nCR+VGPR</td>
<td>44 (67)</td>
<td>26 (74)</td>
</tr>
<tr>
<td>At least PR</td>
<td>66 (100)</td>
<td>35 (100)</td>
</tr>
</tbody>
</table>
Early Versus Delayed Autologous Transplantation After Immunomodulatory Agents-Based Induction Therapy in Patients With Newly Diagnosed Multiple Myeloma

Shaji K. Kumar, MD; Martha Q. Lacy, MD; Angela Dispenzieri, MD; Francis K. Buadi, MD; Suzanne R. Hayman, MD; David Dingli, MD; Francesca Gay, MD; Shirshendu Sinha, MD; Nelson Leung, MD; William Hogan, MD; S. Vincent Rajkumar, MD; and Morie A. Gertz, MD
Phase 3: MPR versus tandem ASCT

Induction

- n=402
- Rd (four 28-d cycles)
  - Lenalidomide 25 mg/d, d1-21
  - Low-dose dex 40mg/d, d 1,8,15,22

Consolidation

- n=202
- MPR (six 28-d cycles)
  - Melphalan 0.18 mg/kg/d, d 1-4
  - Prednisone 2 mg/kg/d, d 1-4
  - Len 10 mg/d, d 1-21

- n=200
- MEL 200
  - Tandem Mel 200mg /m² plus stem cell support

Maintenance

- No maintenance
- Maintenance Len 10 mg/d, d 1-21
  - 28-d course until relapse

Primary end point: PFS

Palumbo et al. ASH 2011 (Abstract 3069), poster presentation
## Phase 3: MPR versus Tandem ASCT

Median follow up 26 mos

<table>
<thead>
<tr>
<th></th>
<th>MPR (n=202)</th>
<th>MEL 200 (n=200)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>20%</td>
<td>25%</td>
<td>0.49</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>60%</td>
<td>58%</td>
<td>0.24</td>
</tr>
<tr>
<td>2-yr PFS</td>
<td>54%</td>
<td>73%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-yr OS</td>
<td>87%</td>
<td>90%</td>
<td>0.19</td>
</tr>
<tr>
<td>2-yr PFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard-risk pts</td>
<td>46%</td>
<td>78%</td>
<td>0.007</td>
</tr>
<tr>
<td>High-risk pts</td>
<td>27%</td>
<td>71%</td>
<td>0.004</td>
</tr>
<tr>
<td>Pts who achieved CR</td>
<td>66%</td>
<td>87%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pts who achieved PR</td>
<td>56%</td>
<td>77%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 3/4 neutropenia</td>
<td>55%</td>
<td>89%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 3/4 infections</td>
<td>0%</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gr 3/4 GI toxicity</td>
<td>0%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DVT</td>
<td>2.44%</td>
<td>1.13%</td>
<td>0.43</td>
</tr>
<tr>
<td>Second tumors</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Palumbo et al. ASH 2011 (Abstract 3069), poster presentation
Proposed IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)

Randomize

- RVD\textsuperscript{x3}
- CY (3g/m\textsuperscript{2}) MOBILIZATION
  Goal: 5 \times 10^6 cells/kg
- Melphalan 200mg/m\textsuperscript{2} + ASCT
- RVD \times 2
- Revlimid 12 mos

Stratification ISS, FISH
Systematic GEP, CGH
\rightarrow risk-adapted strategy

- RVD\textsuperscript{x3}
- CY (3g/m\textsuperscript{2}) MOBILIZATION
  Goal: 5 \times 10^6 cells/kg
- RVD \times 5
- Revlimid 12 mos
- SCT at relapse
  MEL 200 mg/m\textsuperscript{2} if <65 yrs
  \geq 65 yrs 140mg/m\textsuperscript{2}
Second ASCT as salvage therapy?  

Yes

Jimenez-Zepeda, Biol Blood Marrow Transplant 2011, Nov4  
[Epub ahead of print]

Cook, Biol Blood Marrow Transplant 2011, 17:1638-1645
Issue of stem cell collection in the era of novel agents!!
ORIGINAL ARTICLE

International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100)

S Giralt¹, EA Stadtmauer², JL Harousseau³, A Palumbo⁴, W Bensinger⁵, RL Comenzo⁶, S Kumar⁷, NC Munshi⁸, A Dispenzieri⁷, R Kyle⁷, G Merlini⁹, J San Miguel¹⁰, H Ludwig¹¹, R Hajek¹², S Jagannath¹³, J Blade¹⁴, S Lonial¹⁵, MA Dimopoulos¹⁶, H Einsele¹⁷, B Barlogie¹⁸, KC Anderson⁸, M Gertz¹⁷, M Attal¹⁹, P Tosi²⁰, P Sonneveld²¹, M Boccadoro¹, G Morgan²², O Sezer²³, MV Mateos¹⁶, M Cavo²⁴, D Joshua²⁵, I Turesson²⁶, W Chen²⁷, K Shimizu²⁸, R Powles²⁹, PG Richardson⁸, R Niesvizky³⁰, SV Rajkumar⁷ and BGM Durie³¹ on behalf of the IMWG³²
Stem cell collection

- Single agent filgrastim: current gold standard; after chemomobilization (Cyclophosphamide) more CD34+ cells, but failure rate identical to that of G-CSF alone

- Minimum target: 4 million CD34+ cells/kg; if feasible: average of 8-10 million CD34+ cells/kg be collected (at least 2 autografts)

- Risk factors for poor stem cell mobilization:
  - Age
  - Melphalan exposure
  - Extensive prior therapy (and/or radiotherapy)
  - Exposure to lenalidomide

1. Stiff PJ. Bone Marrow Transplant. 1999;23(suppl 2):S29-S33
Stem cell collection with G-CSF alone in patients treated with Bortezomib-dex induction therapy

**Table 1** Stem cell harvest

<table>
<thead>
<tr>
<th>Patients</th>
<th>VAD Arm (A = A1 + A2, N = 242)</th>
<th>Bortezomib–dexamethasone arm, (B = B1 + B2, N = 240)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation population for stem collection, N</td>
<td>216</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>Median yield after one mobilization with G-CSF, 10^6 CD34+ cells/kg</td>
<td>8.50 (0–27.9)</td>
<td>6.80 (0–23.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean number of cytaphereses</td>
<td>1.63</td>
<td>2.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with yields &lt;5 x 10^6 cells/kg</td>
<td>11%</td>
<td>23%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Patients with yields &lt;2 x 10^6 cells/kg</td>
<td>2%</td>
<td>3%</td>
<td>0.10</td>
</tr>
<tr>
<td>Patients undergoing second mobilization with cyclophosphamide</td>
<td>13%</td>
<td>25%</td>
<td>0.0009</td>
</tr>
<tr>
<td>Patients with yields &lt;5 x 10^6 cells/kg after two mobilizations</td>
<td>5%</td>
<td>6%</td>
<td>0.75</td>
</tr>
<tr>
<td>Patients with yields &lt;2 x 10^6 cells/kg after two mobilizations</td>
<td>0%</td>
<td>0.4%</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: G-CSF, granulocyte-colony-stimulating factor; VAD, vincristine–doxorubicin–dexamethasone.

Stell cell collection with G-CSF alone
IFM 2007-02 trial

<table>
<thead>
<tr>
<th></th>
<th>VD N = 90</th>
<th>VTD N = 91</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 34/kg</td>
<td>7.4 x 10^6</td>
<td>6.4 x 10^6</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt; 2 x 10^6</td>
<td>93 %</td>
<td>80 %</td>
<td>0.001</td>
</tr>
<tr>
<td>Failure rate after second mobilization with cyclophosphamide</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Stem cell collection with cyclophosphamide + G-CSF - Gimema trial

|                                | VTD  
|--------------------------------|------
|                                | N = 209 |
| CD 34+                         | 9.75 x 10^6/kg |
| Sufficient yields for double transplantation | 95 % |

Stem cell collection with VRD induction

28 patients

Median CD34+ : 5.6 x 10^6/kg (2.3 – 20.1)
Potential benefits of plerixafor

*Improved collection predictability*
- Of plerixafor resulted in a median 4.8-fold increase in circulating CD34+ cells in the peripheral blood, allowing patients and doctors to predictably schedule apheresis sessions
- Myeloma patients who received plerixafor achieved 3 x as many cells on day 1 than with G-CSF alone (median 6.86 million vs. 2.29 million)

*Reduction of SCT costs*
- Using less resources (that is, less apheresis procedures)
- In the phase III study, plerixafor patients achieved ≥6 million CD34+ cells/kg in a median of 3 fewer days with plerixafor vs. G-CSF alone

*Potential of collecting more cells*
- Which allows for more frequent use of high-dose therapy with stem cell support as a salvage treatment
- Which allows for exploration of improving stem cell transplant outcomes by exploring megadoses of CD34+ cells (that is, >10 million CD34 per kg)
- Which allows for collecting patients previously exposed to high dose therapy

Conclusions

- Upfront ASCT remains the standard of care in 2012
- Triplet combination: IMiD + bortezomib + dexamethasone = effective induction therapy
- Aim of stem cell collection: allow 2 autografts
- G-CSF (+ cyclophosphamide) = gold standard
- Plerixafor: effective in poor-mobilizers
Case

- 58 year-old male
- Fatigue
- Hemoglobin: 9.9 g/dL
- Serum electrophoresis: M-spike, IgG kappa: 57g/L
- X-rays: bone lesions skull
- Normal creatinine, beta-2 microglobulin 4.2 mg/L, albumin level 38 g/L
- Bone marrow aspiration: 32% plasma cells
- FISH: del13, no t(4.14), no 17p

Symptomatic de novo Multiple Myeloma, ISS 2
Treatment plan: high-dose therapy and autologous stem-cell transplantation

What is your induction regimen prior to ASCT?

1. VAD?
2. Thalidomide + dexamethasone: TD?
3. Bortezomib + dexamethasone: VD?
4. Bortezomib + Thalidomide + dexamethasone: VTD?
5. Bortezomib + Lenalidomide + dexamethasone: VRD?
6. Bortezomib + Cyclophosphamide + dexamethasone: VCD?
Case

- The patient received 3 courses of VTD
- M-spike decreased from 57 to 5 g/L: VGPR is achieved. Blood count: normal; peripheral neuropathy grade 1
- You need to harvest stem cells to proceed to ASCT
For stem cell collection, are you using?

1. 10 μg/kg G-CSF, 5 days?

2. Pegfilgrastim?

3. Cyclophosphamide 3 g/m² + G-CSF?

4. Plerixafor + G-CSF?
Case

- After cyclophosphamide 3 g/m$^2$ + G-CSF, total CD34+ stem cells: 4.9 x 10$^6$ / kg

- Adequate stem cell mobilization for a single transplant

- Patient underwent ASCT, prepared by melphalan 200 mg/m$^2$; all stem cells were infused

- Hematopoietic recovery: excellent

- 2 months after HDT: electrophoresis normal, bone marrow aspiration < 5% plasma cells: CR
Question

Given the good results of combinations using novel agents as part of frontline treatment, are you ready to propose to your patients eligible for high-dose therapy a systematic delayed ASCT, i.e. at the time of first relapse?

1. Yes?

2. No?
Case

• 2 years and 9 months after ASCT (patient is 61), serum electrophoresis shows reappearance of M-spike, 11 g/L; Hb level is decreasing;

• Bone marrow aspiration confirms the relapse

• You want to use a second ASCT, but no back-up; a new stem cell collection is needed
For stem cell collection, are you using?

1. 10 μg/kg G-CSF, 5 days?

2. Pegfilgrastim?

3. Cyclophosphamide 3 g/m² + G-CSF?

4. Plerixafor + G-CSF?
Case

• Plerixafor was used: 0.24 mg/kg body weight by subcutaneous (SC) injection, 11 hours prior to initiation of apheresis, during 2 consecutive days.

• In combination with daily morning doses of G-CSF 10 micrograms/kg

→ 5.2 x 10^6 CD34+ cells were harvested

• 2nd ASCT prepared by mel200 was performed

• CR2 was achieved; patient alive and well 9 months later.