Multiple Myeloma Educational Symposia*

*Session supported by an educational grant from Onyx Pharmaceuticals

Wednesday October 16th
11:30am-1:30pm
The Multiple Myeloma (MM) Educational Symposia will provide healthcare professionals with an integrative learning approach consisting of evidenced-based learning principles, case study presentation and best practices for the diagnosis, treatment and management of MM.

Universal Activity# 0761-9999-13-371-L01-P; 2.0 contact hours; Knowledge-based activity

Faculty:
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National Association of Specialty Pharmacy

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West Virginia University School of Pharmacy
The information within this CME/CE activity is for continuing education purposes only, and is not intended to substitute for the medical judgment of the healthcare provider. Recommendations for use of any particular therapeutic agents or methods are based upon the best available scientific evidence and clinical guidelines. Reference in this activity to any specific commercial products, process, service, manufacturer, or company does not constitute its endorsement or recommendation.
Michael graduated from the University of Florida College of Pharmacy in 2008. Worked as a clinical pharmacist for Wellcare Specialty Pharmacy from 2008-2010. Currently employed as a Pharmacist in Charge (PIC) for Publix Pharmacy in Tampa, Florida. Additional assignments have included working with the Specialty Pharma Education Center as a reviewer and author of Continuing Education for Pharmacists and Nurses. Also worked as a subject matter expert to develop the Certified Specialty Pharmacy (CSP) Credential with the Specialty Pharmacy Certification Board. Serves as a Specialty Pharmacy Clinical Consultant for the National Association of Specialty Pharmacy (NASP).
DISCLOSURES

- I do not intend to discuss an off-label use of a product during this activity.

- I have not had any relevant financial relations during the past 12 months to disclose.
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Clinical Assistant Professor
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Morgantown, WV
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Learning Objectives

1. Describe the etiology and pathophysiology of multiple myeloma

2. Identify the clinical characteristics of multiple myeloma

3. Describe diagnostic testing / criteria for multiple myeloma

4. Discuss staging and prognostic systems for multiple myeloma

5. Review treatment considerations and the mechanism of action of antimyeloma and supportive therapies
6. Identify 3 major barriers to treatment adherence in multiple myeloma

7. List the 3 most important clinical points for the specialty pharmacist

8. List the 3 most important non-clinical points for the specialty pharmacist
Multiple Myeloma

Hematologic malignancy

Plasma cells

Infiltration of bone marrow

Overproduction of monoclonal protein

Osteolytic lesions of bone
Epidemiology

1% of all cancers

Second most common hematologic malignancy

20,000 cases / yr in USA

10,000 deaths / yr

Median age 62

Only 2% below age 40

Epidemiology

Risk increases with age

Men > women

Black > white

Chemical / radiation exposure

Familial predisposition

Plasma Cell Antibody Production

Diverse population of plasma cells

Polyclonal antibody production
Myeloma

Monoclonal Population

Monoclonal Protein
Monoclonal Proteins

Major criteria for diagnosis of MM

97% will secrete “M protein”
  Detected in serum and urine

Heavy chains and/or light chains
  Up to 20% light chain only

3% nonsecretory

Immunoglobulin

Heavy Chains
- IgG
- IgA

Light Chains
- Kappa
- Lambda
Evolution of Multiple Myeloma

- MGUS
- Smoldering MM
- Multiple Myeloma
Multistep Development of MM

<table>
<thead>
<tr>
<th>Multistep progressive disease</th>
<th>MGUS</th>
<th>Intramedullary multiple myeloma</th>
<th>Extramedullary multiple myeloma</th>
<th>Plasmacell leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic abnormalities</td>
<td>Hyperdiploidy (50% of patients)</td>
<td>Secondary translocations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-hyperdiploidy (50% of patients)</td>
<td></td>
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</tr>
<tr>
<td>Other molecular alterations</td>
<td>Increased expression of cyclin D1, D2, and D3</td>
<td>Oncogenic activation or mutation (RAS, FGFR3)</td>
<td>MYC dysregulation, TP53 mutation</td>
<td></td>
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</tbody>
</table>

Bone marrow microenvironment

Bone resorption

Angiogenesis

Biology of MM

Adhesion to marrow stromal cells

Secretion of cytokines and growth factors

- IL-6 – autocrine and paracrine growth factor supporting survival of MM cells
- VEGF

Up-regulation of cell cycle regulatory proteins and anti-apoptotic proteins

Signs / Symptoms

Asymptomatic
Bone lesions
Renal dysfunction
Anemia
Recurrent infections
Hypercalcemia
Extramedullary plasmacytomas
Cord compression

Bone Lesions

> 80% of newly diagnosed MM

Osteolytic

Bone pain

Pathologic fracture

Hypercalcemia

Bone lesions

MM causes an imbalance in the function of osteoblasts / osteoclasts

Suppression of osteoblasts
- Secretion of DKK1

Activation of osteoclasts through amplification of RANK pathway

Renal Dysfunction

20-40% of newly diagnosed MM

Direct tubular damage

- Excess immunoglobulin proteins
- Hypercalcemia
- Dehydration

Anemia

Present in majority of new MM patients

Normochromic /normocytic

Marrow infiltration by MM

Renal dysfunction

Fatigue

Infections

Non-functioning immune globulins

Functional hypogammaglobulinemia

Marrow infiltration

Treatment

Neurologic Symptoms

Cord compression

- Back pain, muscle weakness
- Medical emergency

Hyperviscosity

- Headache, blurred vision, altered mental status
- Plasmapheresis

Hypercalcemia

PL is a 58 year old female with type 2 diabetes and a recent history of worsening fatigue and back pain. She has recently developed a persistent cough. In addition to pneumonia, a chest X-Ray ordered by her primary care physician revealed two lytic lesions in her left clavicle. CBC was significant for a Hgb of 9.3 g/dL.
Diagnostic Workup

H&P

CBC / differential + CMP, LDH

Beta-2 microglobulin

Skeletal survey

Bone marrow biopsy
  Cytogenetics and plasma cell labeling index

Identifying the M Protein

Serum

- Quantitative immunoglobulins
- Protein electrophoresis (SPEP)
- Serum immunofixation electrophoresis (SIFE)
- Free light chain assay (kappa / lambda)

Urine – 24 hr urine collection

- Urine protein electrophoresis (UPEP)
- Immunofixation electrophoresis

Other Useful Tests

PET/CT or MRI

Tissue biopsy – plasmacytoma

Baseline bone densitometry

PL’s skeletal survey reveals multiple lytic lesions in the clavicle, humerus, and L5. Serum protein electrophoresis and immunofixation showed IgG kappa monoclonal protein of 7.2 grams/dL. Serum free light chain assay shows kappa 85 mg/dL and lambda 0.48 mg/dL (ratio kappa/lambda is 177). Bone marrow biopsy reveals hypercellular marrow with 28% monoclonal plasma cells. Marrow cytogenetics show normal female karyotype (46XX), however FISH is significant for del(17p).

<table>
<thead>
<tr>
<th>Lab results</th>
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</thead>
<tbody>
<tr>
<td>WBC 4.5 x 10^3</td>
<td></td>
</tr>
<tr>
<td>Hgb 9.3 g/dL</td>
<td></td>
</tr>
<tr>
<td>Platelets 210 x10^3</td>
<td></td>
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<tr>
<td>ANC 2100</td>
<td></td>
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<tr>
<td>SCr 2.1 g/dL</td>
<td></td>
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<tr>
<td>Ca 11.8 g/dL</td>
<td></td>
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<tr>
<td>LDH 320 g/dL</td>
<td></td>
</tr>
<tr>
<td>Beta 2 microglobulin – 8.2 g/dL</td>
<td></td>
</tr>
<tr>
<td>Albumin 3.4</td>
<td></td>
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</tbody>
</table>
# Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>Smoldering Multiple Myeloma</th>
<th>Multiple Myeloma</th>
</tr>
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<tbody>
<tr>
<td><strong>M Protein</strong></td>
<td>&lt; 3 g/dL</td>
<td>&gt; 3 g/dL</td>
<td>&gt; 3 g/dL*</td>
</tr>
<tr>
<td><strong>Marrow Plasma Cells</strong></td>
<td>&lt; 10%</td>
<td>&gt; or &lt; 10%</td>
<td>&gt;10% Or plasmacytoma</td>
</tr>
<tr>
<td><strong>End Organ Damage (CRAB criteria)</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

* Unless true non-secretory myeloma

CRAB

- Calcium elevated (>11.5 g/dL)
- Renal dysfunction (creatinine > 2 g/dL)
- Anemia (Hgb < 10 g/dL or > 2 g/dL below lower limit of normal)
- Bone disease (lytic lesions, severe osteopenia, or pathologic fracture)

PL's skeletal survey reveals multiple lytic lesions in the clavicle, humerus, and L5. Serum protein electrophoresis and immunofixation showed IgG kappa monoclonal protein of 7.2 grams/dL. Serum free light chain assay shows kappa 85 mg/dL and lambda 0.48 mg/dL (ratio kappa/lambda is 177). Bone marrow biopsy reveals hypercellular marrow with 28% monoclonal plasma cells. Marrow cytogenetics show normal female karyotype (46XX), however FISH is significant for del(17p).

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Prognosis and Staging

Median survival 3-4 years
Some may live > 10 years

Durie – Salmon Staging
Originated in 1975

International Staging System (ISS)
Predictive for survival
Stage I – 62 months
Stage II – 44 months
Stage III – 29 months

<table>
<thead>
<tr>
<th>Stage</th>
<th>Durie – Salmon</th>
<th>ISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All of the following</td>
<td>Serum Beta-2 microglobulin &lt; 3.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>• Hgb &gt; 10 g/dL</td>
<td>Serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>• Ca ≤ 12 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Normal skeletal survey or solitary plasmacytoma</td>
<td></td>
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<tr>
<td></td>
<td>• Low M component</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG &lt; 5 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA &lt; 3 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bence Jones protein &lt; 4g/24 hrs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II Neither stage I or stage III</td>
<td>Neither stage I or stage III</td>
</tr>
<tr>
<td>III</td>
<td>One or more of the following</td>
<td>Serum Beta-2 microglobulin ≥ 5.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>• Hgb &lt; 8.5 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ca &gt; 12 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Advanced lytic bone lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High M component</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG &gt; 7 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA &gt; 5 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bence Jones protein &gt; 12g/24 hrs</td>
<td></td>
</tr>
<tr>
<td>Subclassification</td>
<td>A: Normal renal function (Cr &lt; 2 g/dl)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: Abnormal renal function (Cr ≥ 2 g/dL)</td>
<td></td>
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</tbody>
</table>

Other Prognostic Factors

Genetic abnormalities

Standard risk

Hyperdiploidy
\(t(11;14)\)

High risk

Hypodiploidy
17p deletion
Del (13)
\(t(4;14)\)
\(t(14;16)\)

Performance status

Treatment

Asymptomatic disease
- MGUS
- Smoldering MM
- Observation only
- Therapy to delay progression?

Symptomatic disease
- Indication for treatment
Significant advances in recent years

Novel agents

Stem cell transplant

Increased response rates, response durability and survival
Melphalan

1958 sarcolysin benefit in 3 of 6 patients
1962 – improvement in 8 of 24 MM patients

Prednisone

Showed significant benefit in 1960s

Melphalan + prednisone (MP)

MP – 6 month survival improvement vs melphalan alone (1969)
Became standard of care for next 30 years, no improvement in survival until recently

Melphalan

Alkylating agent

Availability

PO – 2mg tablets
IV – 50mg vials

Short stability

Use

Initial therapy in non-transplant candidates

Dose varies depending on combination

0.25mg/kg or 8-9mg/m² PO daily on days 1-4 of each 4-6 week cycle

Preparative regimen for stem cell transplant

140 – 200mg/m² IV
Melphalan

Toxicities

Myelosuppression
N/V
  Delayed in high dose therapy
Pulmonary fibrosis
Secondary malignancies (chronic dosing)

Reduces stem cell collection yield if used as induction therapy
Corticosteroids part of all initial treatment regimens in MM

High dose pulse dexamethasone alone

RR 40-50%

High dose ≥ 480mg/month

Days 1-4, 9-12, 17-20

Adverse effects

Immunosuppressive
Immunomodulatory Drugs (IMiDs)

Thalidomide and derivatives

- Lenalidomide
- Pomalidomide

Immunomodulatory, anti-inflammatory, anti-angiogenic properties

Mechanism in MM: Blocks secretion of VEGF and IL-6, inhibits adhesion to bone marrow stroma, induces apoptosis through caspase-8 activation and blocking of NF-κB
Thalidomide

Removed from market in 40 countries in 1960s

Teratogenicity

Early interest as cancer therapy

1999: First new drug with single agent activity in MM in > 3 decades

Dose in MM: 100-200mg daily

Thal/Dex: 50-200mg daily
Nonenzymatic hydrolysis in plasma

No adjustment needed in renal or hepatic dysfunction

Withhold or reduce dose if constipation, oversedation or peripheral neuropathy
Thalidomide Adverse Effects

Fatigue / Sedation

Neuropathy

Constipation
  Prophylactic bowel regimen

Rash

Thromboembolic complications

Only available through restricted distribution: S.T.E.P.S. Program
Prescribers, pharmacy and patient enrollment

Pregnancy tests
  Within 24 hours of starting thalidomide
  Monthly

Mandatory counseling

Patient-physician agreement form

Phone survey (patient and prescriber)
  Obtain authorization #

Prescription to enrolled pharmacy
Dispensing Thalidomide

Pharmacy registration form

Verify all prescriptions have auth #

Only valid for 7 days

Call Celgene Customer Care Center to obtain confirmation number

Dispense within 24 hours

Dispense no more than 28 day supply

Subsequent Rx only if < 7 days remain

Do not repackage
Lenalidomide

Higher potency than thalidomide

Dosing varies depending on regimen

Lenalidomide / Dexamethasone

   25mg po daily – days 1-21 of 28 day cycle
Lenalidomide Toxicity

Profile differs from thalidomide

- Less sedation / constipation
- Less neuropathy
- No evidence of teratogenicity in animals

Thromboembolism

Myelosuppression

Rash

Edema
Lenalidomide

Renally eliminated mostly unchanged

Renal impairment prolongs half life

Dosing adjustment

- CrCl 30-60ml/min: 10mg once daily
- CrCl < 30ml/min: 15mg every 48 hrs
- Dialysis dependent: 5mg once daily (administer after dialysis on dialysis days)
## Neutropenia management

<table>
<thead>
<tr>
<th>ANC</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1000</td>
<td>Hold treatment, add G-CSF, check CBC weekly</td>
</tr>
<tr>
<td>Returns to ≥ 1000 with neutropenia as only toxicity</td>
<td>Resume at 25mg / day</td>
</tr>
<tr>
<td>Returns to ≥ 1000 with additional toxicities present</td>
<td>Resume at 15mg / day</td>
</tr>
<tr>
<td>Additional drop &lt; 1000</td>
<td>Hold treatment</td>
</tr>
<tr>
<td>Returns to ≥ 1000</td>
<td>Resume at 5mg below previous dose</td>
</tr>
</tbody>
</table>

Revlimid prescribing information. Summit, NJ: Celgene; 2012
# Lenalidomide

## Thrombocytopenia management

<table>
<thead>
<tr>
<th>Platelets</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30,000</td>
<td>Hold treatment, check CBC weekly</td>
</tr>
<tr>
<td>Returns to ≥ 30,000</td>
<td>Resume at 15mg / day</td>
</tr>
<tr>
<td>Additional drop &lt; 30,000</td>
<td>Hold treatment</td>
</tr>
<tr>
<td>Returns to ≥ 30,000</td>
<td>Resume at 5mg below previous dose</td>
</tr>
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</table>

Revlimid prescribing information. Summit, NJ: Celgene; 2012
Prescribers, pharmacy and patient enrollment

Pregnancy tests
  - Within 14 days and 24 hours of writing Rx
  - Subsequent prescriptions

Mandatory counseling

Patient-physician agreement form

Phone survey (patient and prescriber)
  - Obtain authorization #

Prescription form to contract pharmacy
  - Patient counseling, educational material
Dispensing Lenalidomide

Contract with Celgene / registration

Verify all prescriptions have auth #

  Only valid for 7 days (females of childbearing potential)
  14 days for others

Call Celgene Customer Care Center to obtain confirmation number

  Dispense within 24 hours
  Provide appropriate required counseling

Maintain record of each Rx filled and counseling checklist

Dispense no more than 28 day supply

  Subsequent Rx only if < 7 days remain
Pomalidomide

Approved in the US in 2013

Two prior therapies

Approval initially based on response rate

  ORR 43%

Dose: 4mg qd days 1-21 w/ dex 40mg wkly

  Aspirin 325mg daily

CYP 3A, 1A2, p-gp

REMS
Prescriber

- Certification
- Patient counseling
- Negative pregnancy test
- Agreement / survey forms
- Authorization number → Rx
- 4 week supply, no refills
- Sends Rx to certified pharmacy
Pharmacy

Certification w/ REMS program

Obtain confirmation # from Celgene before dispensing

Patient counseling – education and counseling checklist

Dispense with medication guide
Counseling Points

Pregnant or breastfeeding

2 methods of birth control (1 highly effective)

- 4 weeks before / 4 weeks after
- Males - condoms

Pregnancy testing weekly during first 4 weeks

- Repeat q 4 weeks (2 weeks if irregular menses)

Stop if become pregnant

DVT / PE

Do not donate blood (up to 4 weeks after)

Do not break / open capsules
Bortezomib

Proteasome inhibitor

Cell cycle arrest

apoptosis

IV or SubQ administration

1.3mg/m² days 1, 4, 8, 11 of 21 day cycle

Approved for advanced MM in 2003
Mechanism of action of bortezomib in myeloma.

Rajkumar S, et al. JCO 2005;23:630-639
Bortezomib Toxicity

Myelosuppression
  Thrombocytopenia

Peripheral neuropathy

Infection
  HSV prophylaxis

Rash

N/V/GI distress
  Prophylactic antiemetics usually not necessary
Myelosuppression management

Start of cycle: ANC ≥ 1000, Platelets ≥ 70,000

ANC < 500-750
- Withhold dose until ANC recovers
- Reduce 1 dose level if multiple doses held

Platelets < 25–30,000
- Withhold dose until platelets ≥ 50,000
- Reduce 1 dose level if multiple doses held
- Transfuse platelets if needed

These rules may not apply if significant marrow involvement

Carfilzomib

Structurally distinct from bortezomib

FDA approved July 2012

20mg/m²/day on days 1, 2, 8, 9, 15, 16 followed by 12 day rest period (days 17-28)

- Subsequent cycles increase to 27mg/m²
- IV infusion over 2-10 minutes
- Dexamethasone 4mg IV/PO prior to infusion
- Hydration

Carfilzomib

Low risk of peripheral neuropathy

< 2% incidence grade 3/4

Myelosuppressive

Grade 3/4 thrombocytopenia 30%
Anemia

Fatigue, nausea, dyspnea, pneumonia

Congestive heart failure up to 7%

Dose adjustment

Grade 3 or 4 neutropenia or grade 4 thrombocytopenia

Hold dose
If fully recovered before next scheduled dose continue at same dose
If recovered to grade 2 neutropenia or grade 3 thrombocytopenia reduce dose by one dose level
   27mg/m² to 20mg/m²
   20mg/m² to 15mg/m²
May re-escalate dose
General Treatment Considerations

Age

Comorbid conditions

Disease characteristics

Eligibility for stem cell transplant

Patient preference
Approach to Treatment of Myeloma

Newly diagnosed Multiple Myeloma

- Transplant Candidate
- Not a transplant candidate
Stem Cell Transplant in MM

Autologous

- Provides best opportunity to achieve CR and prolong event-free survival
- Single vs. tandem transplant

Role of allogeneic transplant – investigational
Intergroup Francais du Myelome

- N=200
- Stage II or III MM
- Age < 65

Conventional Therapy (n=100)
- ORR
  - 81% vs 57% (p<0.001)
  - CR 22% vs 5%
- 5 year event-free survival
  - 28% vs 10% (p=0.01)
- 5 year overall survival
  - 52% vs 12% (p=0.03)
- Treatment-related mortality
  - 3% for both groups

Autologous Transplant (n=100)

n=185

91 patients received auto transplant after 3-4 treatments (vincristine, doxorubicin, methylprednisolone)

94 patients received auto transplant as rescue therapy (primary resistance or relapse)

No difference in overall survival

Clinical benefit in quality of life for early transplant

Transplant: Single vs. Tandem

Increase dose intensity

Obtain deeper sustained remissions

- Superior CR rates
- Prolongation of event free survival
- Inconsistent results

Subset analyses

- Tandem transplant mainly benefits those who do not enter at least VGPR (>90% decrease in M protein) or CR after first transplant

Identification of eligibility at diagnosis

Affects induction therapy decision

Risk vs benefit for individual patient

Advanced age alone does not rule out

Non-candidates

- Bilirubin > 2 g/dL
- Creatinine > 2.5 g/dL
- ECOG PS 3 or 4 (unless due to bone pain)
- NYHA functional status class III or IV
Transplant in Myeloma

- **Induction Therapy x 4 cycles**
- **Collect peripheral blood stem cells (adequate for 2 transplants)**
- **High dose chemotherapy followed by autologous stem cell transplant** (Second transplant if not in CR or VGPR)
- **Maintenance Therapy?**
- **Continue induction until plateau, reserve stem cells for relapsed / refractory disease**
Induction therapy

- Reduce plasma cells in marrow
- Reduce symptoms
- Prevent further organ damage
- Better response with induction → improved outcomes after transplantation

Avoid melphalan during induction

- Reduces stem cell yield at collection
Induction – Two Drug Regimens

Thalidomide + dexamethasone

- ORR: 63%
- Not considered preferred regimen

Lenalidomide + low dose dexamethasone

- ORR: 70% within 4 cycles
- 1 year OS: 96%
- Lower response rate vs high dose dexamethasone regimen but better 1 yr overall survival
Induction – Two Drug Regimens

Bortezomib – dexamethasone

Vs Vincristine + doxorubicin + dexamethasone (VAD)

- ORR: 79% vs 63%
- CR: 38% vs 15%
- 3 year OS: 81% vs 77% (not significant)

Neuropathy

Induction Therapy – Multidrug Regimens

Bortezomib + dexamethasone +

Lenalidomide OR
Doxorubicin OR
Cyclophosphamide OR
Thalidomide

Improves response rates and progression-free survival but no overall survival data

More toxicity

High risk patients

Stem Cell Collection

≥ 6 million CD34+ cells/kg

Mobilization for peripheral blood stem cell collection

- G-CSF (alone or after cyclophosphamide)
- Plerixafor – CXCR4 antagonist

Lenalidomide may inhibit stem cell collection

- Collect after 3 or 4 cycles

Melphalan 200mg/m²

- More rapid hematologic recovery, lower incidence of severe mucositis, fewer transfusions, shorter hospitalizations, better survival vs. Melphalan + TBI
- Reduced dose in older patients
- Addition of bortezomib currently under investigation

Thalidomide

Several randomized studies
Improvement in progression free survival
OS benefit – less consistent
Peripheral neuropathy

Lenalidomide

Reduces risk of disease progression
Secondary cancers a concern

Initial Therapy: Non-Transplant Candidates

Melphalan + Prednisone

- Standard for >30 years
- ORR: 50%; CR: <5%
- Mostly supplanted by new combinations

Melphalan + Prednisone + Thalidomide (MPT)

- ORR: 75%; CR / near CR: 28%
- Survival benefit less consistent
- More toxic, especially elderly

Initial Therapy: Non-Transplant Candidates

Melphalan + Prednisone + Bortezomib

- ORR: 70-89%; CR: 32%
- Effective in del(13) and IgH translocations
- Longer time to progression vs MP
  - 24 vs 17 months

Melphalan + Prednisone + Lenalidomide

- ORR: 81%; CR: 24%
- 1 year overall survival: 100%
- 2 year progression free survival: 55%

Non-melphalan containing regimens

Lenalidomide + low dose dexamethasone
  3 year OS: 70%
Bortezomib + dexamethasone
  ORR: 80%; CR + nCR: 24%
Thalidomide + dexamethasone
VAD
DVD
Single agent dexamethasone

## IMWG Response Criteria

<table>
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<th>Response Category</th>
<th>Criteria</th>
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<tr>
<td>Complete Response (CR)</td>
<td>Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow</td>
</tr>
<tr>
<td>Stringent CR (sCR)</td>
<td>CR as above, plus: normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.</td>
</tr>
<tr>
<td>Very Good Partial Response (VGPR)</td>
<td>Serum and urine M protein detectable by immunofluorescence but not on electrophoresis or 90% or greater reduction in serum M protein plus urine M protein &lt; 100 mg/24 hrs</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>50% reduction of serum M-protein and reduction in 24 h urinary M-protein by 90% or to &lt; 200 mg / 24 h</td>
</tr>
<tr>
<td></td>
<td>If the serum and urine M-protein are unmeasurable, a 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria</td>
</tr>
<tr>
<td></td>
<td>If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was 30%</td>
</tr>
<tr>
<td></td>
<td>In addition to the above listed criteria, if present at baseline, a 50% reduction in the size of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>Not meeting criteria for CR, VGPR, PR or progressive disease</td>
</tr>
</tbody>
</table>

Relapse

Relapse > 6 months after initial therapy completed

Retreat with initial regimen

Bortezomib or lenalidomide combinations

- Bortezomib + liposomal doxorubicin
- Numerous combinations of novel agents +/- steroids +/- chemotherapy

Stem cell transplant

Supportive Care

Bisphosphonates

- Reduce bone lesions, pathologic fractures
- All patients receiving primary treatment

Local radiotherapy

- Palliation of bone pain

Vertebroplasty or kyphoplasty

Avoid nephrotoxins

- NSAIDs, IV contrast
Supportive Care

Anemia

Consider ESAs (within guidelines)

Infection

IVIG if recurrent infections

Vaccinations

Treatment – induced immunosuppression

  High dose dexamethasone – PCP, antifungal prophylaxis, HSV/VZV prophylaxis
  Bortezomib – herpes zoster prophylaxis

Therapy – Related Adverse Effects

Hematologic toxicity
- Bortezomib, iMiDs, chemotherapy
- Hold treatment if ANC < 500 or platelets < 25,000
- Resume when ANC > 1000; Platelets > 50
- Dose reduction
- G-CSF

Peripheral neuropathy
- Bortezomib, thalidomide
- Dose reduction
- Bortezomib – Once weekly IV or SubQ

IMiD induced thromboembolism

Variable but significant increased risk of VTE

Patient risk factors, concurrent high dose dexamethasone or chemotherapy

Low risk: Aspirin 81-325mg/day

High risk: LMWH (equivalent to enoxaparin 40mg sq daily) or full dose warfarin INR 2-3

If thrombotic event: hold therapy

May resume after improvement

<table>
<thead>
<tr>
<th>Individual Risk Factors</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obesity (BMI ≥ 30)</td>
<td>No Risk Factors or only one myeloma / individual risk factor</td>
</tr>
<tr>
<td>• Prior VTE</td>
<td>• Aspirin 81-325mg/day</td>
</tr>
<tr>
<td>• Central venous access device or pacemaker</td>
<td>&gt; 2 individual / myeloma risk factors</td>
</tr>
<tr>
<td>• Associated disease</td>
<td>• LMWH (equivalent to 40mg enoxaparin SQ per day); OR</td>
</tr>
<tr>
<td>• Diabetes</td>
<td>• Full dose Warfarin (INR 2-3)</td>
</tr>
<tr>
<td>• Cardiac disease</td>
<td></td>
</tr>
<tr>
<td>• Chronic renal disease</td>
<td></td>
</tr>
<tr>
<td>• Acute infection</td>
<td></td>
</tr>
<tr>
<td>• Immobilization</td>
<td></td>
</tr>
<tr>
<td>• Surgery</td>
<td></td>
</tr>
<tr>
<td>• Use of ESA</td>
<td></td>
</tr>
<tr>
<td>• Clotting disorders</td>
<td></td>
</tr>
</tbody>
</table>

| Myeloma risk factors                                                                     |                                                                                     |
| • Diagnosis of myeloma, per se                                                           |                                                                                     |
| • Hyperviscosity                                                                        |                                                                                     |

| Therapy Risk Factors / Action                                                            |                                                                                     |
| Myeloma Therapy                                                                         |                                                                                     |
| • Thalidomide or lenalidomide combined with:                                             |                                                                                     |
|   • High dose dexamethasone (≥ 480mg / month)                                            |                                                                                     |
|   • Doxorubicin or multiagent chemotherapy                                               |                                                                                     |
| • LMWH (equivalent to 40mg enoxaparin SQ per day); OR                                    |                                                                                     |
| • Full dose Warfarin (INR 2-3)                                                           |                                                                                     |
PL is diagnosed with IgG kappa multiple myeloma. She is stage III in both Durie – Salmon and ISS. She also has the adverse prognostic feature of del 17p. However, she is only 58 years old and has a performance status of 0.
1. What are PL’s up-front treatment options?

2. What supportive care agents will she require?

3. What are her treatment options when she relapses?
Conclusions

Myeloma is an incurable disease that arises from plasma cells.

Myeloma damages the kidneys and the bones resulting in a debilitating course.

Autologous stem cell transplant is part of initial treatment in eligible patients.

New agents approved in the past 10-15 years have improved outcomes but have unique toxicities.

Supportive care is an important part of myeloma therapy.
Three Barriers to Adherence

Obtaining oral MM therapies – cost barriers, strict prescribing restrictions

Treatment side effects

- neuropathy
- fatigue
- infection
- steroid side effects

Cyclical dosing may be difficult for some patients to follow
Three Most Important Clinical Points

MM patients often have renal dysfunction as a result of their disease.

Patients generally fall into two major categories – transplant candidates and non-transplant candidates.

MM patients often require many supportive care agents (antibiotic prophylaxis, antithrombotic agents, bisphosphonates).
Immune modulating agents (IMiDs) have strict REMS programs due to fetal risk prescribed by registered providers dispensed through certified pharmacies

Therapies are extremely expensive
High out-of-pocket for oral therapies

Medications require significant patient counseling
What is the most frequently encountered complication of multiple myeloma at diagnosis?

a. Renal dysfunction
b. Bone lesions
c. Anemia
d. Spinal cord compression
Question 2

Which characteristic would prevent a patient from being eligible for autologous stem cell transplant for multiple myeloma?

a. Age = 70
b. ECOG PS 3 due to severe bone pain at diagnosis
c. Marrow involvement > 70%
d. None of the above would rule a patient out for transplant
Question 3

Which agent should be avoided during the induction phase in autologous transplant candidates?

a. Melphalan
b. Bortezomib
c. Thalidomide
d. Cyclophosphamide
Question 4

Which statement regarding thalidomide is true?

a. Myelosuppression is a common dose-limiting toxicity
b. Peripheral neuropathy is a common dose-limiting toxicity
c. Thalidomide requires dose adjustment in renal dysfunction
d. All of the above are true statements
Question 5

Bortezomib does not require dose adjustment for

a. Renal dysfunction
b. Hepatic dysfunction
c. Peripheral neuropathy
d. All the above require dose adjustment
Thank you!
Discussion / Q & A