Understanding Multiple Myeloma, Its Treatment, and New Discoveries: Part 1

Presented as a Live Webinar
Wednesday, August 12, 2015
12:00 p.m. – 1:00 p.m. EDT

On-demand Activity
Live webinar recorded and archived to be watched at your convenience
Available after October 1, 2015

www.ashpadvantage.com/multmyeloma

Planned by ASHP Advantage and supported by an educational grant from Onyx Pharmaceuticals Inc., a subsidiary of Amgen Inc.
Understanding Multiple Myeloma, Its Treatment, and New Discoveries: Part 1

Activity Overview

This educational activity will provide an overview of multiple myeloma, including its pathophysiology, typical presentation, and current therapies. Patient case scenarios will be used to highlight decision points in staging patients and managing therapy.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Review the pathophysiology, epidemiology, clinical features, and disease progression of multiple myeloma.
- Explain current therapies for the treatment of multiple myeloma.
- Assist in the development of a therapeutic plan for patients with multiple myeloma based on state-of-the-art clinical trial data.

List of Abbreviations

For a list of abbreviations used in the activity, please see pages 23-24.

Continuing Education Accreditation

ASHP is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-15-452-L01-P for the live activity and ACPE activity #0204-0000-15-452-H01-P for the on-demand activity).

Participants will process CPE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home-study activity.

Webinar Information

Visit www.ashpadvantage.com/multmyeloma to find

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information

Additional Educational Activities

- Live webinar featuring Part 2 of this series on August 19, 2015 (1 hour CPE)
- On-demand activities based on Part 1 and Part 2 live webinars (1 hour CPE for each activity, available after October 1, 2015) – Please note that individuals who claim CPE credit for the live webinar are ineligible to claim credit for the on-demand activity

www.ashpadvantage.com/multmyeloma
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- R. Donald Harvey, Pharm.D., FCCP, BCOP, declares that he has served as an advisor for Bristol-Myers Squibb, Onyx Pharmaceuticals Inc., and Takeda Pharmaceuticals. He has also participated in research activities funded by Acetylon Pharmaceuticals, Inc.; Bristol-Myers Squibb; Calithera Biosciences; Celgene Corporation; Cleave Biosciences; Novartis Pharmaceuticals; Onyx Pharmaceuticals Inc.; Sanofi; and Takeda Pharmaceuticals.
- All other faculty and planners report no financial relationships relevant to this activity.
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Disclosures

• R. Donald Harvey, Pharm.D., FCCP, BCOP
  – Research funding (through Emory University):
    Acetylon Pharmaceuticals, Inc.; Bristol-Myers Squibb (BMS); Calithera Biosciences; Celgene Corporation; Cleave Biosciences; Novartis Pharmaceuticals; Onyx Pharmaceuticals Inc.; Sanofi; and Takeda Pharmaceuticals
  – Advisory boards: BMS, Onyx Pharmaceuticals Inc., and Takeda Pharmaceuticals
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Learning Objectives

• Review the pathophysiology, epidemiology, clinical features, and disease progression of multiple myeloma
• Explain current therapies for the treatment of multiple myeloma
• Assist in the development of a therapeutic plan for patients with multiple myeloma based on state-of-the-art clinical trial data

Epidemiology

• Multiple myeloma is a clonal plasma cell dyscrasia
• 26,850 new cases to be diagnosed in the U.S. in 2015
• 11,240 estimated deaths in U.S. in 2015
• The median age of diagnosis is 69
• The disease has a higher incidence in men and African Americans


Multiple myeloma is a disorder that primarily involves which of the following cell types in the marrow?

a. Platelets
b. Neutrophils
c. Eosinophils
d. Plasma cells

Plasma Cell Dyscrasias


See enlargement p. 15
What Really Is MM? A Progressive B-cell Disorder


MGUS <10% of cells (red stain)
BM Increased angiogenesis
Lytic bone lesions Plasma cells in blood

MM = multiple myeloma
MGUS = monoclonal gammopathy of undetermined significance
BM = bone marrow

Signs and Symptoms of Myeloma

See enlargement p. 15

Myeloma Diagnostic Evaluation

• Medical history and physical examination
• Routine testing
  – CBC
  – Serum chemistries, including serum calcium
  – Serum and urine protein electrophoresis with immunofixation
  – Quantification of serum and urine monoclonal protein
  – Measurement of serum free light chains
• Bone marrow analysis
  – Trephine biopsy and aspirate of bone marrow cells for morphologic features, cytogenetic analysis and fluorescence in situ hybridization for chromosomal abnormalities
• Imaging
  – Skeletal survey, MRI if skeletal survey is negative


Myeloma Diagnostic Criteria

• Any one or more of the following biomarkers of malignancy
  – Clonal bone marrow plasma cell percentage ≥60%
  – Involved:uninvolved serum free light chain ratio ≥100
  – >1 focal lesion on MRI studies

**International Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>β-2-Microglobulin (mg/L)</th>
<th>Albumin (g/dL)</th>
<th>Median survival (months)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>&lt;3.5</td>
<td>≥3.5</td>
<td>62</td>
<td>25</td>
</tr>
<tr>
<td>Stage II</td>
<td>3.5-5.4</td>
<td>NA</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>Stage III</td>
<td>≥5.5</td>
<td>NA</td>
<td>29</td>
<td>40</td>
</tr>
</tbody>
</table>


**IMWG Uniform Response Criteria**

**Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>IMWG Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR (stringent complete response)</td>
<td>CR as defined below plus normal free light chain (FLC) ratio and absence of clonal cells in the marrow by immunohistochemistry or immunofluorescence</td>
</tr>
<tr>
<td>CR (complete response)</td>
<td>Negative immunofixation of serum and urine and disappearance of any soft tissue plasmacytomas and &lt;5% plasma cells in bone marrow</td>
</tr>
<tr>
<td>VGPR (very good partial response)</td>
<td>Serum and urine M-component detectable or ≥90% reduction in serum M-component + urine &lt;100 mg/24 hour</td>
</tr>
<tr>
<td>PR (partial response)</td>
<td>≥50% reduction of serum M protein and reduction in 24-hr urinary M protein by ≥90% or to &lt;200 mg per 24 hour</td>
</tr>
</tbody>
</table>

**Risk Stratification by Cytogenetics**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Abnormalities</th>
<th>Incidence</th>
<th>Median OS (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>t(11;14), t(6;14), Trisomies</td>
<td>60%</td>
<td>8 to 10</td>
</tr>
<tr>
<td>Intermediate</td>
<td>FISH: t(4;14), 1q gain, Del13 or hypodiploidy, Complex karyotype</td>
<td>20%</td>
<td>4 to 5</td>
</tr>
<tr>
<td>High</td>
<td>FISH: Del 17p, t(14;16), GEP – High risk signature</td>
<td>20%</td>
<td>3</td>
</tr>
</tbody>
</table>

OS = overall survival  
FISH = fluorescence in situ hybridization  
GEP = gene expression profile  

**Patient Case Scenario**

- MR is a 62-year-old woman who presents with high serum protein and SCr of 2.3 mg/dL
- Work up revealed  
  - IgG kappa monoclonal protein 4 g/dL  
  - Skeletal survey normal  
  - No anemia  
- Bone marrow biopsy showed 45% clonal plasma cell population

Which of the following regimens would be most appropriate for induction treatment in this patient?

a. Melphalan-prednisone  
b. Panobinostat  
c. Bortezomib-lenalidomide-dexamethasone  
d. Pomalidomide-dexamethasone
Drug Therapy for Myeloma


Oral melphalan and prednisone

High-dose melphalan

Autologous bone marrow transplantation

High-dose dexamethasone

Thalidomide

Carfilzomib

Panobinostat

See enlargement p. 16

Immunomodulatory Drugs (IMiDs) - Pharmacology


Bisphosphonates

MM cells

Thalidomide/IMiDs

A. Thalidomide/IMiDs

B. Thalidomide/IMiDs

C. Thalidomide/IMiDs

D. Thalidomide/IMiDs

E. Thalidomide/IMiDs

F. Thalidomide/IMiDs

VEGF

bFGF

IL-6

IFN

Bortezomib/Carfilzomib

VEGF

bFGF

Bone Marrow Vessels

Bone Marrow Stromal Cells

Bone Marrow

See enlargement p. 16

Proteasome Inhibitors - Pharmacodynamics

Cavo M. Leukemia. 2006; 20:1341-52.

Myeloma Cells

Bone Marrow Vessels

Bone Marrow Stromal Cells

MM Cell Growth

TNFα

VEGF

Bortezomib/Carfilzomib

See enlargement p. 17

Panobinostat - Pharmacology


Histones

DNA

Histone deacetylase

HDAC

Tumor suppressor gene inactive

Tumor suppressor gene functions

HDAC = histone deacetylase

See enlargement p. 17

HDAC Pharmacodynamics

HDACi


Cell Cycle (p21, cyclins)

Mutlity (α-tubulin)

Immunity and inflammation (STAT3, TNFα)

Angiogenesis (HIF-1α, VEGF)

Extrinsic Apoptosis (Death receptors and ligands)

Intrinsic Apoptosis (Bcl-2, Bax)

Metabolism (GLUT1)

Monoclonal Antibodies in Myeloma - Pharmacology


Monoclonal antibody

Intact C1

Plasma cell

Target antigen

Fc receptor

Killer cell

ADCC = antibody dependent cellular cytotoxicity

See enlargement p. 18
Treatment Determination

Not a transplant candidate based on physiologic age, performance status, and co-morbidity

Potential transplant candidate

Conventional chemotherapy or clinical trial

Nonalkylator-based induction with a goal of achieving CR/VGPR

Stem cell harvest


Managing A Multi-Compartmental Treatment Model

Transplant -eligible Patients

Consolidation

Maintenance

Relapsed disease

Transplant -ineligible Patients

Supportive care

Initial therapy

Consolidation/maintenance/continued therapy


mSMART

- Multiple myeloma is increasingly recognized as more than one disease, characterized by marked cytogenetic, molecular and proliferative heterogeneity
- The result is widely varied outcome ranging from low to very high risk disease
- Treatment is evolving rapidly as more efficacious agents and combinations become available
- mSMART (Mayo Stratification for Myeloma and Risk-adapted Therapy) is a consensus opinion that takes into account genetically determined risk status and the various treatment strategies currently available
- Risk stratification and individualizing treatment options is complex and based not just on cytogenetic classification but also on host factors, disease stage and a variety of other prognostic factors


Patient Case Scenario (continued)

- MR finished induction with bortezomib-lenalidomide-dexamethasone x 4 cycles and achieved a VGPR
- Given the patient’s overall good health, a decision was made to offer her autologous stem cell transplant as consolidation therapy

- MR finished induction with bortezomib-lenalidomide-dexamethasone x 4 cycles and achieved a VGPR
- Given the patient’s overall good health, a decision was made to offer her autologous stem cell transplant as consolidation therapy

Which of the following is a reasonable treatment goal with autologous stem cell transplant for this patient?

a. Cure of the disease
b. Minimal benefit above standard dose chemotherapy
c. Preparation for future allogeneic stem cell transplant
d. Improved chance for CR & potential longer remission duration


Transplant Eligible

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomies Only</td>
<td>T(11;14), t(4;14), Trisomies +IgH</td>
<td>T(4;14) Del17p, t(14;16), t(14;20)</td>
</tr>
<tr>
<td>4 cycles of Rd</td>
<td>4 cycles of CyBorD</td>
<td>4 cycles of CyBorD</td>
</tr>
<tr>
<td>Collect autologous PBSC</td>
<td>Autologous SCT</td>
<td>Autologous SCT</td>
</tr>
<tr>
<td>Continue Rd</td>
<td>Bortezomib based therapy x 1 year</td>
<td>Bortezomib or CyBorD x 1 year</td>
</tr>
</tbody>
</table>

See enlargement p. 18
RVD (Bortezomib, Lenalidomide, Dexamethasone) Induction

- Phase II trial from IFM with 31 patients aged less than 65 years all who were transplant eligible
- Median follow-up 39 months
- Treatment
  - Lenalidomide 25 mg PO daily on days 1 – 14
  - Bortezomib 1.3 mg/m² IV on days 1, 4, 8, 11
  - Dexamethasone 40 mg PO on days 1, 8, 15
  - Every 21 days x 3 cycles (RVD)
  - Followed by autologous SCT (preceded by cyclophosphamide/GCSF stem cell mobilization)
  - Followed by RVD consolidation x 2 cycles
  - Followed by lenalidomide maintenance for 1 year

Efficacy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results at Completion of All Therapy (n=31)</th>
<th>Results at Completion of Induction (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (response rate)</td>
<td>97%</td>
<td>93%</td>
</tr>
<tr>
<td>CR</td>
<td>58%</td>
<td>23%</td>
</tr>
<tr>
<td>VGPR</td>
<td>26%</td>
<td>35%</td>
</tr>
<tr>
<td>Minimal residual disease negative</td>
<td>58%</td>
<td>16%</td>
</tr>
<tr>
<td>3-year PFS (progression free survival)</td>
<td>77%</td>
<td>NR</td>
</tr>
<tr>
<td>3-year OS</td>
<td>100%</td>
<td>NR</td>
</tr>
<tr>
<td>High-risk cytogenetics subgroup 3-year PFS</td>
<td>86%</td>
<td>NR</td>
</tr>
<tr>
<td>Patients receiving planned therapy</td>
<td>97%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Toxicity – Grade III/IV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results at Completion of All Therapy (n=31)</th>
<th>Results with RVD Induction or Consolidation (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>65%</td>
<td>35%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19%</td>
<td>13%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Enterocolitis infection</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Rash</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Deep venous thrombosis (DVT)</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Pulmonary embolism (PE)</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Dose reduction (AE)</td>
<td>74%</td>
<td>39%</td>
</tr>
<tr>
<td>Discontinuation (AE)</td>
<td>23%</td>
<td>3%</td>
</tr>
</tbody>
</table>

AE = adverse effect

Who Gets Autologous Stem Cell Transplant?

- Age is not a limiting factor
- Poor performance status limits patients from becoming a SCT candidate
- Single vs. tandem SCT remain controversial given mixed clinical trial results
- Timing of SCT is variable
  - Immediately post-induction
  - Delayed
  - Salvage

Efficacy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCT+M</th>
<th>SCT</th>
<th>MPR+M</th>
<th>MPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>54.7 mo</td>
<td>37.4 mo</td>
<td>34.2 mo</td>
<td>21.8 mo</td>
</tr>
<tr>
<td>5-year OS</td>
<td>78.4%</td>
<td>66.6%</td>
<td>70.2%</td>
<td>58.7%</td>
</tr>
<tr>
<td>Median PFS – completion of consolidation</td>
<td>43 mo</td>
<td>43 mo</td>
<td>22.4 mo</td>
<td>22.4 mo</td>
</tr>
<tr>
<td>Median PFS – from start of maintenance</td>
<td>41.9 mo</td>
<td>21.6 mo</td>
<td>41.9 mo</td>
<td>21.6 mo</td>
</tr>
<tr>
<td>CR after maintenance</td>
<td>35.7%</td>
<td>15.7%</td>
<td>33.8%</td>
<td>20%</td>
</tr>
</tbody>
</table>

SCT = stem cell transplant
MPR = melphalan-lenalidomide-prednisone
M = maintenance

See enlargement p. 19
**Toxicity – Grade III/IV**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SCT (n=141)</th>
<th>MPR (n=132)</th>
<th>Maintenance (n=116)</th>
<th>No Maintenance (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>94%</td>
<td>52%</td>
<td>23%</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>94%</td>
<td>8%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>23%</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>16%</td>
<td>1%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Systemic</td>
<td>13%</td>
<td>2%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>0</td>
<td>0</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Second primary cancer</td>
<td>0</td>
<td>0</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>


**Allogeneic Stem Cell Transplant**

- Role is controversial and poorly defined
- Potential exists for graft-versus-myeloma effect
- Clinical trial data compared with autologous SCT is conflicting
- Higher CR rates are counterbalanced with higher treatment-related mortality
- Allogeneic SCT is reserved for young, fit patients with a suitable match or for investigation in clinical trials


**Transplant - Ineligible**

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomies Only</td>
<td>T(11;14), T(14;14)</td>
<td>T(4;14)</td>
</tr>
<tr>
<td>Rd</td>
<td>Weekly CyBorD for 12 months</td>
<td>RVD for 12 months</td>
</tr>
<tr>
<td>Until Progression</td>
<td>Followed by observation</td>
<td>Bortezomib maintenance x 1 year</td>
</tr>
</tbody>
</table>


**Bortezomib-Melphalan-Prednisone First Line (VISTA Trial)**

- Final analysis of randomized, international phase III clinical trial
  - Median follow-up 60.1 months


**5-Year Follow-up Data**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VMP (n=344)</th>
<th>MP (n=338)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr OS (%)</td>
<td>46.0</td>
<td>34.4</td>
<td></td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>56.4</td>
<td>43.1</td>
<td>0.696* (0.567-0.852)</td>
</tr>
<tr>
<td>Median time to next treatment (mo)</td>
<td>27.0</td>
<td>19.2</td>
<td>0.557* (0.462-0.671)</td>
</tr>
<tr>
<td>Median treatment-free interval (mo)</td>
<td>16.6</td>
<td>8.3</td>
<td>0.573* (0.476-0.69)</td>
</tr>
</tbody>
</table>

*P = 0.0004  †P < 0.0001


**Patient Case Scenario (continued)**

- After recovery following autologous stem cell transplant, MR and her physician discuss maintenance therapy
- MR is offered a trial of lenalidomide maintenance
Which of the following toxicities of lenalidomide requires long-term follow up?

a. Hepatotoxicity
b. Mucositis
c. Secondary primary malignancies
d. Hemorrhagic cystitis

First Trial

Randomized, international Phase III clinical trial
- Primary endpoint: PFS
- Median follow-up 37 months

Patients with previously untreated MM, transplant ineligible (N=1623)

- Antithrombotic prophylaxis mandated
- Bisphosphonate support allowed


Efficacy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rd Continuous (n=535)</th>
<th>Rd 18 Months (n=541)</th>
<th>MPT (n=547)</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>25.5 mo</td>
<td>20.7 mo</td>
<td>21.2 mo</td>
</tr>
<tr>
<td>4-Year OS</td>
<td>59%</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>35 mo</td>
<td>22.1 mo</td>
<td>22.3 mo</td>
</tr>
<tr>
<td>RR</td>
<td>75%</td>
<td>73%</td>
<td>62%</td>
</tr>
<tr>
<td>CR</td>
<td>15%</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>VGPR</td>
<td>28%</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>Time to second-line therapy</td>
<td>39.1 mo</td>
<td>28.5 mo</td>
<td>26.7 mo</td>
</tr>
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MPT = melphalan-prednisone-thalidomide


Toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rd Continuous</th>
<th>Rd 18 Months</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>29%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28%</td>
<td>26%</td>
<td>45%</td>
</tr>
<tr>
<td>Anemia</td>
<td>18%</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>6%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>12%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>8%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>8%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>1%</td>
<td>1%</td>
<td>9%</td>
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Secondary Malignancies

- Continuous Rd
  - 17 patients reported total
  - 15 patients diagnosed with solid tumors
- Rd for 18 cycles
  - 30 patients reported total
  - 29 patients reported with solid tumors
- MPT
  - 27 patients reported total
  - Acute myeloid leukemia or myelodysplastic syndrome reported in 12 of the patients

CyBorD Induction

• Phase II trial published with 2 cohorts
• Regimen
  – Cyclophosphamide 300 mg/m² PO on days 1, 8, 15, 22
  – Bortezomib 1.3 mg/m² IV days 1, 4, 8, 11
  – Dexamethasone 40 mg PO on days 1-4, 9-12, 17-20
  – Cycle: 28 days x 4 cycles
  – Bortezomib changed to 1.5 mg/m² IV on days 1, 8, 15, 22 and dexamethasone to 40 mg PO weekly for cycles 3 and 4 with a second cohort of patients


Efficacy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort 1 (n=33)</th>
<th>Cohort 2 (n=30)</th>
<th>All (n=63)</th>
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<tr>
<td>ORR (%)</td>
<td>88%</td>
<td>93%</td>
<td>90%</td>
</tr>
<tr>
<td>CR/nCR (%)</td>
<td>39%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>VGPR or better (%)</td>
<td>61%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>After 4 cycles (n=28)</td>
<td>(n=27)</td>
<td>(n=55)</td>
<td></td>
</tr>
<tr>
<td>ORR (%)</td>
<td>96%</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>CR/nCR (%)</td>
<td>46%</td>
<td>48%</td>
<td>47%</td>
</tr>
<tr>
<td>VGPR (%)</td>
<td>71%</td>
<td>63%</td>
<td>67%</td>
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</table>

ITT = intention to treat
ORR = overall response rate


Toxicity – Grade III/IV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort 1 (n=33)</th>
<th>Cohort 2 (n=30)</th>
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</thead>
<tbody>
<tr>
<td>Any AE (%)</td>
<td>48%</td>
<td>37%</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>21%</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia (%)</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>9%</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy (%)</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy (ALL grades)</td>
<td>64%</td>
<td>57%</td>
</tr>
<tr>
<td>Bortezomib dose reduction (%)</td>
<td>21%</td>
<td>13%</td>
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</tbody>
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Next Webinar

• Role of treatment in the salvage setting
• Drug development pipeline
• Supportive care for patients with myeloma
  – Modification of agents for end-organ dysfunction
  – Managing renal and bone disease
  – Thromboembolism

Key References


Conclusion

• Multiple myeloma is a clonal disease of plasma cells with multiple systemic complications
• Therapies, while not curative, have improved disease control significantly over the past decade
• Selection and personalization of treatment should be based on a number of clinical and laboratory-based criteria

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Plasma Cell Dyscrasias


- MGUS
- Smoldering Myeloma
- Intramedullary Myeloma
- Extramedullary Myeloma
- Myeloma cell line

BM stromal cell dependence

IL-6 dependence

Angiogenesis

Bone destruction

Increased DNA-labelling index, NF kappa B


Signs and Symptoms of Myeloma


- M – Protein spillage
- Neuropathy (33%)
- Renal compromise (30%)
- Infection (15%)
- Hypercalcemia (15 – 20%)
- Bone pain (75%)
- Lytic lesions (70%)
- Anemia (70%)

hyperCalcemia

Renal disease

Anemia

Bone disease

Plasma Cells in Blood

(Multiple myeloma)
Drug Therapy for Myeloma


Immunomodulatory Drugs (IMiDs) - Pharmacology

Proteasome Inhibitors - Pharmacodynamics

Cavo M. Leukemia. 2006; 20:1341-52.

Panobinostat - Pharmacology

HDAC Pharmacodynamics

HDACi --- HDACs

- Cell Cycle (p21, cyclins)
- Motility (α-tubulin)
- Immunity and Inflammation (NFκB, STAT3, TNFα)
- Angiogenesis (HIF-1α, VEGF)
- Metabolism (GLUT1)
- Intrinsic Apoptosis (Bcl-2, Bax)
- Extrinsic Apoptosis (Death receptors and ligands)

HDAC Pharmacodynamics


Transplant Eligible

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
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<tbody>
<tr>
<td>Trisomies Only</td>
<td>T(11;14), t(6;14), Trisomies +IgH</td>
<td>T(4;14)</td>
</tr>
<tr>
<td>4 cycles of Rd</td>
<td>4 cycles of CyBorD</td>
<td>4 cycles of RVD</td>
</tr>
<tr>
<td>Collect autologous PBSC</td>
<td>Autologous SCT</td>
<td>Autologous SCT, esp. if not in CR</td>
</tr>
<tr>
<td>Continue Rd</td>
<td>Autologous SCT</td>
<td>Bortezomib or CyBorD x 1 year</td>
</tr>
<tr>
<td>2 x Rd then lenalidomide maintenance</td>
<td>Bortezomib based therapy x 1 year</td>
<td></td>
</tr>
</tbody>
</table>


Rd = lenalidomide-dexamethasone
CyBorD = cyclophosphamide-bortezomib-dexamethasone
Autologous Stem Cell Transplant

- Primary endpoint: PFS

Newly diagnosed MM received induction therapy with Rd (N=273)

Median follow-up 51.2 months

Melphalan 200 mg/m² IV with ASCT x 2 as 4-month cycles

Melphalan 0.18 mg/kg PO on days 1 – 4
Lenalidomide 10 mg PO on days 1 – 21
Prednisone 2 mg/kg PO on days 1 - 4
Every 28 days x 6 cycles

Maintenance within 3 months of completion of consolidation:
Lenalidomide 10 mg PO daily on days 1 – 21 every 28 days until progression/toxicity

No Maintenance


Transplant - Ineligible

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomies Only</td>
<td>T(11;14), t(6;14), Trisomies +IgH</td>
<td>Del17p, t(14;16), t(14;20)</td>
</tr>
<tr>
<td>Rd</td>
<td>Weekly CyBorD for 12 months</td>
<td>RVD for 12 months</td>
</tr>
<tr>
<td>Until Progression</td>
<td>Followed by observation</td>
<td>Bortezomib maintenance x 1 year</td>
</tr>
</tbody>
</table>

Rd based therapy x 1 year

Weekly CyBorD for 12 months

Bortezomib based therapy x 1 year

Bortezomib-Melphalan-Prednisone First Line (VISTA Trial)

- Final analysis of randomized, international phase III clinical trial
  - Median follow-up 60.1 months

Patients with previously untreated MM (N=682)

VMP
Bortezomib 1.3 mg/m² IV on days 1, 4, 8, 11, 22, 25, 29, 32 for 4 cycles; Days 1, 8, 22, 29 for 5 cycles +
Melphalan 9 mg/m² PO daily on days 1-4 +
Prednisone 60 mg/m² PO daily on days 1-4 (n=344)

MP
Melphalan 9 mg/m² PO daily on Days 1-4 +
Prednisone 60 mg/m² PO daily on Days 1-4 (n=388)

Nine 6-wk cycles


MPR-R vs. MPR vs. MP

HR = hazard ratio
MPR-R = melphalan, prednisone, lenalidomide followed by lenalidomide
MPR = melphalan, prednisone, lenalidomide followed by placebo
MP = melphalan, prednisone, placebo followed by placebo

Lenalidomide maintenance reduced the risk of progression by 60%

Median PFS
- MPR-R 31 Months
- MPR 14 Months
- MP 13 Months

Median follow-up 25 months

HR 0.395
P < .001

HR 0.796
P = .135

FIRST Trial

Randomized, international
Phase III clinical trial
- Primary endpoint: PFS
- Median follow-up 37 months

Patients with previously untreated MM, transplant ineligible
(N=1623)

- Antithrombotic prophylaxis mandated
- Bisphosphonate support allowed

Self-assessment Questions

These questions will be discussed during the activity. Record the answers here for your future reference.

1. Multiple myeloma is a disorder that primarily involves which of the following cell types in the marrow?
   a. Platelets
   b. Neutrophils
   c. Eosinophils
   d. Plasma cells

Questions 2-4 refer to the following patient case scenario.

MR is a 62-year-old woman who presents with high serum protein and SCr of 2.3 mg/dL. Work up revealed immunoglobulin G (IgG) kappa monoclonal protein 4 g/dL, skeletal survey normal, and no anemia. Bone marrow biopsy showed 45% clonal plasma cell population.

2. Which of the following regimens would be appropriate for induction treatment in this patient?
   a. Melphalan-prednisone
   b. Panobinostat
   c. Bortezomib-lenalidomide-dexamethasone
   d. Pomalidomide-dexamethasone

3. MR finished induction with bortezomib-lenalidomide-dexamethasone (4 cycles) and achieved a VGPR (very good partial response). Given the patient’s overall good health, a decision was made to offer her autologous stem cell transplant as consolidation therapy. Which of the following is a reasonable treatment goal with autologous stem cell transplant for this patient?
   a. Cure of the disease
   b. Minimal benefit above standard dose chemotherapy
   c. Preparation for future allogeneic stem cell transplant
   d. Improved chance for CR & potential longer remission duration

4. After recovery following autologous stem cell transplant, MR and her physician discuss maintenance therapy. MR is offered a trial of lenalidomide maintenance. Which of the following toxicities of lenalidomide requires long-term follow up?
   a. Hepatotoxicity
   b. Mucositis
   c. Secondary primary malignancies
   d. Hemorrhagic cystitis
List of Abbreviations Used in Presentation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCC</td>
<td>antibody dependent cellular cytotoxicity</td>
</tr>
<tr>
<td>AE</td>
<td>adverse effect</td>
</tr>
<tr>
<td>ASCT</td>
<td>autologous stem cell transplant</td>
</tr>
<tr>
<td>bFGF</td>
<td>basic fibroblast growth factor</td>
</tr>
<tr>
<td>BM</td>
<td>bone marrow</td>
</tr>
<tr>
<td>BP</td>
<td>bisphosphonate</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CRAB</td>
<td>hyperCalcemia, Renal disease, Anemia, Bone disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CyBorD</td>
<td>cyclophosphamide-bortezomib-dexamethasone</td>
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<tr>
<td>EMP</td>
<td>Extramedullary plasmacytoma</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>FLC</td>
<td>free light chain</td>
</tr>
<tr>
<td>GCSF</td>
<td>granulocyte colony stimulating factor</td>
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<tr>
<td>GEP</td>
<td>gene expression profile</td>
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<tr>
<td>HDAC</td>
<td>histone deacetylase</td>
</tr>
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<td>HDACi</td>
<td>histone deacetylase inhibitor</td>
</tr>
<tr>
<td>HIF</td>
<td>hypoxia-inducible factors</td>
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<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>ICAM</td>
<td>intercellular adhesion molecule</td>
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<tr>
<td>IFM</td>
<td>Intergroupe Francophone du Myélome</td>
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<td>IFN γ</td>
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<td>IL</td>
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<td>IMWG</td>
<td>International Myeloma Working Group</td>
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<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
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<tr>
<td>MGUS</td>
<td>monoclonal gammopathy of undetermined significance</td>
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<tr>
<td>MM</td>
<td>multiple myeloma</td>
</tr>
<tr>
<td>MP</td>
<td>melphalan-prednisone</td>
</tr>
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Understanding Multiple Myeloma, Its Treatment, and New Discoveries: Part 1

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>MPR</td>
<td>melphalan, prednisone, lenalidomide</td>
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<td>MPR-R</td>
<td>melphalan, prednisone, lenalidomide followed by lenalidomide</td>
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<td>MPT</td>
<td>melphalan-prednisone-thalidomide</td>
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<td>MRI</td>
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<td>mSMART</td>
<td>Mayo Stratification for Myeloma and Risk-adapted Therapy</td>
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<td>NF-κB</td>
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<td>NK</td>
<td>Natural killer cells</td>
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<td>ORR</td>
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<td>OS</td>
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<tr>
<td>PBMC</td>
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<td>peripheral blood stem cell</td>
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<td>progression free survival</td>
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<td>PR</td>
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<td>response rate</td>
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<td>sCR</td>
<td>stringent complete response</td>
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<td>Scr</td>
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<td>TNFα</td>
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<td>VAD</td>
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<td>very good partial response</td>
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