Hematopoietic cell transplantation for multiple myeloma
Marcelo C. Pasquini, MD, MS

WBMT Symposium
Cape Town, South Africa
November 2014
Multiple Myeloma

• B-cell malignancy derived from antibody-producing plasma cells in the bone marrow.
• Myeloma cells crowd out and interfere with the development and function of normal cells in the bone marrow
• The abnormal accumulation of myeloma cells in the bone marrow and production of M-protein have direct and indirect effects on the blood, skeleton, and kidneys

Multiple Myeloma

- Proliferation
- Production

Alterations in the Microenvironment
- Bone destruction
- Hypercalcemia

Immune dysregulation

Correlation with disease burden
Assessment of disease response

- Anemia
- Dysfunctional humoral immunity
- Organ failure
- Hyperviscosity
Natural Selection of Myeloma Progression

Initiation
- Germinal centre
- Post-germinal-centre B cell

Progression
- Bone marrow
- MGUS
- Smouldering myeloma
- Myeloma
- Peripheral blood
- Plasma cell leukaemia

Inherited variants
- Primary genetic events:
  - IGH@ translocations
  - Hyperdiploidy

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

Competition selection for bone marrow niche
- Clonal advantage
- Migration and founder effect

Tumour cell diversity
- Genetic lesions

Criteria for Symptomatic Myeloma
i.e Needs treatment for “cancer”

Criteria for Symptomatic MM (all 3 required)

| 1 | ≥ 10% monoclonal plasma cells in bone marrow |
| 2 | Monoclonal protein in serum and/or urine |
| 3 | Presence of end-organ damage (at least one of the below) |

- Calcium: Serum calcium ≥11.5 mg/100 mL
- Renal: Serum creatinine >1.73 mmol/L
- Anemia: Hb <10 g/100 mL or >2 g/100 mL below normal
- Bone: Lytic lesions, severe osteopenia, pathologic fractures
- “Infections”: Repetitive bacterial infections

Additional “soft signs” – Neuropathy, Osteoporosis, Frequent infections, Proteinuria

MM Therapy

Standard of Care Therapies

1960
1970
1980
1990
2000
2010

FDA Approvals in MM

1958 Melphalan
1962 Prednisone
1969 Melphalan + Prednisone

1983 Autologous Transplantation

2003 Bortezomib

2006 Thalidomide
2006 Lenalidomide

2007 Doxil

2012 Carfilzomib

2013 Pomalidomide

Overall survival from diagnosis of multiple myelomas.
Continued Improvement in Survival Since the Introduction of Novel Agents

- 1,056 pts grouped into 2001–2005 and 2006–2010 cohorts
- Survival improved over time, particularly in pts aged > 65 years (p = 0.001)


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<tbody>
<tr>
<td>Median OS, yrs</td>
<td>4.6</td>
<td>NR</td>
<td>0.001</td>
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<tr>
<td>1-yr survival, %</td>
<td>83</td>
<td>90</td>
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<tr>
<td>5-yr estimated OS, %</td>
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<td></td>
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<tr>
<td>Overall</td>
<td>48</td>
<td>66</td>
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<tr>
<td>&gt; 65 yrs</td>
<td>31</td>
<td>56</td>
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<td>&lt; 65 yrs</td>
<td>63</td>
<td>73</td>
<td>NS</td>
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Myeloma Treatment Roadmap

Induction → Consolidation → Maintenance

Tumour burden

- Presentation
- PR
- VGPR
- CR
- sCR
- Cure
- Relapse
- Cure

Time to progression

Time

Brioli A et al. British Journal of Haematology 2014
# Classes of Drugs With Anti-MM Activity

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Immuno-modulatory Agents</th>
<th>Proteasome Inhibitors</th>
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<tr>
<td>Prednisone</td>
<td>Thalidomide</td>
<td>Bortezomib</td>
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<td>Dexamethasone</td>
<td>Lenalidomide</td>
<td>Carfilzomib</td>
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<td>Pomalidomide</td>
<td>Ixazomib</td>
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<td></td>
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<td>Oprozomib</td>
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<td></td>
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<td>Marizomib</td>
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<td>CEP-18770 (Delanzomib)</td>
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## Classes of Drugs With Anti-MM Activity

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<tr>
<th>Cytotoxic CT</th>
<th>HDAC inhibitors</th>
<th>mTOR inhibitors</th>
<th>mAbs</th>
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<tr>
<td>Melphalan</td>
<td>Vorinostat</td>
<td>Perifosine</td>
<td>Elotuzumab</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Panobinostat</td>
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<td>Daratumumab</td>
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<td>BCNU</td>
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<td></td>
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<tr>
<td>Bendamustine</td>
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<tr>
<td>Anthracyclines</td>
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<tr>
<td>PACE</td>
<td></td>
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<tr>
<td>DCEP</td>
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</table>
Anti-myeloma Initial Therapy

- Initial disease de-bulking
- Reduction of the paraprotein
- Decreasing the intra-clonal heterogeneity
EVOLUTION, Phase II

Newly Diagnosed Multiple Myeloma

- **VDR**
  - Bortezomib
  - Dexamethasone
  - Lenalidomide

- **VDCR**
  - Bortezomib
  - Dexamethasone
  - Cyclophosphamide
  - Lenalidomide

- **VDC**
  - Bortezomib
  - Dexamethasone
  - Cyclophosphamide

Bortezomib x 24 weeks

<table>
<thead>
<tr>
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<th>VDCR N = 41</th>
<th>VDR N = 42</th>
<th>VDC N = 32</th>
<th>VDC-modified* N = 15</th>
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<tbody>
<tr>
<td><strong>CR</strong></td>
<td>20%</td>
<td>24%</td>
<td>22%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>≥ VGPR</strong></td>
<td>59%</td>
<td>55%</td>
<td>47%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>≥ PR</strong></td>
<td>93%</td>
<td>93%</td>
<td>91%</td>
<td>93%</td>
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</tbody>
</table>

Compare to RVD regimen phase II – 67-74% VGPR rate. Richardson et al JCO 2011

Kumar et al. JCO
Combinations in the Upfront Treatment of MM

Combination therapy incorporating novel agents results in near 100% ORRs.

- Carf
- RD
- V or P
- Bortezomib
- A - Adriamycin
- T – Thalidomide
- R – Revlimid; C - Cyclophosphamide

Induction Choices

• Transplant “eligible”
  – 3 drug combination excellent VGPR rate in phase II
  – Another 3 drug regimen PAD (Bz+Doxo+Dex)
  – Comparison to 2 drug combination unlikely to happen in US.
  – 4 drugs – CVRD or RVDD (anthracycline) – no evidence of benefit at this time
  – 4 drugs regimens maybe a role in relapsed setting / plasma cell leukemia induction
Induction Choices

• Transplant “ineligible”
  – 2 or 3 drug combination
  – Bortezomib or lenalidomide + dexamethasone
  – Melphalan/pred/bortezomib or len or thalidomide
  – Length of therapy: 2 to 12 months
  – Goal is disease control not necessary Complete Response
Consolidation

• Maximize disease control
• Goal: to reach complete response or better
• Further reduce inter-clonal heterogeneity
Autologous HCT vs. Chemotherapy for Newly Diagnosed Myeloma

- **Graphs showing survival rates**
  - **Overall Survival (%)**
    - Conventional dose
    - High dose
  - **Month**
    - Conventional dose: 63 (53–73), 35 (22–50), 12 (1–40)
    - High dose: 69 (58–78), 61 (50–71), 52 (36–67)

- **Survival rates**
  - Standard therapy: 200, 129, 70, 30, 8
  - Intensive therapy: 201, 148, 79, 38, 8

- **Statistical analysis**
  - P = 0.03 by Wilcoxon test
  - P = 0.04 by log-rank test

References:
Indications for Hematopoietic Stem Cell Transplants in the US, 2011

- Multiple Myeloma
- NHL
- AML
- ALL
- MDS/MPD
- CML
- Aplastic Anemia
- CLL
- Other Non-Malignant Disease
- Other Cancer
- HD

Number of Transplants

- Allogeneic (Total N=7,892)
- Autologous (Total N=12,047)
Overall Survival of Autotransplantation in MM

MYELOMA SURVIVAL
Over Time

Autologous HCT for multiple myeloma in US and Canada within 12 months from diagnosis from 1995 to 2010 registered with CIBMTR

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<tr>
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</tr>
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<tbody>
<tr>
<td>Registered patients</td>
<td>2226</td>
<td>6408</td>
<td>11644</td>
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<tr>
<td>Number of centers</td>
<td>189</td>
<td>195</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Median Age</td>
<td>54 (19-77)</td>
<td>57 (22-80)</td>
<td>58 (18-89)</td>
<td></td>
</tr>
<tr>
<td>18-50 years</td>
<td>734 (33)</td>
<td>1445 (23)</td>
<td>2079 (18)</td>
<td>&lt;0.001</td>
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<tr>
<td>50-65 years</td>
<td>1330 (60)</td>
<td>3875 (61)</td>
<td>6945 (60)</td>
<td></td>
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<tr>
<td>65-80 years</td>
<td>162 (7)</td>
<td>1088 (17)</td>
<td>2620 (23)</td>
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</table>

Costa L. et al
## Subset of patients from Research CIBMTR centers

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<td>Number of patients</td>
<td>686</td>
<td>1464</td>
<td>2223</td>
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<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
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<tr>
<td>Abnormal</td>
<td>26 (4)</td>
<td>57 (4)</td>
<td>487 (22)</td>
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<td>Normal</td>
<td>105 (15)</td>
<td>78 (5)</td>
<td>473 (21)</td>
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<tr>
<td>Untested/Missing</td>
<td>555 (81)</td>
<td>1329 (91)</td>
<td>1263 (57)</td>
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<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CR/PR</td>
<td>539 (79)</td>
<td>1273 (87)</td>
<td>1966 (88)</td>
<td>&lt;0.001</td>
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<tr>
<td>Mobilization</td>
<td></td>
<td></td>
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<tr>
<td>GCSF alone</td>
<td>167 (24)</td>
<td>358 (24)</td>
<td>921 (41)</td>
<td>&lt;0.001</td>
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<tr>
<td>Conditioning regimen</td>
<td></td>
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<tr>
<td>Melphalan alone</td>
<td>370 (54)</td>
<td>1363 (93)</td>
<td>2198 (99)</td>
<td>&lt;0.001</td>
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</table>
Ratio between first transplants/ newly diagnosed MM cases in U.S.A

1995-1999:
- 18-49: 37.2%
- 50-64: 26.3%
- >=65: 3.2%

2000-2004:
- 18-49: 39.5%
- 50-64: 26.3%
- >=65: 5.8%

2005-2010:
- 18-49: 33.2%
- 50-64: 0.6%
- >=65: 0%

Ratio between upfront transplants (<12 months)/ newly diagnosed MM cases in U.S.A.

1995-1999:
- 18-49: 28.3%
- 50-64: 18.6%
- >=65: 0.3%

2000-2004:
- 18-49: 23.3%
- 50-64: 8.2%
- >=65: 3.8%

2005-2010:
- 18-49: 14.5%
- 50-64: 3.2%
- >=65: 2.0%

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Maintenance

• Long term treatment with an anti-myeloma agent that is tolerable and effective
• Maximize disease control
• Prevent the inception of “new” subclones
CALGB 100104 Schema

Registration

D-S Stage 1-3, ≤ 70 years
≥ 2 cycles of induction
Attained SD or better
≤ 1 yr from start of therapy
> 2 x 10^6 CD34 cells/kg

Restaging

Days 90–100

Mel 200

ASCT

CR

PR

SD

Randomization

Placebo

Lenalidomide*

10 mg/d with
↑↓ (5–15 mg)

* provided by Celgene Corp, Summit, NJ

Stratification based on registration β-2M level and prior thalidomide and lenalidomide use during Induction. Primary Endpoint: powered to determine a prolongation of TTP from 24 months to 33.6 months (9.6 months)
ITT Analysis with a median follow-up from transplant of ~48 months p<0.001 Median TTP: 50 months versus 27 months with 86 of 128 non-progressing placebo patients receiving lenalidomide at study un-blinding in Jan 2010

CALGB 100104 IMW 2013 follow up to January 7, 2013

Estimated HR=0.51 (95% CI = 0.39 to 0.66),

146/229 events (64%) on placebo
104/231 events (45%) on lenalidomide
CALGB 100104 IMW 2013 follow up to January 7, 2013

ITT Analysis with a median follow-up from transplant of ~48 months. p= 0.008, Median OS: not reached versus 73 months

Estimated HR=0.61
(95% CI = 0.41 to 0.87)

69/229 (30%) deaths on placebo
47/231 (20%) deaths on lenalidomide
R maintenance vs No maintenance

**Progression-free survival**
- 48% reduced risk of progression

**Overall survival**
- 38% reduced risk of death

**Median PFS**
- R maint. 37 months
- No maint. 26 months

**5-year OS**
- R maint. 75%
- No maint. 58%

**HR**
- R maint. HR 0.52, 95% CI 0.40-0.67, P <.0001
- No maint. HR 0.62, 95% CI 0.42-0.93, P =.02
BMT CTN 0702 - STaMINA

N=750 pts (250 in each arm)

Register and Randomize → MEL 200mg/m² → VRD x 4* → Lenalidomide Maintenance

Register and Randomize → MEL 200mg/m² → Lenalidomide Maintenance

Bortezomib 1.3mg/m²
days 1, 4, 8, 11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg
days 1, 8, 15

**Lenalidomide x 3 years:
10mg /d for 3 cycles, then 15 mg /d
Caveats with Continuous Treatment

• Does using all “active” drugs at once favors the inception of resistant subclones?
R maintenance vs No maintenance

**PFS from diagnosis**
- HR 0.52, 95% CI 0.40-0.67, P <.0001

**OS from relapse**
- HR 0.82, 95% CI 0.55-1.22, P =.32

- **Delayed clonal evolution**
- **Faster clonal evolution**

R, lenalidomide
Caveats with Continuous Treatment

• Does using all “active” drugs at once favors the inception of resistant subclones?

• Does this treat strategy work for all patients?
High Risk Myeloma Markers

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<tr>
<th>Parameter</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>Age, years</td>
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<tr>
<td>&gt; 65 v ≤ 55</td>
<td>1.63</td>
<td>1.25 to 2.13</td>
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<td>β2-microglobulin, mg/L</td>
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<tr>
<td>&gt; 5.5 v ≤ 5.5</td>
<td>2.19</td>
<td>1.65 to 2.90</td>
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<tr>
<td>Creatinine, μmol/L</td>
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<tr>
<td>&gt; 180 v ≤ 180</td>
<td>1.96</td>
<td>1.30 to 2.96</td>
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<td>Calcemia, mmol/L</td>
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<td>&gt; 2.8 v ≤ 2.8</td>
<td>1.95</td>
<td>1.31 to 2.88</td>
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<td>Platelets, g/L</td>
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<td>≤ 120 v &gt; 120</td>
<td>2.34</td>
<td>1.37 to 3.90</td>
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<td>Hemoglobin, g/dL</td>
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<tr>
<td>≤ 11 v &gt; 11</td>
<td>1.42</td>
<td>1.08 to 1.86</td>
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<td>t(4;14)</td>
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<td>Yes v no</td>
<td>2.73</td>
<td>1.95 to 3.82</td>
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<td>del17p</td>
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<td>&gt; 60 v ≤ 60</td>
<td>3.33</td>
<td>2.01 to 5.21</td>
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<td>del13</td>
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<td>&gt; 40 v ≤ 40</td>
<td>1.74</td>
<td>1.35 to 2.24</td>
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<td>1q gain</td>
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<tr>
<td>Yes v no</td>
<td>2.00</td>
<td>1.56 to 2.58</td>
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Abbreviation: HR, hazard ratio.

Avet-Loiseau H et al JCO 2012
High-risk Chromosomal Abnormalities (MDACC; N=679; 2006 – 2010)
## High Risk FISH abnormalities

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<thead>
<tr>
<th>Abnormality</th>
<th>Frequency</th>
<th>Prognosis</th>
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<tr>
<td>Hyperdiploidy</td>
<td>50%–60%</td>
<td>Good/neutral</td>
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<td>t(4;14)</td>
<td>15%</td>
<td>Poor (neutral if bortezomib therapy)</td>
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<tr>
<td>t(11;14)</td>
<td>20%</td>
<td>Neutral</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>3%</td>
<td>Poor/neutral</td>
</tr>
<tr>
<td>Monosomy 13</td>
<td>45%</td>
<td>Neutral if by FISH</td>
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<tr>
<td>del(17p)</td>
<td>8%</td>
<td>Poor</td>
</tr>
<tr>
<td>1q gain</td>
<td>35%</td>
<td>Poor</td>
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<td>del(1p)</td>
<td>30%</td>
<td>Poor</td>
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<tr>
<td>5q gain</td>
<td>50%</td>
<td>Good</td>
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<tr>
<td>del(12p)</td>
<td>10%</td>
<td>Poor</td>
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</table>

*The Impact of Genomics on the Management of Myeloma*
Jill Corre and Hervé Avet-Loiseau - JNCCN Mar 2012 ; 10 (3)
Progression-free survival
According to age, response, cytogenetics

< 60 years

CR

≥ 60 years

No CR

No t(4;14), t(14;16) or del17

No t(4;14), t(14;16) or del17

HR 0.73
P=.05

HR 0.36
P=.0006

HR 0.53
P=.0005

HR 0.39
P<.0001

HR 0.69
P=.009

HR 0.77
P=.31
Overall Survival after Second Autologous HCT, stratified by “Time from first HCT to first progression”

- <36 months (N = 151)
  - (HR 1.91, P = 0.02)

- ≥36 months (N = 38)

(Source: Txz11_7) MM09-02-11_23.ppt

Michaelis L et al, BBMT 2011
Final Results of Phase III US Intergroup Trial S9321

Barlogie et. Al. JCO 2006
Allogeneic Transplant

- Controversial
- US Trial – Negative (ASCT+ Allo no better than ASCTx2)
- European Trials – OS benefit esp. in high risk disease

Giaccone et al 2011 117: 6721-6727  
Krishnan/Pasquini et al Lancet Oncol 2011;12: 1195–203
Multiple Myeloma meeting eligibility criteria

High-dose melphalan (200 mg/m²) + autologous PBSC transplant

60 to 120 days

No eligible HLA-matched sibling donor

High-dose melphalan (200 mg/m²) + autologous PBSC transplant

Observation

Biologic assignment *

Eligible HLA-matched sibling donor

Non-myeloablative conditioning TBI 200 cGY allogeneic PBSC transplant

Thalidomide Dexamethasone x12 months.

Randomization †

HLA typing of all patients with siblings

* Biologic assignment occurred when HLA-typing results were available after enrollment.

† Randomization occurred once patients were assigned to auto-auto

PRIMARY ENDPOINT: 3yr Progression Free Survival
Progression-free Survival by Treatment Arm

- **Standard Risk**
  - **Auto/Auto** (n=435)
  - **Auto/Allo** (n=189)

- **Probability, %**
  - 100%
  - 80%
  - 60%
  - 40%
  - 20%
  - 0%

- **Years Post 1st Transplant**
  - 0
  - 2
  - 4
  - 6
  - 8

- **P-value = 0.1089**

- **At 6 years**
  - **Auto/Auto**: 27 (22-31)
  - **Auto/Allo**: 21 (15-27)
Why not give up Allotransplant?

- Intriguing European studies
- Longer follow up for a difference to show
- Young high risk pt – what to do?
- Low TRM - ~5% in the best centers
- Allo → Maintenance paradigm
- Backing off from “Mini” regimens

Reduction in risk p = 0.006
Difference in HR after 36 mo = 0.04

Bjorkstrand JCO 2011; 29: 3016 -22
- 20% circulating plasma cells or $>2 \times 10^9$/L absolute
- Consider plasma cell leukemia when:
  - 5% circulating plasma cells or $>0.5 \times 10^9$/L absolute
a  Transplant candidate

<p>| Bortezomib-based induction plus chemotherapy +/- IMID (i.e. VTD-PACE, HyperCVAD-VTD, PAD, VCD) |</p>
<table>
<thead>
<tr>
<th>Age ≤ 50 yrs and suitable donor</th>
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<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Consider Myeloablative Allo-SCT</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Consider Allo-RIC</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Consolidation/maintenance Bortezomib +/- Lenalidomide-based (indefinite)</td>
</tr>
<tr>
<td>&gt;50 yrs</td>
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<td>ASCT (Melphalan 200)</td>
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Multiple Myeloma Treatment: Future Perspective

• Myeloma now is a chronic disease
  – Patients are living longer than ever
  – Although mostly incurable
• Better stratification of patients with the highest risk
  – CRAB criteria is becoming outdated.
• Modified targeted therapy paradigm
  – Risk adapted or molecular signature adapted
  – Change from continuous to non-continuous treatment when appropriate – response adapted treatment
Conclusions

- Transplant remains the main backbone for the treatment of myeloma.
- Myeloma outcomes are now much better with combination of novel agents and transplant.
- High risk myeloma remains a challenge and novel approaches are needed.
- Allogeneic HCT remains investigational, but could be considered in patients with high risk disease.
Transplants for Multiple Myeloma

- Multiple myeloma is an incurable plasma cell disorder.
- Clinical presentation includes:
  - Anemia, lytic bone lesion, kidney failure, hypercalcemia and repetitive infections
- Most common indication of autologous transplants
- Many new regimens available for disease control.