Multiple Myeloma in the Aging Adult

Ashley Rosko, MD
Assistant Professor-Clinical
Division of Hematology
The Ohio State University Wexner Medical Center

Myeloma Dynamic Field Epidemic
57% Increase by 2030

Hematologic Malignancy

Estimated New Cases (%) of Leukemia, Lymphoma, and Myeloma, 2014*

Myeloma 15%
24,000 cases

Leukemia 33%
72,500 cases

Lymphoma 51%
92,900 cases

Total cases: 156,420

Figure 2. Source: Cancer Facts & Figures, 2014: American Cancer Society, 2014.
*Total percentage does not add up to 100% due to rounding in the calculation of individual percentages.

Myeloma is a disease of aging adults

- Median age diagnosis: 69

Surveillance, Epidemiology, and End Results (SEER) Program Populations
U.S. Census Bureau

MM is a rare blood cancer

Blood Cancer 4th

Common Types of Cancer

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2015</th>
<th>Estimated Deaths 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer Female</td>
<td>231,200</td>
<td>41,700</td>
</tr>
<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>221,300</td>
<td>156,000</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td>209,800</td>
<td>27,100</td>
</tr>
<tr>
<td>4. Colorectal Cancer</td>
<td>152,700</td>
<td>49,700</td>
</tr>
<tr>
<td>5. Bladder Cancer</td>
<td>74,900</td>
<td>16,900</td>
</tr>
<tr>
<td>6. Melanoma of the Skin</td>
<td>72,670</td>
<td>8,940</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>71,890</td>
<td>17,790</td>
</tr>
<tr>
<td>8. Thyroid Cancer</td>
<td>62,180</td>
<td>1,530</td>
</tr>
<tr>
<td>9. Kidney and Renal Pelvis Cancer</td>
<td>61,960</td>
<td>14,960</td>
</tr>
<tr>
<td>10. Esophageal Cancer</td>
<td>54,970</td>
<td>10,170</td>
</tr>
<tr>
<td>11. Stomach Cancer</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12. Liver Cancer</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13. Lung Cancer Male</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14. Myeloma</td>
<td>26,850</td>
<td>11,240</td>
</tr>
</tbody>
</table>

Surveillance, Epidemiology, and End Results (SEER) Program Populations

- Older adults
- Male : Female 1.5:1
- 2-3X African American Population
- 3.7 fold higher risk (+) family member
Myeloma Highly Treatable: Not Curable

Challenges: Age Disparities in MM Survival
- 5 year survival: 48.5%
- Significant improvement in long term survival
- Modest improvements in survival for aging adults

Improved long-term survival in multiple myeloma up to the age of 80 years
S Y Kristinsson, W F Anderson and O Landgren Leukemia May 2014

Multiple Myeloma
Smoldering Myeloma
MGUS
Plasma Cell Dyscrasias

PLASMA CELL DISORDERS
- Plasma cell leukemia
- Plasmacytoma
- POEMS
- Cryoglobulinemia
- AL Amyloidosis
- MGRS
- Necrobiotic Xanthogranuloma
- Non-Hodgkin Lymphoma
- Waldenstroms
- Heavy Chain Disease

Multiple Myeloma: Clonal expansion of malignant plasma cells
Normal: 2-3% Bone marrow population Polyclonal
C: Calcium elevated
- fatigue, drowsiness, confusion
- severe abdominal pain

R: Renal failure
- poor urine output
- swelling of legs / feet
- poor control of electrolytes and minerals

A: Anemia
fatigue, sob, exhaustion

B: Bone disease
lytic lesions
severe osteoporosis
fractures

*****E: Extra
- Clonal plasma cells in BM ≥ 60%
- Serum FLC ratio ≥ 100
- > 1 MRI focal lesion ≥ 5 mm on MRI

Definitions:
SPEP: Quantification of abnormal protein
IFE: Identification of an abnormal protein
FLC: Serum quantification of free lambda and kappa light chains (16% MM)
Bence Jones Proteinuria: 24 UPEP
Quantitative Immunoglobulins:
Serum quantification: IgG (50%), IgA (21%), IgM (IgD 2%)

IgM Paraprotein signal = Waldenstroms

Diagnosis: Multiple Myeloma
Presence of malignant plasma cells
And end organ damage
Anemia Under recognized: Not a normal part of aging

Anemia work-up
- 2/3 MM have Anemia at Dx
- Protein-albumin – 97% M protein

Artz 2008 Semin Hematol

Half of patients will have bone disease at presentation

Hypercalcemia
- 1/3 Patients At diagnosis

Primary and Secondary Osteoporosis Challenge in MM Population

Primary osteoporosis:
Deterioration of bone unassociated with other chronic illness and is related to aging and decreased gonadal function.

Secondary osteoporosis:
2/2 chronic conditions that accelerated bone loss

Clinically, distinguishing fragility fractures related to primary osteoporosis from MM induced compression fractures is problematic:
- Steroid use
- Tempo? Sudden onset more than 1 fracture
- Other bone pain

How do you image?

- Bone Scan = osteolytic and osteoblastic activity
- Bone Surveys (Plain x-rays) = pick up lytic lesions
  MM unopposed osteolytic activity
- 50% of bone needs to be gone to pick them up
  - Osteoporosis
- MRI and sometimes PET scans
  - Extramedullary disease 7%
  - Non-secretory disease
- Supportive care: Bisphosphonates and/or Radiation

Half of MM patients present with Renal Disease

Renal Injury = TREATMENT ASAP

Renal Recovery?
Type of Protein
Underlying Renal Disease
Medications (NSAIDS, contrast)

Renal Entities
- MGRS
- Hyperviscosity
- Controversial
- Plasma exchange

International Staging System for Myeloma

How proliferative is MM and how much End organ damage?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>ISS</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>(\beta_2\text{-M} &lt; 3.5 \text{ mg/L, and serum albumin} \geq 3.5 \text{ g/dL} )</td>
<td>1</td>
<td>62 (58-65)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Not stage I or III</td>
<td>2</td>
<td>44 (42-46)</td>
</tr>
<tr>
<td>Stage III</td>
<td>(\beta_2\text{-M} \geq 5.5 \text{ mg/L} )</td>
<td>3</td>
<td>29 (26-32)</td>
</tr>
</tbody>
</table>


Cytogenetics Highly Informative

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(14;16)</td>
<td>Deletion 13 by karyotyping</td>
<td>t(11;14)</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>hypodiploidy</td>
<td>t(6;14)</td>
</tr>
<tr>
<td>1q abnormality profiling</td>
<td></td>
<td>Normal cytogenetic</td>
</tr>
<tr>
<td>Complex Karyotype</td>
<td>Del 13 by FISH (molecular)</td>
<td></td>
</tr>
<tr>
<td>Del 17p or P53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Revised International Staging System (R-ISS)

- Presence of Del(17p), t(4;14), or t(14;16) were considered high risk.

<table>
<thead>
<tr>
<th>R-ISS</th>
<th>ISS</th>
<th>iFISH</th>
<th>LDH</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>j2M &lt; 3.5, Alb ≥ 3.5</td>
<td>Standard</td>
<td>Normal</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>j2M ≥ 3.5</td>
<td>High risk or high</td>
<td>83 mos.</td>
<td>43 mos.</td>
</tr>
</tbody>
</table>

Palumbo A et al. Revised International Staging System for Multiple Myeloma: A report from the international myeloma working group. JCO 33, 3-Aug-2015.

Majority of Myeloma Patients do not receive Transplant

Approach to treatment based on Physiologic Reserve

Biologic age ≠ chronologic age

Transplant Eligible?
- Comorbid conditions
- Disease response
- ADLs/IADLS
- Psychosocial support
- Patient goals of care

Treatment: Standard of Care Autologous Hematopoietic Stem Cell Transplant
Prompt Recognition and Referral: Early Death in Older Adults with Myeloma

- MM deaths overall are highest: aged 75 years and greater
- Early mortality (death within one year of diagnosis) is most common in those 70 years and older

Targeted Novel Therapy: Pills, shots, and immunotherapy

- **IMiDs**
  - Lenalidomide
  - Thalidomide
  - Pomalidomide
- **Proteasome inhibitors**
  - Velcade
  - Carfilzomib
  - Oprozomib
  - Ivacinib
- **Alkylators**
  - Melphalan
  - Cytoxan
  - Bendamustine
- **Antibodies**
  - Daratumumab
  - Elotuzumab

Diagnosis Of Multiple Myeloma and Treatment of Transplant Eligible Patients

Yvonne Efebera, MD, MPH
Associate Professor-Clinical
Division of Hematology
The Ohio State University Wexner Medical Center
Objectives

- Know the difference between MGUS, smoldering Myeloma, Symptomatic multiple Myeloma
- Understand the general clinical features of plasma cell myeloma including the diagnosis, and steps required for evaluation.
- Understand Treatment strategy:
  - Newly diagnosed Multiple Myeloma Patients Eligible for Transplant
  - Newly diagnosed Multiple Myeloma Patients not Eligible for Transplant – Ashley Rosko

Revised IMWG Diagnostic Criteria for Multiple Myeloma*

<table>
<thead>
<tr>
<th>MGUS</th>
<th>Smoldering</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein &lt; 3 g/dL and clonal plasma cells in BM &lt; 10% No myeloma defining events</td>
<td>M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine) Clonal plasma cells in BM 10% to 60% No myeloma-defining events</td>
<td>Clonal BM plasma cells ≥ 10% or ≥ 1 biopsy-proven plasmacytoma AND 1 or more MM-defining events: ≥ 1 CRAB† feature Biomarkers of malignancy-MDE Clonal plasma cells in BM ≥ 60% Serum FLC ratio ≥ 100 &gt; 1 MRI focal lesion ≥ 5 mm on MRI, positive PET or CT.</td>
</tr>
</tbody>
</table>

†: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)
*New criteria associated with ≥ 80% risk of progression to MM within 2 yrs.


Risk of MGUS → Myeloma

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Relative Risk</th>
<th>Risk @ 20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest risk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. M protein &lt; 1.5 g/dL</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>2. IgG subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Normal FLC ratio (K/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any 1 factor abnormal</td>
<td>5.4</td>
<td>21%</td>
</tr>
<tr>
<td>Any 2 factors abnormal</td>
<td>10.1</td>
<td>37%</td>
</tr>
<tr>
<td>All 3 factors abnormal</td>
<td>20.8</td>
<td>58%</td>
</tr>
</tbody>
</table>

Rajkumar, V et al. Blood. 2005

Smoldering Multiple Myeloma (SMM)

<table>
<thead>
<tr>
<th>Mayo Clinic Criteria</th>
<th>% of cases that transition from Smoldering Myeloma to Multiple Myeloma in 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 criteria:</td>
<td>1/3</td>
</tr>
<tr>
<td>1. M-protein ≥ 3 g/dL</td>
<td></td>
</tr>
<tr>
<td>2. ≥10% clonal bone marrow plasma cells</td>
<td></td>
</tr>
<tr>
<td>3. Free light-chain &lt;0.125 or &gt;8</td>
<td></td>
</tr>
</tbody>
</table>

25% | 51% | 76%

NO consensus on
1: if to treat SMM
2: When to start treatment
Clinical trials ongoing
Currently: watch until Progression to MM
Symptomatic Multiple Myeloma

- About 20,000-22,000 new cases a year in the US
- 10% of hematologic malignancies – 2nd most common blood Cancer
- 1% of all cancers
- About 75,000 patients living with MM in the US today
- Blacks > white (2:1) Males > Females (1.4:1)
- About 700 new cases in Ohio annually
- Causes: mainly unknown, but some environmental exposures are associated:
  - Ionizing radiation, organophosphates, benzene, agent orange,
  - First responders at WTC on 9/11/01

Most Important: it is not Curable BUT VERY TREATABLE

Every Myeloma Doc’s Nightmare

International Staging System for Symptomatic Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>$\beta_2$-M $&lt; 3.5$ mg/L and serum albumin $\geq 3.5$ g/dL</td>
</tr>
<tr>
<td>Stage II</td>
<td>Not stage I or III</td>
</tr>
<tr>
<td>Stage III</td>
<td>$\beta_2$-M $\geq 5.5$ mg/L</td>
</tr>
</tbody>
</table>

OLD and Older treatments used

**Risk stratification: multiple myeloma is not one disease!**

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p deletion</td>
<td>t(4;14)</td>
<td>Hyperdiploidy (trisomies)</td>
</tr>
<tr>
<td>t(14;10)</td>
<td>Deletion 13 by karyotyping</td>
<td>t(11;14)</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>hypodiploidy</td>
<td>t(6;14)</td>
</tr>
<tr>
<td>High risk gene expression profiling</td>
<td>Del 13q abnormality</td>
<td>Normal cytogenetic</td>
</tr>
<tr>
<td>Complex Karyotype</td>
<td>Del 13 by FISH (molecular)</td>
<td></td>
</tr>
<tr>
<td>Del 17p or PS3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Myeloma patients are risk-stratified at initial diagnosis based on fluorescence in situ hybridization (FISH) studies on the bone marrow for t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), del17p13, and trisomies of odd numbered chromosomes. If FISH is unavailable, conventional cytogenetics can be used as an alternative, but is much less sensitive.


**Revised ISS and Novel agents**

- Goal was to incorporate CD138-selected interphase FISH and tested for del(13), del(17p), and 14q32 translocations.
- Presence of Del(17p), t(4;14), or t(14;16) were considered high risk.

<table>
<thead>
<tr>
<th>R-ISS</th>
<th>ISS</th>
<th>iFISH</th>
<th>LDH</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>β2M &lt; 3.5, Alb ≥ 3.5</td>
<td>Standard Normal</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>β2M ≥ 5.5</td>
<td>High risk or high</td>
<td>83 mos.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>β2M ≥ 5.5</td>
<td>High risk or high</td>
<td>43 mos.</td>
<td></td>
</tr>
</tbody>
</table>

Palumbo A et al. Revised International Staging System for Multiple Myeloma: A report from the international myeloma working group. JCO 33, 3-Aug-2015.

**History of Multiple Myeloma**

- 1844 First reported case of soft, fragile bones, heat soluble substance in urine abnormal cells in bone marrow – Sarah Newbury
- 1873 “Multiple Myeloma” term used
- 1889 Detailed pathologic description published
- 1903 Lytic lesions seen on radiographs
- 1939 Serum electrophoresis employed
- 1956 “Bence Jones” proteinuria described
- 1962 First use of melphalan
- 1964 First use of cyclophosphamide
- 1967 First use of corticosteroids
- 1983 First use of autologous stem cell transplantation
- 1990s Thalidomide found to be effective
- 2000s Revlimid and Velcade are FDA approved

**Myeloma foot soldiers: Novel agents**

1. Steroids
   - Dexamethasone
   - Prednisone
2. Proteasome inhibitors
   - Velcade
   - Carfilzomib
   - Ixazomib
3. IMiDs
   - Thalidomide
   - Lenalidomide
   - Pomalidomide
4. HDACi
   - Panobinostat
   - AR-42
   - ACY-241
5. Adjuvants
   - Elotuzumab
   - GVAX
   - 4SCT
6. CD38 Ab
   - Daratumumab
   - SAR650984
   - SINE
   - KPT-330
   - KPT-8802

Oncolytic viruses
- CAR-T, CAR-NK
- BiTe, TRiKE
- Alphoemo
- BT082
- GSK2857916
- INLL-00X
- ABBV-438
### Overall Survival from Time of Diagnosis in 6-yr Intervals based on date of Diagnosis

![Graph showing overall survival from time of diagnosis in 6-yr intervals.](Image)

Kumar SK et al, Blood 2008: 111: 2516

### 2015: A GREAT YEAR for Myeloma

- **4 New drugs approved for relapsed/refractory MM**
  - Daratumumab: Nov 16, 2015: monoclonal ab, anti-CD38, single agent
  - Elotuzumab: Nov 30, 2015: monoclonal ab, SLAM-7 and NK cell activation, in combination with lenalidomide and Dex
  - Ixazomib: Nov 20, 2015: oral proteasome inhibitor, in combination with lenalidomide and Dex
  - Panobinostat: Feb 28, 2015: HDAC inhibitor, in combination with bortezomib and Dex

<table>
<thead>
<tr>
<th>Approved Newly Dx MM</th>
<th>Newly Diagnosed Regimen</th>
<th>Approved Relapsed MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (T)</td>
<td>VTD</td>
<td>Pomalidomide (P)</td>
</tr>
<tr>
<td>Lenalidomide (R)</td>
<td>VTD</td>
<td>Carfilzomib (K)</td>
</tr>
<tr>
<td>Bortezomib (V)</td>
<td>CRD</td>
<td>Panobinostat</td>
</tr>
<tr>
<td>Dexamethasone (D)</td>
<td>RD</td>
<td>Daratumumab</td>
</tr>
<tr>
<td>Prednisone (P)</td>
<td>VD</td>
<td>Ixazomib</td>
</tr>
<tr>
<td>Thalidomide (T)</td>
<td>VTD</td>
<td>Elotuzumab</td>
</tr>
<tr>
<td>Lenalidomide (R)</td>
<td>VTD</td>
<td></td>
</tr>
<tr>
<td>Bortezomib (V)</td>
<td>CRD</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone (D)</td>
<td>RD</td>
<td></td>
</tr>
<tr>
<td>Prednisone (P)</td>
<td>VD</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (C)</td>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>Dyosil</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>Melphalan</td>
<td></td>
</tr>
</tbody>
</table>

### Standard Induction treatment for fit patients

<table>
<thead>
<tr>
<th>Drug (VRD)</th>
<th>Type</th>
<th>Mode</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>Steroid</td>
<td>Pill, weekly</td>
<td>Insomnia, weight gain</td>
</tr>
<tr>
<td>Revlimid</td>
<td>IMiDs</td>
<td>Pill, daily</td>
<td>Blood clots, diarrhea</td>
</tr>
<tr>
<td>Velcade</td>
<td>Proteasome Inhibitors</td>
<td>Shot 2x / wk subcutaneous</td>
<td>Tingling numbness in hands or feet</td>
</tr>
</tbody>
</table>

1. **Standard Induction treatment for fit patients**
   - **1.** Dexamethasone, cyclophosphamide, vincristine, doxorubicin, dexamethasone
   - **2.** Autologous transplant = High dose IV melphalan (Leads to 30 months of remission on average)
   - **3.** Revlimid (pill) maintenance (Adds 18-23 months of remission on average)

### Auto transplant in Eligible patients

- **Melphalan 200 mg/m² autologous transplant improves survival over standard cytotoxic chemotherapy**
- **Who can be transplanted safely?**
  - Age ≤ 75 y.o. (140 mg/m² 71-75 y.o.)
  - Functionally able to work at a “desk job”
  - Normal functioning liver by enzymes and PT/PTT, low risk PFTs, LVEF > 40%
  - No other interfering comorbidity
  - Dialysis patients are eligible for auto SCT (140 mg/m2)

Bortezomib, Thalidomide and Dexamethasone (VTD) is Superior to Bortezomib, Cyclophosphamide and Dexamethasone (VCD) as induction therapy prior to Autologous Stem Cell Transplantation for Patients with De Novo Multiple Myeloma. Results of the Prospective IFM 2013-04 Trial. Philippe Moreau et al

VTD x 4 versus VCD x 4 as induction therapy prior to ASCT
Symptomatic de novo MM less than 66 years
Primary end-point: VGPR rate after cycle 4
340 patients overall (170 per arm).

Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. Cavo et al leukemia:2015, 2429-2431

Toxicity

<table>
<thead>
<tr>
<th></th>
<th>VTD, n = 169</th>
<th>VCD, n = 169</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Aes</td>
<td>63.9%</td>
<td>68.2%</td>
<td>0.40</td>
</tr>
<tr>
<td>Anemia</td>
<td>4.1%</td>
<td>9.5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16.9%</td>
<td>33.1%</td>
<td>0.003</td>
</tr>
<tr>
<td>Infection</td>
<td>7.7%</td>
<td>10.1%</td>
<td>0.45</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4.7%</td>
<td>10.6%</td>
<td>0.04</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1.8%</td>
<td>1.8%</td>
<td>0.99</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>1.2%</td>
<td>0%</td>
<td>0.16</td>
</tr>
<tr>
<td>Cystitis</td>
<td>0%</td>
<td>0.6%</td>
<td>0.32</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>5.3%</td>
<td>3.5%</td>
<td>0.42</td>
</tr>
<tr>
<td>Periph. Neuropathy</td>
<td>7.7%</td>
<td>2.9%</td>
<td>0.05</td>
</tr>
<tr>
<td>PN grade 2-4</td>
<td>21.9%</td>
<td>12.9%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Toxicities assessed according to NCI CTCAE, version 4.0.

Dose and schedule same as Moreau et al. except V and C given IV, 3 cycles each before SCT.
### Toxicity

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>VRd (n=236)</th>
<th>VCD (n=236)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3 or 4 adverse event</td>
<td>64 (27%)</td>
<td>61 (26%)</td>
<td>0.754</td>
</tr>
<tr>
<td>Skin rash</td>
<td>19 (8%)</td>
<td>2 (1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>17 (7%)</td>
<td>5 (2%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Gastrointestinal events</td>
<td>15 (6%)</td>
<td>8 (3%)</td>
<td>0.135</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>5 (2%)</td>
<td>8 (3%)</td>
<td>0.399</td>
</tr>
<tr>
<td>Any grade 3 or 4 hematological adverse event</td>
<td>32 (14%)</td>
<td>26 (11%)</td>
<td>0.224</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 (8%)</td>
<td>16 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>0.399</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (&lt;1%)</td>
<td>10 (4%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Study protocol discontinuation during induction therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic effects</td>
<td>8 (3%)</td>
<td>4 (2%)</td>
<td>0.242</td>
</tr>
<tr>
<td>Disease progression</td>
<td>0</td>
<td>3 (1%)</td>
<td>0.124</td>
</tr>
<tr>
<td>Early death</td>
<td>1 (&lt;1%)</td>
<td>2 (1%)</td>
<td>0.580</td>
</tr>
</tbody>
</table>

**Conclusion**

- The combination of a proteosome inhibitor (bortezomib), and an immune modulator (thalidomide, lenalidomide) as induction treatment is a superior regimen
- 3-drug regimen with Novel agents is superior to 2-drug regimen with Novel agent as Induction regimen
Autologous SCT as consolidation in newly Dx MM vs continuation of Therapy (Early vs delayed SCT) in the ERA of Novel Therapies

<table>
<thead>
<tr>
<th>Overall Survival - Using older regimens</th>
<th>Old regimen (VAD regimen)</th>
<th>New regimen incorporating Novel agents and maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (ORR)</td>
<td>50-60%</td>
<td>80-100%</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>16-25%</td>
<td>40-60%</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>5-10%</td>
<td>20-30%</td>
</tr>
<tr>
<td>5 yr Overall survival (OS)</td>
<td>~30-40%</td>
<td>60-80%</td>
</tr>
<tr>
<td>Median time to disease progression (PFS)</td>
<td>15 months</td>
<td>47-53 mos</td>
</tr>
</tbody>
</table>


Transplant vs. NO Transplant in era of the Novel drugs as part of upfront Therapy? any benefit?

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

**RP MAINTENANCE**

- 28-day courses until relapse
- R: 10 mg/day, days 1-21
- P: 50 mg every other day

**R MAINTENANCE**

- 28-day courses until relapse
- R: 10 mg/day, days 1-21

**Rd four 28-day courses**

- R: 25 mg/d, days 1-21
- D: 40 mg/d, days 1, 8, 15, 22

**CRD six 28-day courses**

- C: 300 mg/sqm, days 1, 8, 15
- R: 25 mg/d, days 1-21
- D: 40 mg/days 1, 8, 15, 22

**MEL200-ASCT**

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

**RP MAINTENANCE**

- 28-day courses until relapse
- R: 10 mg/day, days 1-21
- P: 50 mg every other day

**R MAINTENANCE**

- 28-day courses until relapse
- R: 10 mg/day, days 1-21

R, lenalidomide; D, dexamethasone; C, cyclophosphamide; P, prednisone; Rd, lenalidomide-dexamethasone; CRD, cyclophosphamide-lenalidomide-dexamethasone; MEL200-ASCT, melphalan 200 mg/m2 followed by autologous stem cell transplantation; ISS, International Staging System

**Patients Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>MEL200-ASCT (n=127)</th>
<th>CRD (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>ISS Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>51%</td>
<td>45%</td>
</tr>
<tr>
<td>II</td>
<td>36%</td>
<td>50%</td>
</tr>
<tr>
<td>III</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>Chromosomal Abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t (4;14)</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>t (14;16)</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>del 17</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>High-risk [t (4;14) or t(14;16) or del17]</td>
<td>18%</td>
<td>23%</td>
</tr>
</tbody>
</table>

**Subgroup Analysis of PFS**

**Overall Maintenance**

- MEL200-ASCT: 2.51 (1.60, 3.94)
- CRD: 2.18 (1.23, 3.88)

**Lenalidomide-Prednisone**

- MEL200-ASCT: 2.66 (1.50, 4.71)
- CRD: 2.01 (1.06, 3.80)

**Age**

- ≤60: 1.78 (1.07, 2.97)
- >60: 1.97 (1.08, 3.60)
- ISS I: 3.15 (1.62, 6.13)
- ISS II: 1.81 (1.83, 7.93)
- ISS III: 2.12 (1.06, 4.24)

**Cytogenetic risk**

- Standard: 2.01 (1.06, 3.80)
- High: 1.72 (0.76, 3.90)

**Interaction p**

- .126

**Months**

- Median follow-up from consolidation: 47 months
- Median PFS: MEL200-ASCT 43.3 months, CRD 28.6 months

**Subgroup Analysis of PFS**

- HR (95% CI): Interaction p

**Overall**

- MEL200-ASCT: 2.51 (1.60, 3.94)
- CRD: 2.18 (1.23, 3.88)

**Lenalidomide**

- MEL200-ASCT: 2.66 (1.50, 4.71)
- CRD: 2.01 (1.06, 3.80)

**Prednisone**

- MEL200-ASCT: 2.01 (1.06, 3.80)
- CRD: 1.72 (0.76, 3.90)

**ISS**

- I: 3.15 (1.62, 6.13)
- II: 1.81 (1.83, 7.93)
- III: 2.12 (1.06, 4.24)

**Cytogenetic risk**

- Standard: 2.01 (1.06, 3.80)
- High: 1.72 (0.76, 3.90)

**Interaction p**

- .126

CRD vs MEL200-ASCT

**Median PFS**

- MEL200-ASCT: 43.3 months
- CRD: 28.6 months

**Median follow-up from consolidation: 47 months**

- HR 2.51 95% CI 1.60-3.94 P< 0.0001
CRD vs MEL200-ASCT

Median follow-up from consolidation: 47 months

Overall survival

<table>
<thead>
<tr>
<th></th>
<th>MEL200-ASCT</th>
<th>CRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-year OS</td>
<td>86%</td>
<td>73%</td>
</tr>
</tbody>
</table>

Overall survival

HR 2.40 (1.32, 4.38)  P= 0.004

Subgroup Analysis of OS

<table>
<thead>
<tr>
<th></th>
<th>MEL200-ASCT</th>
<th>CRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 60</td>
<td>0.89 (0.43, 1.86)</td>
<td>7.83 (2.00, 25.56)</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>1.59 (0.66, 3.52)</td>
<td>1.59 (0.66, 3.52)</td>
</tr>
<tr>
<td>ISS I</td>
<td>4.59 (1.26, 16.75)</td>
<td>1.42 (0.51, 3.93)</td>
</tr>
<tr>
<td>ISS II</td>
<td>1.59 (0.66, 3.52)</td>
<td>1.42 (0.51, 3.93)</td>
</tr>
<tr>
<td>ISS III</td>
<td>1.42 (0.51, 3.93)</td>
<td>1.42 (0.51, 3.93)</td>
</tr>
<tr>
<td>Cytogenetic risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>1.46 (0.54, 3.96)</td>
<td>.27</td>
</tr>
<tr>
<td>High</td>
<td>1.79 (0.73, 4.37)</td>
<td>.27</td>
</tr>
</tbody>
</table>

IFM/DFCI 2009 Study (US and France) Newly Diagnosed MM (N=1,360 combined)

Randomize

- RVDx3
  - CY (3g/m²) MOBILIZATION Goal: 5 x 10⁶ cells/kg
  - Melphalan 200mg/m² + ASCT
  - RVD x 2
  - Lenalidomide*

Induction

- RVDx3
  - CY (3g/m²) MOBILIZATION Goal: 5 x 10⁶ cells/kg
  - Melphalan 200mg/m² + ASCT
  - RVD x 2
  - Lenalidomide*

Consolidation

- RVD x 5
  - SCT at relapse

Maintenance

- Lenalidomide*

Best Response

<table>
<thead>
<tr>
<th></th>
<th>RVD arm N=350</th>
<th>Transplant arm N=350</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>49%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>29%</td>
<td>29%</td>
<td>0.02</td>
</tr>
<tr>
<td>PR</td>
<td>20%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>&lt;PR</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

At least VGPR

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg MRD by FCM</td>
<td>228 (65%)</td>
<td>280 (80%)</td>
</tr>
</tbody>
</table>

3 yr PFS: 61% HDT vs 48% no HDT

IFM 2009: OS (9/2015)

3 yr OS: 88% both arms

IFM 2009: PFS

<table>
<thead>
<tr>
<th>Overall</th>
<th>Transplant / Nb of events</th>
<th>RVD Arm / Nb of patients</th>
<th>Hazard Ratio for Progression or death</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>158 / 350</td>
<td>204 / 350</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60 years</td>
<td>84 / 185</td>
<td>123 / 196</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>&gt;=60 years</td>
<td>74 / 165</td>
<td>81 / 154</td>
<td>0.20</td>
</tr>
<tr>
<td>ISS</td>
<td>SI</td>
<td>44 / 118</td>
<td>58 / 115</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>SII</td>
<td>81 / 171</td>
<td>103 / 170</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>SIII</td>
<td>33 / 61</td>
<td>43 / 65</td>
<td>0.97</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Standard</td>
<td>87 / 213</td>
<td>118 / 212</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>High Risk</td>
<td>28 / 46</td>
<td>31 / 44</td>
<td>0.53</td>
</tr>
<tr>
<td>Response after induction</td>
<td>At least VGPR</td>
<td>93 / 180</td>
<td>122 / 190</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>PR SD PD</td>
<td>66 / 164</td>
<td>77 / 154</td>
<td>0.69</td>
</tr>
</tbody>
</table>

RVD arm better  
Transplant better


<table>
<thead>
<tr>
<th>RVD arm N=48</th>
<th>Transplant N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma, n (%)</td>
<td>40/48 (83%)</td>
</tr>
<tr>
<td>Toxicity, n (%)</td>
<td>4/48 (8%)</td>
</tr>
<tr>
<td>SPM (AML/MDS)</td>
<td>1/48 (2%)</td>
</tr>
<tr>
<td>Others</td>
<td>3/48 (6%)</td>
</tr>
</tbody>
</table>
IFM 2009: Conclusions

- This second interim analysis demonstrates that transplantation:
  - Is feasible: 93%
  - Is associated with an acceptable Transplant Related Mortality: 1.4%.
  - Is associated with an increased rate of neg MRD (80% vs 65%, p<0.01).
  - Is associated with an improved 4-year PFS (47% vs 35%, p<0.001).
  - Is associated with an improved 4-year TTP (49% vs 35%, p<0.001).

- A longer follow up is required to draw any conclusion concerning OS.
  - Since the 4-year survival is high in both arms (80% vs 83%).
  - However, transplantation is already associated with a reduced risk of death due to myeloma, but has a higher rate of toxicity (acute and long term)

- in the era of new drugs, Transplantation is “A Standard of Care” but key questions remain.

Conclusion

- In the era of novel agents, Autologous SCT remains important in the management of newly diagnosed MM- improved PFS and maybe OS
- HOWEVER
- Could this be affected by a longer maintenance?(indefinite)- the importance of the US study.

Lenalidomide vs Placebo Post auto SCT


Estimated HR=0.51 (95% CI = 0.39 to 0.66)
49% reduction in risk of progression

Estimated HR=0.61 (95% CI = 0.41 to 0.87)
39% reduction in the risk of death

Time to Progression
Len (R ) Placebo P-value
Med PFS 46 mos 27 mos <0.001
Med OS NR NR
1 yr OS 88% 80% 0.03
SPM 7.8% 2.6%

Death

69229 (30%) deaths on placebo
47031 (20%) deaths on lenalidomide

IMW 2013 Update _ Courtesy Dr. McCarthy

ITT Analysis; median follow-up from transplant ~48 months
Median TTP: 50 months versus 27 months p=0.001
Median OS: Not reached versus 73 months P=0.008
86 of 128 (67%) non-progressing placebo patients received lenalidomide at study un-blinding in Jan 2010
The cumulative incidence risks of death (p<0.001) progressive disease (p=0.004) and were greater in the placebo group. Overall 67% benefit with maintenance.

The cumulative incidence risk of second primary cancers was greater in the lenalidomide group (p=0.034).

**Current studies to assess role of SCT**

- Newly Dx MM All stages, Age ≤70y/o
  - VRd x 4 cycles
  - IFM/DFCI
  - BMT/CTN 0702

- Newlly Dx MM All stages Age ≤70y/o Any induction treatment
  - SD PR VQPR CR
  - All Pts 1st ASCT
  - Consolidate VRd x 4
  - 2 nd ASCT
  - Maint. R x 2 yrs

**Relapse Patients**

- Use any novel drug combinations that have not been used before.
- Repeat drugs that have been used before.
- Participate in clinical trials using other new drugs in development
- Older regimen in Combinations with novel drugs
- Repeat Autologous stem cell transplant
- Allogeneic stem cell transplant in selected patients (always on study)
Thank you.