Induction Therapy & Stem Cell Transplantation for Myeloma

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Goals of Therapy

- Control the myeloma disease activity
- Improve disease symptoms
  - Bone damage, (pain and fractures)
  - High calcium (weakness)
  - Anemia (fatigue, shortness of breath)
  - Kidney problems (fatigue)
  - Reduce frequent infections
- Minimize treatment related symptoms
- Cure (ideally)
Managing myeloma: the components

Transplant Eligible Patients

Transplant Ineligible Patients

Initial Therapy

Consolidation Auto Tx

Maintenance

Consolidation/ Maintenance/ Continued therapy

Supportive Care

Treatment of Relapsed disease
## Drugs for MM

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>dexamethasone, prednisone</td>
</tr>
<tr>
<td>Alkylators</td>
<td>cyclophosphamide, melphalan, bendamustine</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>doxorubicin, PEG-DOX</td>
</tr>
<tr>
<td>IMiDs</td>
<td>thalidomide, lenalidomide, pomalidomide</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>bortezomib, carfilzomib</td>
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</table>
Measuring Treatment Response

- **Remission**
  No sign of disease. Sometimes the terms complete remission (response) or partial remission (response) are used.

- **Complete response (CR)**
  No sign of M protein in blood and urine by SPEP/UPEP. Immunofixation negative. Normal percent of plasma cells or no sign of myeloma cells in marrow (5% plasma cells in bone marrow), stable bones on skeletal survey.
  (nearCR immunofixation positive)

- **Partial response**
  More than a 50% decrease in M protein in the blood and reduction in 24-h urinary M-protein by 90%.
Rationale for Stem Cell Transplantation For Multiple Myeloma

High doses of chemotherapy (HDC) with or without radiation are more effective than regular dose chemotherapy against malignant diseases.

Autologous (patient) or allogeneic (donor) stem cells can restore marrow function in patients who have received HDC.

Allogeneic stem cells can provide an additional “graft-versus-myeloma” effect capable of eliminating any remaining myeloma cells after HDC.
Three Sources of Stem Cells:
Peripheral Blood,
Marrow,
Umbilical Cord Cells

Three Types of Transplants:
Autologous,
Allogeneic,
Syngeneic (Twins)
Autologous Stem Cell Transplantation

• Considered important therapy for eligible myeloma patients
• High response rate
• Low mortality
• Little age limitation
• No donor limitation
• Documented survival benefit*-patients who undergo ASCT and achieve CR have the best survival

Indications for Hematopoietic Stem Cell Transplants in the US, 2011

- Allogeneic (Total N=7,892)
- Autologous (Total N=12,047)

Number of Transplants

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

Mobilization and Leukapheresis of Patient Stem Cells

Autologous Stem Cells

High Dose Chemotherapy

Autologous Stem Cells

Cryopreservation of Patient Stem Cells

-190°C Freezer

Thawing and infusion of patient stem cells
# ASCT Improves Major Responses After Traditional or Novel Induction

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimens</th>
<th>No</th>
<th>( \geq )near CR%</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>After Induction</td>
<td>After TX</td>
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<tr>
<td>Cavo</td>
<td>VcTD x3</td>
<td>241</td>
<td>31*</td>
<td>52*</td>
<td></td>
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<tr>
<td></td>
<td>TD x3</td>
<td>239</td>
<td>11</td>
<td>31</td>
<td></td>
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<tr>
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<td>VcD x4</td>
<td>223</td>
<td>15*</td>
<td>35*</td>
<td></td>
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<td></td>
<td>VAD x4</td>
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<td>6</td>
<td>18</td>
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<tr>
<td>Hovon</td>
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<td>11*</td>
<td>30*</td>
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<tr>
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<td>51</td>
<td>85</td>
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<td></td>
<td>CVcTD x4</td>
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<td>44</td>
<td>77</td>
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<tr>
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<td>CyBorD x4</td>
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<td>46</td>
<td>72</td>
<td></td>
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<tr>
<td>IFM</td>
<td>VcRD x3</td>
<td>31</td>
<td>23</td>
<td>42</td>
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</table>
Autologous Stem Cell Transplantation: Timing

• Most trials incorporate SCT as consolidation therapy after initial treatment
• Trials comparing timing of transplant, as part of initial treatment or after relapse, show better disease free survival with initial SCT but equivalent overall survival
• Tandem autoTx beneficial for some patients
• Currently there is some debate about the role of SCT when novel drugs are used for initial treatment
• With all the new drugs, do you need a transplant?
Trial RVD Induction ± AutoTx + RVD Consolidation + Maintenance

- Randomized, international, phase III trial in previously untreated MM patients who are candidates for HDT-PBSCT
- Patients: Symptomatic MM with measurable disease
  - £65 yrs and transplant-eligible; ECOG ≤2 (KPS ≥60%)

**Randomization within 1st cycle**

**Initial Therapy**
- RVD Cycle 1

**Randomize**

**Arm A** (RVD 8)
- RVD Cycles 2-3
- HD Cytoxan and SC collection
- RVD Cycles 4-8
- Maintenance Lenalidomide to progression
  (HD Melphalan + SCT at relapse)

**Arm B** (RVD 5)
- RVD Cycles 2-3
- HD Cytoxan and SC collection
- HD Melphalan + PBSCT
- RVD for additional 2 cycles
- Maintenance Lenalidomide to progression

**Primary Endpoint:** PFS

**Secondary Endpoints:** RR, TTP, OS, toxicity, quality of life, pharmacoeconomics, define genetic prognostic groups and best treatment for each group
402 patients (younger than 65 years) randomized from 62 centers

Patients: Symptomatic disease, organ damage, measurable disease

**RD-> MPR v. ASCT x2**

- **Rd**
  - *four 28-day courses*
  - R: 25 mg/d, days 1-21
  - d: 40 mg/d, days 1, 8, 15, 22

- **MPR**
  - *six 28-day courses*
  - M: 0.18 mg/Kg/d, days 1-4
  - P: 2 mg/Kg/d, days 1-4
  - R: 10 mg/d, days 1-21

- **MEL200**
  - *two courses*
  - M: 200 mg/m² day -2
  - Stem cell support day 0

- **2° MAINTENANCE**
  - 28-day courses until relapse
  - R: 10 mg/day, days 1-21

NO MAINTENANCE

*Thromboprophylaxis randomization: aspirin vs low molecular weight heparin
R, lenalidomide; d, low-dose dexamethasone; M, melphalan; P, prednisone; MEL200, melphalan 200 mg/m²

Palumbo, et al ASH 2011
## RD-> MPR v. ASCT x2

<table>
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<tr>
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<th>PFS</th>
<th>p</th>
<th>OS 4y</th>
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<tr>
<td>MPR</td>
<td>25mo</td>
<td>0.0002</td>
<td>71%</td>
<td>0.71</td>
</tr>
<tr>
<td>ASCT</td>
<td>39mo</td>
<td></td>
<td>72%</td>
<td></td>
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</table>

49% reduced risk of progression
Median followup 45 months

Boccadoro, ASCO 2013 #8509
Phase III Trial: ASCT vs CyRD and Maintenance with Lenalidomide ± Prednisone in NDMM

- 389 patients (younger than 65 yrs) randomized from 59 centers
- Patients: symptomatic disease, organ damage (CRAB), measurable disease

**Rd**
four 28-day courses

- **CyRD**
six 28-day courses
  - **RP MAINTENANCE**
    28-day courses until PD

- **CyRD**
six 28-day courses
  - **R MAINTENANCE**
    28-day courses until PD

- **MEL200**
  2 courses†
  - **RP MAINTENANCE**
    28-day courses until PD

- **MEL200**
  2 courses†
  - **R MAINTENANCE**
    28-day courses until PD

*CRD vs MEL 200; RP maintenance vs R maintenance; Rd (R: 25 mg/day Days 1-21; d: 40 mg/day Days 1,8,15,22), CRD (C: 300 mg/m²/day Days 1,8,15; d: 40 mg/day Days 1,8,15,22; R: 25 mg Days 1-21), MEL200 (M: 200 mg/m² Day -2); RP maint (R: 10 mg/day Days 1-21; P: 50 mg every other day); R maint (R: 10 mg/day Days 1-21)

†1 course MEL 200 if patients achieves VGPR after cycle 1.

RD-> CyRD v. ASCT x2

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>p</th>
<th>PFS 3y</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyRD</td>
<td>Not reached</td>
<td>0.003</td>
<td>38%</td>
<td>0.0003</td>
</tr>
<tr>
<td>ASCT</td>
<td>28mo</td>
<td></td>
<td>60%</td>
<td></td>
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</table>

PFS: Mel200-RP>Mel200-R>CyRD-RP=Cy-R

Overall survival: no differences

Median followup 31 months

Palumbo, ASH 2013 #763
Patients Who Benefit Least From Autologous Transplants

• Aggressive phenotypes
• Cytogenetic abnormalities, ie, deletion 17, translocation 4;14
• High LDH
• Other prognostic factors
  – High beta-2-microglobulin
  – Low albumin

Note: Patients who have received melphalan, BCNU, or radiation to the spine or pelvis may not be good candidates for autologous SCT because of the reduced number of stem cells that can be collected.
Strategies to Improve Outcomes With Autologous Transplantation

- Stem cell contamination
  - Purging: ineffective
- Myeloma remaining after single transplant
  - Tandem autologous transplants
  - Targeted radiotherapy:
    - $^{153}\text{Samarium}$
    - Novel induction regimens
    - Maintenance
    - Allogeneic transplant
Tandem Autologous Stem Cell Transplantation

• Patient has two planned autologous SCT within six months
  – Collected once before the initial transplant
  – Half of the stem cells are used for each procedure
• Second transplant may be beneficial to patients who:
  – Do not respond to 1st transplant
  – Achieve a marginal PR or CR after 1st transplant
## Preliminary Results of Single Versus Double SCT for Myeloma

<table>
<thead>
<tr>
<th></th>
<th>#</th>
<th>Single</th>
<th>Double</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>IFM 94</td>
<td>399</td>
<td>10%</td>
<td>20%</td>
<td>p &lt; 0.03</td>
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<tr>
<td>HOVON</td>
<td>255</td>
<td>47%</td>
<td>43%</td>
<td>NS</td>
</tr>
<tr>
<td>Bologna 96</td>
<td>178</td>
<td>74%</td>
<td>71%</td>
<td>NS</td>
</tr>
<tr>
<td>French MAG</td>
<td>193</td>
<td>27</td>
<td>22</td>
<td>NS</td>
</tr>
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</table>
Autologous Transplant for Multiple Myeloma after $^{153}$Sm-EDTMP + Mel200

- 46 patients, fixed dose $^{153}$SM-EDTMP
- Good tolerance, no dose limiting toxicities
- Normal engraftment
- Responses
  - CR  n=15 (33%)
  - VGPR  n=12 (26%)
- Survival compared favorably historical group of patients receiving Mel200 alone
  - Med OS 6.2 v. 4.8 yrs

Dispenzieri, et al. AmJHem 2010
Allogeneic Stem Cell Transplantation
+/- Total Body Irradiation

High Dose Chemotherapy

HLA-Matched Donor Stem Cells

Anti-Rejection/Anti-GVHD Drugs
Mini (Non-Myeloablative) Allogeneic Transplantation

- Relies on “graft-versus-leukemia" effect
- There is no currently proven standard, thus experimental procedure
- Potential benefits include:
  - Low toxicity and mortality
  - Low anticipated late effects
  - Treatment of elderly patients is feasible
  - Suitable for treatment of patients with comorbid conditions
  - Can be carried out on an outpatient basis
  - Fast recovery with few complications and less infection
Non-Ablative Allografts for Multiple Myeloma: A Work in Progress

- Randomized trials
  > Bruno: tandem auto-miniallo improves OS compared to tandem auto
  = Garban: tandem auto-miniallo not better than tandem auto for high risk MM patients
  = Krishnan: tandem auto-miniallo not better than tandem auto (early followup)
  > Bjorkstrand: tandem auto-miniallo improves OS compared to tandem auto
By indirectly targeting radiation to CD45 cells in marrow and other areas we should be able to deliver significant doses of radiation capable of eradicating disease, without excess toxicity.
Conclusions

• Novel drug combinations have become a standard of care for newly diagnosed transplant eligible patients.

• High dose melphalan->autologous transplant improves the depth of remission regardless of induction regimens, this translates to better PFS with novel agents

• After RD induction, tandem autoTX produces better PFS than MPR x6 or CyRD x6

• Allotransplants still investigational