Survival after Auto transplant for Myeloma, 2003-2013

By Year of Transplant

- 2000-2003 (n=8,432)
- 2004-2007 (n=10,760)
- 2008-2011 (n=15,617)
- 2012-2013 (n=9,706)

Probability, %

0 20 40 60 80 100

0 1 2 3 4 5 6

Treatment Related Mortality = <1%

NON CURATIVE INDICATION FOR HCT

p<0.001

CIBMTR Summary Slides 2015

By Year of Transplant
Transplant for MM: Is it still needed? If so, when… (still upfront or ok to wait)?

Newer drugs:
- Carfilzomib
- Pomalidomide
- Elotuzumab
- Daratumumab
- Panabinostat
Phase 3 MPR Consolidation vs Tandem MEL200

**Lenalidomide + low-dose Dexamethasone Induction**
4 cycles
(N = 402)

- **MPR**
  6 cycles
  (n = 202)
  - Lenalidomide Maintenance
    10 mg, d 1-21
    (n = 98)
  - No Maintenance
    (n = 104)

- **MEL 200**
  (n = 200)
  - Lenalidomide Maintenance
    10 mg, d 1-21
    (n = 100)
  - No Maintenance
    (n = 100)

**GIMEMA NEJM 2014**
- 402
- RD x4
- MPR x6
- ASCT x2
- 22mo median
- 43mo* PFS
- 65% 4y
- 81%* OS

**Induction**
Four 28-day cycles of lenalidomide (25 mg on days 1–21) and dexamethasone (40 mg on days 1, 8, 15, and 22)

**Collection**

**Consolidation**

**Maintenance**

**High-dose Melphalan + ASCT**

- **CY (3g/m²) MOBILIZATION**
  - High-dose Melphalan + ASCT
    - Lenalidomide
    - Lenalidomide + Prednisone

**Cyclophosphamide, Lenalidomide, Dexamethasone**

- **CY (3g/m²) MOBILIZATION**
  - Lenalidomide
  - Lenalidomide + Prednisone

---

**Primary objective:** PFS

**Secondary objectives:** ORR, MRD, TTP, OS, Safety

*VRD: bortezomib 1.3 mg/m² IV on Days 1, 4, 8, 11 + lenalidomide 25 mg on Days 1-14 + dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12.

** till POD in US trial and 12 months in IFM trial

†Included PBSC collection with cyclophosphamide 3 g/m² + G-CSF after cycle 3.
Patients with newly diagnosed MM

**Induction Therapy**
- Bortezomib
- Cyclophosphamide
- Dexamethasone

**R1**
- Bortezomib, melphalan, and prednisone (VMP) (4 cycles)

**R2**
- Consolidation: bortezomib, lenalidomide, dexamethasone
- Lenalidomide Maintenance
- No consolidation

**High-dose melphalan plus single or double ASCT**

European Myeloma Network

### New drug vs. Auto-Transplant Studies

<table>
<thead>
<tr>
<th>Group</th>
<th>No</th>
<th>Induction</th>
<th>Comparator</th>
<th>&gt; VGPR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GIMEMA NEJM 2014</strong></td>
<td>402</td>
<td>RD x4</td>
<td>MPR x6 ASCT x2</td>
<td>63</td>
<td>22mo median</td>
<td>65% 4y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59</td>
<td></td>
<td>81%*</td>
</tr>
<tr>
<td><strong>MultiCenter Lancet Oncol 2015</strong></td>
<td>389</td>
<td>RD x4</td>
<td>CDR x6 ASCT x2</td>
<td>50</td>
<td>29mo</td>
<td>68% 4y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54</td>
<td>43mo*</td>
<td>77%*</td>
</tr>
<tr>
<td><strong>IFM 2009 ASH 2015</strong></td>
<td>700</td>
<td>VRD x3</td>
<td>VRD x5 ASCT + VRD x2</td>
<td>78</td>
<td>34mo</td>
<td>83% 4y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88*</td>
<td>43mo*</td>
<td>81%</td>
</tr>
<tr>
<td><strong>EMN ASH 2016</strong></td>
<td>1192</td>
<td>VCD x3-4</td>
<td>VMP x4 ASCT 1 or 2</td>
<td>74</td>
<td>57% @ 3 yrs</td>
<td>NS (short fu)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85*</td>
<td>65%</td>
<td>HR 0.73*</td>
</tr>
</tbody>
</table>
**EMN02/HO95 Results**

**PFS from first randomization – ASCT vs VMP**

<table>
<thead>
<tr>
<th>Study Population</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCT</strong></td>
<td><strong>VMP</strong></td>
</tr>
<tr>
<td>n=695</td>
<td>n=497</td>
</tr>
<tr>
<td>PFS, months</td>
<td>NR</td>
</tr>
<tr>
<td>3-year PFS Rate</td>
<td>65%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.61-0.88)</td>
</tr>
<tr>
<td>P value</td>
<td>.001</td>
</tr>
</tbody>
</table>

Median follow-up 25 months.

- Patients with high-risk cytogenetics derived the most significant benefit
- Adverse events included GI concerns and mucositis

**ASCT improves PFS over high dose therapy for MM patients**

IFM/DFCI—PFS According to MRD (FCM) Post Consolidation

VRD Arm

- Positive MRD
- Negative MRD

Transplant Arm

- Positive MRD
- Negative MRD

N at risk
- MRD pos: 89, 75, 54, 22, 2
- MRD neg: 140, 135, 113, 72, 14

N at risk
- MRD pos: 65, 57, 43, 30, 4
- MRD neg: 172, 166, 151, 86, 17

Beyond Auto Transplantation for Myeloma

- Approaches to prevent relapse
- CONSOLIDATION
- MAINTENANCE
- ALLOTRANSPLANT & IMMUNE THERAPY
MM Requiring Therapy Age ≤ 70 y, Karnofsky score ≥ 70, N = 758

Induction Therapy*

First ASCT Mel 200 mg/m²

R

Consolidation RVD × 4 cycles

No Consolidation

2nd ASCT Mel 200 mg/m²

Lenalidomide Maintenance (10 mg/d – 15 mg/d)

*Induction therapy was not specified. Patients must have had ≥ 2 cycles of systemic therapy, within 2-12 mos of therapy initiation and Available autograft ≥ 4 × 10⁶ CD34+ cell/kg.

Median follow-up: 37.8 mos

ClinicalTrials.gov. NCT01109004.
Stamina Study Results

No significant difference between the study arms

<table>
<thead>
<tr>
<th>Post induction + ASCT-1 followed by:</th>
<th>R Maint only n=257</th>
<th>RVD→R n=254</th>
<th>Double ASCT→R n=247</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>52.2</td>
<td>56.7</td>
<td>56.5</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>83.4</td>
<td>85.7</td>
<td>82.0</td>
</tr>
<tr>
<td>High-risk patients, n</td>
<td>59</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>40.2</td>
<td>48.3</td>
<td>42.2</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>79.5</td>
<td>77.5</td>
<td>79.3</td>
</tr>
<tr>
<td>Second malignancies, n</td>
<td>10</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Cumulative incidence, %</td>
<td>4.0</td>
<td>6.0</td>
<td>5.9</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov. NCT01109004.
EMN02/H095

**ASCT vs VMP After CyBorD Induction**

**Patients with newly diagnosed MM**

- Induction Therapy
  - Bortezomib
  - Cyclophosphamide
  - Dexamethasone

**R1**

- Bortezomib, melphalan, and prednisone (VMP) (4 cycles)

**Consolidation: bortezomib, lenalidomide, dexamethasone**

- High-dose melphalan plus single or double ASCT

- No consolidation

- Lenalidomide Maintenance

**R2**

**European Myeloma Network**

Consolidation

- PFS from second randomization (R2) – consolidation with VRD vs no consolidation
  - 3-year PFS from R2 = 62%
    - 65% VRD vs 60% without consolidation
    - Median PFS not reached
  - Prolonged PFS after adjustment for R1 with an HR=0.78; \( P = 0.13 \)
- 3-year OS 86% vs 87%
- PFS benefit in subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ISS stage III</td>
<td>.67</td>
<td>.26</td>
</tr>
<tr>
<td>VMP at R1</td>
<td>.76</td>
<td>.19</td>
</tr>
<tr>
<td>HDM at R1</td>
<td>.79</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Low-risk cytogenetics</strong></td>
<td>.68</td>
<td>.03</td>
</tr>
<tr>
<td><strong>High-risk cytogenetics</strong></td>
<td>1.03</td>
<td></td>
</tr>
</tbody>
</table>

Consolidation improves PFS for most subgroups, but there was no benefit for high risk patients

EMN02/H095 Single vs Double ASCT

- PFS ITT population, single vs double
  - 45 mo vs NR
- 3-year PFS rate single vs double:
  - 60% vs 73% (HR=0.66; P=.030)
- Patients with high-risk cytogenetics benefit most from double ASCT

STaMINA and EMN02/H095 Differences

• Pre-transplant induction regimen differences
  – Patients in the European study received bortezomib, cyclophosphamide, Dex
  – Most patients on the CTN study received RVD induction

<table>
<thead>
<tr>
<th>Post induction + ASCT-1 followed by:</th>
<th>R Maint only n=257</th>
<th>RVD→R n=254</th>
<th>Double ASCT→R n=247</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD, %</td>
<td>57.1</td>
<td>52.8</td>
<td>55.6</td>
</tr>
<tr>
<td>CyBorD, %</td>
<td>13.4</td>
<td>13.8</td>
<td>15.6</td>
</tr>
<tr>
<td>Rd, %</td>
<td>9.7</td>
<td>11</td>
<td>8.6</td>
</tr>
<tr>
<td>Vd, %</td>
<td>11.3</td>
<td>12.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Other, %</td>
<td>8.5</td>
<td>9.8</td>
<td>7.8</td>
</tr>
</tbody>
</table>

• Longer term follow-up needed
What should be the standard of care?

- Proteasome Inhibitor + IMID + Steroid induction
- Single auto transplant
- Lenalidomide Maintenance
  - Who should no maintenance? Bortezomib? For how long?

For patients not in CR after 4 cycles of initial therapy, further induction should be attempted to induce VGPR or CR pre transplant

True or False?
“Improving the Modern Triple Sequence”
Induction AutoHCT and Maintenance

- Randomized trials – Achievement of VGPR/CR or better
- Emerging data – NGS / PET / Flow based deep remissions

INITIAL
3 Drug Induction

CONSOLIDATE
Consolidation w/Transplant

ONGOING THERAPY
Maintain with Lenalidomide or Bortezomib

RELAPSE MONITORING
TREATMENT of RELAPSE
Biochemical or Clinical

- MRD directed ?
- When to stop ?
- Implications of prolonged therapy
KRd Induction and Consolidation

**Patients with newly diagnosed MM <65 yr**

**INDUCTION**

- **KRd (4 cycles)**
- **ASCT**
  - N=46

**CONSOLIDATION**

- **KRd (4 cycles)**
- **sCR**
  - 26/46 (57%)
  - 28/46 (61%)
  - 32/46 (70%)
  - 23/34 (68%)

**MAINTENANCE**

- **Lenalidomide**

**Response after Consolidation**

<table>
<thead>
<tr>
<th>Response after Consolidation</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>26/46</td>
<td>57</td>
</tr>
<tr>
<td>sCR + CR</td>
<td>28/46</td>
<td>61</td>
</tr>
<tr>
<td>MRD - CMF</td>
<td>32/46</td>
<td>70</td>
</tr>
<tr>
<td>MRD - NGS</td>
<td>23/34</td>
<td>68</td>
</tr>
</tbody>
</table>

**Efficacy**

- Median PFS not reached
- 2-year PFS 91%
- 78% VGPR at ASCT
- 70% MRD negative after consolidation

**Safety**

- 17% cardiac and vascular AE

**KRd induction and consolidation is effective; cardiac toxicity is a concern**

Zimmerman et al. ASH abstract 2016
Transplant is the most cost effective therapy in MM

• KRD or VRD in the USA:
  – Approximate monthly cost – 30-50 000 USD/mo
  – Addition of Daratumumab – 12-23 000 USD more
  – Recurring nature of the cost
  – Limitation of Time without treatment
Why is Autotransplant for MM still important?

- Auto Transplant Debuking
- Lymphodepletion

Maintenance/Consolidation

Stasis or Punctuated Equilibrium

POST TRANSPLANT STRATEGY SHOULD PREVENT RESURGENCE OF AGGRESSIVE CLONES & RESTORE IMMUNE SURVEILLANCE

Multiclonal disease with clonal heterogeneity

Morgan et al Nat Rev Cancer. 2012 Apr 12
Immunotherapy after AutoHCT

- Minimal TRM
- Immune effect without GVHD

Immune therapy is ideal for post AUTO HCT SETTING

- Minimal residual disease state
- Elimination of competing and suppressor cells
- Tumor antigen release from high dose chemotherapy
- Favorable cytokine milieu
Adoptive Cellular Therapy

• Autologous marrow derived myeloma Infiltrating Lymphocytes
• NK cell therapies (from donors or expanded third party)
• Re-engineered T cells
• Vaccines – BMT CTN 1401 study

Antigenic targets for CAR – T cells:
- BCMA – B cell Maturation Antigen
- NY ESO -1 / LAGE
- SLAM F7
- CD 56
- NKG2L
- Kappa Light Chain
- CD19 / CD38 / CD70 / CD138

**PD-1 inhibition after Auto**

- Effects of anti-PD-1 on T- and NK-cell function
- Correlation of immune cell phenotypes in the autologous graft and outcomes

- Graft Sample
- Blood Samples
To Cryopreserve or Not?

• Is it worth investing in cryopreservation?
  – IMO – resounding YES!
  – Recover initial outlay in first transplant
  – Annual Cost 150 – 200 USD / year
  – Use cells at relapse in eligible patients
    – Reinduction / Transplant / Diff Maintenance
  – Multiply relapsed pts – cells to recover counts
Second Salvage Transplants

• Freeze additional cells vs. Re-mobilize
  – What you gain in storage costs – will lose in Plerixafor
• Second transplant at relapse may be better than tandem upfront in the modern era
• IMWG consensus recommends salvage second transplant if PFS from first transplant is >18 mo
Early Relapse After Auto HCT – is a high risk group

Post Auto Relapse within 12 mo.
Post Auto Relapse within 18 mo.

3 years from relapse <40% are alive

Autotransplants 2008 – 2012
How many pts relapse early?

IFM 2009

10% of MRD Neg
30% of MRD Pos

P < 0.001

Patients (%)

N at risk
MRD pos 65 57 43 30 4
MRD neg 172 166 151 86 17

Months of follow-up

Attal M et al Blood 2015 126:391
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 $\rightarrow$ Maintenance paradigm
- Backing off from “Mini” regimens

Bjorkstrand JCO 2011; 29: 3016-22

Reduction in risk p = 0.006
Difference in HR after 36 mo = 0.04
Pay attention to Melphalan
MEL Pharmacokinetics

• Inter-individual variability
  – Creatinine Clearance
  – Fat free mass
  – Hematocrit

• Higher MEL exposure—increased toxicity and efficacy

• Unbound MEL—sensitive predictor of toxicity and efficacy

• How do we optimize conditioning?

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

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Registered patients</td>
<td>2226</td>
<td>6408</td>
<td>11644</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>50-65 years</td>
<td>1330 (60)</td>
<td>3875 (61)</td>
<td>6945 (60)</td>
<td></td>
</tr>
<tr>
<td><strong>65-80 years</strong></td>
<td><strong>162 (7)</strong></td>
<td><strong>1088 (17)</strong></td>
<td><strong>2620 (23)</strong></td>
<td></td>
</tr>
</tbody>
</table>

How old is too old?

Costa L. et al. BBMT
What We Know and Don’t Know

• New drugs improve induction CRs → higher CRs after ASCT
  – Beyond VRD which drug combinations are optimal for pts proceeding to transplantation?
• Do higher response rates observed after novel drug combinations plus ASCT improve survival?
• If a pt achieves MRD neg CR after induction therapy is transplantation optional? Which MRD technique?

Myeloma is still incurable: IMWG analysis of double refractory

TRANSPLANT OFTEN and TRANSPLANT EARLY

Median PFS – 5 mo
Median OS – 13 mo
Milwaukee