Management of Multiple Myeloma: 
The Changing Paradigm

High-Dose Chemotherapy 
and Stem Cell Transplantation

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Case Presentation

- RM is a 64-year-old man with a history of hypertension and newly diagnosed IgG/kappa multiple myeloma who first presented with left hip pain
  - Plain films revealed a lytic lesion in his left proximal femur as well as additional smaller lytic lesions
  - He was noted to be anemic (Hgb 9.8 g/dL) and his serum calcium and creatinine were within normal limits
  - Serum protein electrophoresis demonstrated an IgG/kappa paraprotein measuring 4.8 gm/dL and urine protein electrophoresis demonstrated a serum free kappa light chain measuring 200 mg/24 hours
  - His bone marrow biopsy revealed 60% plasma cells with normal cytogenetics and FISH
Case Presentation

Question 1

Does RM require therapy?
A. Yes
B. No
C. I don’t know

*He has symptomatic multiple myeloma with bone lesions and anemia.
Case Presentation

Question 2

Is RM a good transplant candidate?
A. Yes
B. No
C. I don’t know

*He is young, he has a good performance status, and he has minimal comorbidities.
Case Presentation
Question 3

What is the optimal regimen to start?

Ever-changing field
Case Presentation

- RM starts chemotherapy with RVD
  - Bortezomib (Velcade)
  - Lenalidomide (Revlimid)
  - Dexamethasone
- After four cycles of chemotherapy his paraprotein has completely disappeared from his blood and urine
- A bone marrow biopsy demonstrates no evidence of multiple myeloma by routine immunohistochemistry
- He is referred to a transplant center for consideration of autologous stem cell transplant

What is the rationale for a transplant?

- Based upon the principle of the dose-response curve
What is the rationale for a transplant?

- Based upon the principle of the dose-response curve
- Limitation on how high of a dose can be given because of side effects

Response

log\[Dose\]

Limited Response

Excessive Bone Marrow Toxicity

What is the rationale for a transplant?

- Based upon the principle of the dose-response curve
- Limitation on how high of a dose can be given because of side effects

Response

log\[Dose\]
What is the rationale for a transplant?

- Based upon the principle of the dose-response curve
- Limitation on how high of a dose can be given because of side effects
- If higher dose is administered, the bone marrow would be destroyed

How do we protect the bone marrow?

- Autologous stem cell transplant
  - Remove bone marrow stem cells from the patient and give them back after the chemotherapy is done
- Allogeneic stem cell transplant
  - Use cells from a matched donor
Types of Stem Cell Transplantation

- **Transplant Type**
  - Autologous*
    - Your own cells
  - Allogeneic
    - A donor’s cells (requires a match)
    - Syngeneic

- **Stem Cell Source**
  - Peripheral blood
  - Bone marrow

- **Transplant Process**
  - Mini-allo
  - Tandem

*Most common

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Autologous Stem Cell Transplant Overview

1. Induction therapy
   ~4–6 cycles
Autologous Stem Cell Transplant Overview

1. Induction therapy
   - Stem cell mobilization
     - Neupogen
     - Leukine
     - Cytoxan
     - Mozobil

2. Collection of stem cells from the bloodstream

3. Freezing of stem cells

So when do you clean the stem cells before you give them back?
Autologous Stem Cell Transplant Overview

1. Induction therapy
2. Collection of stem cells from the bloodstream
3. Freezing of stem cells
4. High-dose chemotherapy
5. Thawing and infusion of stem cells

*Melphalan used

Complications of SCT

<table>
<thead>
<tr>
<th>Bone Marrow Suppression</th>
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<tbody>
<tr>
<td>Low WBC</td>
<td>Infection</td>
</tr>
<tr>
<td>Low hemoglobin</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Low platelets</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Reactivation of infections</td>
<td>Shingles/hepatitis</td>
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<table>
<thead>
<tr>
<th>GI Tract</th>
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<tbody>
<tr>
<td>Lining of mouth</td>
<td>Mouth sores</td>
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<tr>
<td>Colon</td>
<td>Diarrhea</td>
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<table>
<thead>
<tr>
<th>Miscellaneous</th>
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<tr>
<td>Heart, liver, kidneys</td>
<td>Often stressed by transplant</td>
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</table>

Prophylactic antibiotics
G-CSF/GM-CSF
Red blood cell transfusions
Platelet transfusion
Acyclovir
Cryotherapy pain medications
Imodium
Treatment of infection
Remission Accomplished!

Disease burden

Newly diagnosed $1 \times 10^{12}$

Disease burden

CR

Stringent CR

Molecular/flow CR

Cure?

1

×

$10^8$

1

×

$10^4$

$10^4$

0.0

Autologous Stem Cell Transplant Overview

1. Induction therapy

~4–6 cycles

2. Collection of stem cells from the bloodstream

3. Freezing of stem cells

4. High-dose chemotherapy*

5. Thawing and infusion of stem cells

6. Consolidation maintenance therapy

Blood stem cells

-190°C Freezer

*Melphalan used

Stem cell mobilization

- Neupogen

- Leukine

- Cytoxan

- Mozobil
Does doing a second (tandem) transplant improve outcomes?

<table>
<thead>
<tr>
<th></th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>IFM-94</td>
<td>Longer remissions and survival with tandem transplant</td>
</tr>
<tr>
<td>HOVON</td>
<td>Higher complete response rates with tandem transplant</td>
</tr>
<tr>
<td>Bologna</td>
<td>No difference</td>
</tr>
<tr>
<td>MAG 95</td>
<td>No difference</td>
</tr>
</tbody>
</table>

IFM-94 Trial: OS benefit only noted in patients who had not achieved a very good partial response after the first autologous stem cell transplant.

**Using Revlimid to Maintain Remissions: French Experience**

**Duration of maintenance: 24 months**

### PFS

- **Median PFS**
  - Placebo: 24 Months
  - Lenalidomide: 46 Months

- **PFS and OS from Relapse**

### OS

- **Median OS**
  - Placebo: 81 Months
  - Lenalidomide: 100 Months

- **PFS**

- **OS**
Using Revlimid to Maintain Remissions: US Experience

Time to Progression

ITT Analysis with a median follow-up from transplant of ~48 months. \( P < 0.001 \) median TTP: 50 months vs 27 months.

- Estimated HR=0.51
  \( (95\% \text{ CI} = 0.39 \text{ to } 0.66) \)

Overall Survival

Analysis including placebo patients crossing over within 12 months of randomization on lenalidomide arm with a median follow-up of ~48 months. \( P=0.003 \)

- Estimated HR=0.61
  \( (95\% \text{ CI} = 0.41 \text{ to } 0.87) \)

Consolidation

Chemotherapy Afterwards to Improve Remissions

- Consolidation is utilized to further improve response and the duration of disease control after ASCT
- A number of trials have shown that the use of a three-drug regimen have dramatically improved the quality and depth of response:
  - VTD
  - RVD
  - KRd

Cavo M et al. Blood. 2012;120:9
Phase 3 Stamina Trial: BMT CTN0702

Any induction therapy → Randomize → MEL 200 mg/m² ASCT → VRD × 4* → Lenalidomide maintenance† → Lenalidomide maintenance† → Lenalidomide maintenance† → Bortezomib 1.3mg /m² days 1, 4, 8, 11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15
†Lenalidomide 15 mg daily × 3 years

- Estimated study completion date: 2020
- Estimated primary initial completion date: 5/2016

ClinicalTrials.gov Identifier: NCT01109004

Stamina Trial Preliminary Results

Progression Free Survival

Overall Survival

0 20 40 60 80 100
0 12 24 38
Probability, %
months from randomization

0 20 40 60 80 100
0 12 24 38
Probability, %
months from randomization

Auto/Auto → Auto/RVD → Auto/Maint
Long-Term Treatment Before and After Autologous Stem Cell Transplant

![Graph showing response rates](chart.png)

Following Transplantation: Possible Consideration of Maintenance Therapy

- NINLARO: Oral proteasome inhibitor
  - Maintenance with NINLARO
- VELCADE-BASED TREATMENT
  - Supported by several smaller studies
  - Velcade alone or in combination with other myeloma drugs:
    - Velcade + Thalidomide
    - Velcade + Prednisone
- REVLIMID
  - Reduces myeloma progression (3 large studies)
  - Improved survival (1 of 3 studies)
  - Small risk of second cancers when used after melphalan

Talk to your doctor about whether maintenance therapy is right for you.
Should I get a transplant after induction therapy or should I wait until after I relapse?

Ongoing Clinical Trial

- **Initial therapy**
  - RVD: 3 cycles
- **Stem cell collection**
  - Cytoxan
- **Group A:**
  - Early ASCT
  - High-dose chemotherapy + ASCT
  - Consolidation: RVD: 2 cycles
  - Maintenance: Revlimid
  - ASCT at relapse
- **Group B:**
  - ASCT at relapse
  - Continue RVD: 5 cycles
  - Maintenance: Revlimid
  - ASCT at relapse

**RVD:** Revlimid, Velcade, dexamethasone; **Cytoxan,** cyclophosphamide;
**Consolidation:** Additional therapy post-ASCT

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**Early vs Late Transplant Preliminary Results**

- Better response rates with early transplant
- Longer remissions when transplant done early (34 months vs 43 months)
- Overall survival at 4 years was not significantly different

*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.
Case Presentation

Question

Patient RM: 64-year-old man with IgG/kappa myeloma who enters a CR after four cycles of RVD. Now what?

A. Collect his stem cells. Continue with RVD and plan for transplant at the time of relapse.
B. Proceed to a single autologous stem cell transplant with maintenance lenalidomide.
C. Proceed to tandem autologous stem cell transplants with maintenance lenalidomide.
D. Proceed to single autologous transplant followed by chemotherapy with RVD and maintenance lenalidomide.
E. Option B, C, or D with 2 years of maintenance lenalidomide.
F. I listened to the entire talk and I still don’t know what to do.

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, what is the role of high-dose chemotherapy and stem cell transplantation?
  - Which patients achieve the greatest benefit?
  - When is the best time to undergo transplantation?
  - What is the role of maintenance therapy? How long should patients remain on maintenance therapy?
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?