Management of Multiple Myeloma: The Changing Paradigm

High-Dose Chemotherapy and Stem Cell Transplantation in the Era of Novel Therapies

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**Introduction: Example Patient Case**

- RW is a 65 year old African American man with back pain, fatigue
- Workup showed lytic lesions in the spine, compression fracture in L1, anemia with Hgb 9.5, M-spike 3.1 g/dL, Kappa Light Chains 205 mg/L, Ca 11, 60% PCs on Bx
  - He underwent Vertebroplasty to L1 and started monthly Zometa
- He was treated with 4 cycles of Velcade/Revlimid/Dex induction therapy
  - He achieved a Near CR (M-spike now only Faint/Unquantifiable in serum and 24 hr urine, BMBx now clean
- He then underwent an autologous stem cell transplant (ASCT) as consolidation
  - He had a fever and some mouth sores but engrafted day 11 and discharged day 12 without complications
  - Day 90 restaging showed Stringent Complete Remission, then started on maintenance low dose Revlimid
High-Dose Chemotherapy and Stem Cell Transplantation

- Offers best chance for durable remission based on current data
  - Outcomes improving with the use of newer drugs prior to transplantation
  - New trials comparing novel drugs vs transplant (results so far still favor SCT in 1st Remission)
- Can be done as part of frontline therapy or at relapse (or both)
- More patients considered candidates than in the past
  - Based on overall health and age
  - Criteria varies by cancer center
  - Talk to your Dr to see if you qualify
  - We transplant up to age ~ 75 at UTSW, Europe to 65
# Types of Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Transplant Type</th>
<th>Stem Cell Source</th>
<th>Transplant Process</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous (ASCT)</strong></td>
<td>• Peripheral Blood&lt;br&gt;• Bone Marrow Harvest (Not done for Myeloma)</td>
<td>• Single Auto (Most Common for Myeloma)</td>
</tr>
<tr>
<td>− Your own cells</td>
<td></td>
<td>• Tandem Auto (only proven benefit if not in &gt;90% Remission after 1st Auto)</td>
</tr>
<tr>
<td><strong>Allogeneic</strong></td>
<td></td>
<td>• Tandem Auto/ Mini Allo</td>
</tr>
<tr>
<td>− A donor’s cells (requires a match)</td>
<td></td>
<td></td>
</tr>
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</table>

*Most common*
Overview: ASCT

1. Induction therapy
   ~3–6 cycles

2. Collection of stem cells from the bloodstream
   Stem cell mobilization
   - Neupogen
   - Neulasta
   - Leukine
   - Cytoxan
   - Mozobil

3. Freezing of stem cells

4. High-dose chemotherapy (Consolidation)
   - Melphalan

5. Day of Rest

6. Thawing and infusion of stem cells

Stem cells
ASCT vs Conventional Chemotherapy

Overall Survival (%)

High dose (ASCT)

Conventional dose

High Dose (Auto SCT)

Standard therapy

Mos

0 15 30 45 60

0 20 40 60 80


Effect of Novel Agents on Outcome in Newly Diagnosed Myeloma

OS From Diagnosis

MM Survival Is Improving With Novel Agents

Median: 7.3 yrs

2006-2010

2001-2005

5-Yr Survival by Age, %

<table>
<thead>
<tr>
<th></th>
<th>≤ 65 Yrs</th>
<th>&gt; 65 Yrs</th>
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</thead>
<tbody>
<tr>
<td>2006-2010</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>2001-2005</td>
<td>63</td>
<td>31</td>
</tr>
</tbody>
</table>

Should I Get a Transplant After Induction Therapy or Can I Wait Until After I Relapse? 

Ongoing Clinical Trial

Initial therapy
RVD: 3 cycles

Stem cell collection/Storage with Cytoxan

Group A: Early ASCT
High-dose chemotherapy + ASCT
Consolidation: RVD: 2 cycles
Maintenance: Revlimid 12 months (Until PD in US)

Group B: ASCT at relapse
Continue RVD: 5 cycles
Maintenance: Revlimid 12 months (Until PD in US)
ASCT at relapse

RVD, Revlimid, Velcade, dexamethasone; Cytoxan, cyclophosphamide;
Consolidation: Additional therapy post-ASCT
Should I Get a Transplant After Induction Therapy or Should I Wait Until After I Relapse?

Initial Results of French Study

- Early ASCT conveys benefit in Progression Free Survival (PFS) but so far not in Overall Survival
- Early ASCT higher rate of Deep Remissions
- 1 year of maintenance therapy (per IFM study) conveys MRD negativity benefit but could longer maintenance overcome need for early ASCT?

**Continuous therapy with lenalidomide maintenance until progression to be addressed by US study.**

Following Transplantation: Possible Consideration of Maintenance Therapy

- What are the benefits vs risks?
- Who should get maintenance therapy?
- How long should patients get maintenance therapy?

Talk to your doctor about whether maintenance therapy is right for you.

**NINLARO**
Oral proteasome inhibitor

**VELCADE-BASED TREATMENT**
Supported by several smaller studies

**REVLIMID**
Reduction in myeloma progression (3 large studies)
Improved survival (1 of 3 studies)
Small risk of second cancers when used after melphalan
Mini (Nonmyeloablative) Allogeneic Transplantation

- Reduced-intensity allograft approach (Mini or RIC)
- Not a proven standard; experimental procedure
- Potential benefits:
  - Lower toxicity than myeloablative Allo (10-15% instead of 40% treatment related death within 100 days)
  - More candidates (elderly, comorbid conditions)
  - Outpatient treatment possible
  - Fast recovery, few complications, less infection
  - Small subset with long term remission
- However, most still relapse and many get Graft vs Host Disease so new methods needed and should be done only on a clinical trial
# Immune Cell Therapy and Vaccines in Development

<table>
<thead>
<tr>
<th>Type</th>
<th>Trial</th>
<th>Patient Types</th>
<th>Study Phase</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR T</td>
<td>CAR-T for multiple myeloma (BCMA or CD19)</td>
<td>Salvage ASCT after early relapse following first ASCT</td>
<td>1</td>
<td>University of Pennsylvania NIH Dana Farber</td>
</tr>
<tr>
<td>MILs</td>
<td>Tadalafil and lenalidomide maintenance with or without activated marrow infiltrating lymphocytes (MILs) in high-risk myeloma</td>
<td>Newly diagnosed; relapsed (without prior ASCT)</td>
<td>2</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td></td>
<td>Adoptive immunotherapy with activated MILs and cyclophosphamide graft-versus-host disease prophylaxis in patients with relapse of hematologic malignancies after allogeneic hematopoietic cell transplantation</td>
<td>Relapsed/ refractory after alloSCT</td>
<td>1</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td>DLI</td>
<td>CD3/CD28 activated Id-KLH primed autologous lymphocytes</td>
<td>Post-transplant</td>
<td>2</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Dendritic cell fusion vaccine + CT-011 (monoclonal antibody)</td>
<td>Post-transplant</td>
<td>2</td>
<td>Beth Israel Deaconess Medical Center Dana-Farber</td>
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<tr>
<td></td>
<td>Hiltonol (MAGE-A3 vaccine Poly-ICLC)</td>
<td>Post-transplant</td>
<td>2</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td></td>
<td>PVX-410</td>
<td>Post-transplant</td>
<td>2</td>
<td>Emory University</td>
</tr>
<tr>
<td></td>
<td>Dendritic Cell /Myeloma Fusions</td>
<td>Post-transplant</td>
<td>2</td>
<td>BMT CTN</td>
</tr>
</tbody>
</table>
CAR-BCMA T Cell Therapy in MM: Study Design

• First-in-human phase I trial
• BCMA = B Cell Maturation Antigen = Plasma Cell Specific

Pts with advanced R/R MM; ≥ 3 prior lines of therapy; normal organ function; clear BCMA expression (N = 12)

Cyclophosphamide 300 mg/m²
Fludarabine 30 mg/m²
QD for 3 days

CAR-BCMA T cells*
Single infusion

*Dose escalation of CAR+ T cells/kg
  0.3 x 10⁶
  1.0 x 10⁶
  3.0 x 10⁶
  9.0 x 10⁶

• CAR-BCMA expression determined by flow cytometry

CAR-BCMA T Cells in MM: Response

<table>
<thead>
<tr>
<th>Pt</th>
<th>Myeloma Type</th>
<th>CAR-BCMA Dose (T cells/kg)</th>
<th>Response</th>
<th>Response Duration, Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>κ light chain only</td>
<td>0.3 x 10^6</td>
<td>PR</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>IgA λ</td>
<td>0.3 x 10^6</td>
<td>SD</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>κ light chain only</td>
<td>0.3 x 10^6</td>
<td>SD</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>κ light chain only</td>
<td>1.0 x 10^6</td>
<td>SD</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>IgG κ</td>
<td>1.0 x 10^6</td>
<td>SD</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>IgG λ</td>
<td>1.0 x 10^6</td>
<td>SD</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>IgG λ</td>
<td>3.0 x 10^6</td>
<td>SD</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>κ light chain only</td>
<td>3.0 x 10^6</td>
<td>VGPR</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>κ light chain only</td>
<td>3.0 x 10^6</td>
<td>SD</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>IgA λ</td>
<td>9.0 x 10^6</td>
<td>sCR</td>
<td>12+</td>
</tr>
<tr>
<td>11</td>
<td>IgG λ</td>
<td>9.0 x 10^6</td>
<td>PR</td>
<td>6+</td>
</tr>
<tr>
<td>12</td>
<td>IgA λ</td>
<td>3.0 x 10^6</td>
<td>SD</td>
<td>2</td>
</tr>
</tbody>
</table>

CAR-BCMA T Cells in MM: Pt 10

- Pt 10: chemotherapy-resistant IgA MM with 3 prior lines of therapy
  - Relapse 3 mos after ASCT with 90% bone marrow plasma cells
  - BCMA expression on pt’s myeloma cells was uniform but dim
- After CAR-BCMA T-cell infusion, the pt experienced cytokine release syndrome (including fever, hypotension, tachycardia, high creatinine kinase, liver enzymes) which resolved within 2 wks
  - ANC < 500/µL at time of infusion and for 40 days after
  - Pt was platelet transfusion dependent for 9 wks after infusion
- Pt achieved ongoing sCR after CAR-BCMA T-cell infusion
  - Serum, urine immunofixation negative at 14 wks post infusion
  - Bone marrow negative by flow cytometry 14 wks post induction
- MM eliminated from bone marrow cells after infusion with CAR-BCMA
- Eliminates Plasma Cells so will likely need lifelong IVIG

Questions To Ask Your Doctor

• Am I a candidate for high-dose chemotherapy and stem cell transplantation?
• What are the pros and cons of stem cell transplantation in my case?
• When is the best time for me to undergo transplantation?
• Does your center do stem cell transplants? How many transplants has your center performed in multiple myeloma in the last year? Is procedure performed as an inpatient or outpatient?
• How long will I be in the hospital?
• What is the recovery period?
• What kind of changes in my lifestyle will I need to make?
• When do I go back to you for follow-up?
Conclusion: Example Patient Case

- Our patient RW started Maintenance Revlimid after day 90
- He has continued to remain in stringent Complete Remission for 4 years after Transplant
- Working Full Time and tolerating low dose Revlimid 10 mg well (I give 3 weeks on and 1 week off)
- Plan on continuing until relapse or as long as tolerating
- Monthly labs and checkup to watch for low blood counts or relapse
- Doses can be increased from 10 to 15 mg in those not in CR and decreased to 5 to 10 mg in those with low Neutrophils or diarrhea
- Modifying dose and staying on therapy is Key
Summary: High-Dose Chemotherapy and Stem Cell Transplantation

- Offers best chance for long-term remission for eligible patients based on current data
- Research questions:
  - Given the availability of the novel agents, can we delay high-dose chemotherapy and stem cell transplantation until relapse?
  - Which patients achieve the greatest benefit?
  - What is the role of maintenance therapy?
  - How long should patients remain on maintenance therapy?
  - Does MRD Testing affect need for maintenance?