Transplantation in Multiple Myeloma

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At the end of the session, the participant will be able to:

– Describe the appropriate diagnostic workup for patients with newly diagnosed multiple myeloma and optimal treatment of transplant eligible patient
– Review current recommendations regarding timing of transplantation and post transplant maintenance
– Identify strategies to manage adverse effects of treatment in patients with multiple myeloma who receive treatment with systemic therapy in the frontline and/or relapsed setting
– List important factors to provide appropriate care and counsel for patients and families regarding diagnosis and supportive care

Meet Jane

• Jane is a very active 38 year-old mother of 2.
• Stays at home but trained as a nursing assistant.
  Wants to go back to school for RN degree
• On routine physical for school she has the following labs:

  **CBC values**
  - WBC count 3,300/µL
  - Hemoglobin 9.1 g/dL
  - Platelet count 158,000/µL

  **Chemistry Values**
  - Creatinine 1.3 g/dL
  - Calcium 10.2 mg/dL
  - Albumin 3.2 g/dL
  - Total protein 10.4 g/dL

ARS Question

You look at her labs. Which of the result(s) would be most concerning?

a) Anemia. This is most likely from childbirth so not to worry. No further evaluation is needed
b) Elevated Protein level. Make sure she isn’t eating too much protein in her diet
c) Anemia and elevated total protein. These can be signs of multiple myeloma
d) Low white blood cell count. She may have an infection.

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Additional testing to be anticipated:

- Serum protein electrophoresis (SPEP)
- Urine protein electrophoresis (UPEP)
- Bone marrow aspiration and biopsy
- Iron and anemia studies
- All of the above

Case Presentation: Jane

Additional labs were obtained:

• IgG 4,700 mg/dL and kappa 5,200 mg/dL
• M spike 3.8 g/dL
• Kappa free serum is 3500
• 24-hour urine < 0.16 g/24 hours
• β2-microglobulin 3.9 mg/L
• Bone marrow biopsy showed 20% plasma cells
• Bone survey showed osteopenia, lytic lesions in bilateral femurs, calvarium
• Diagnosis?

IgG Kappa MM, stage II ISS
Multiple Myeloma: A Cancer of the Plasma Cells

- Healthy plasma cells produce immunoglobulins in response to foreign body invasion
- Myeloma cells produce abnormal immunoglobulin
  - 65% IgG, 20% IgA
  - 5% to 10% light chains (monoclonal kappa, lambda light chains, Bence Jones proteins)
- Uncommon IgD, IgE, IgM, or nonsecretory disease


CBC = complete blood count; β

- (Skeletal survey, MRI/CT, PET)

Initial Work-Up

<table>
<thead>
<tr>
<th>Test</th>
<th>Possible Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>Anemia, thrombocytopenia</td>
</tr>
<tr>
<td>Chemistries</td>
<td>Renal insufficiency, hypercalcemia, decreased albumin, elevated LDH</td>
</tr>
<tr>
<td>β_m</td>
<td>Often elevated</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>Presence of monoclonal protein</td>
</tr>
<tr>
<td>Urine protein electrophoresis</td>
<td>Presence of Bence Jones protein</td>
</tr>
<tr>
<td>Serum and urine immunofixation</td>
<td>Determines type of monoclonal protein</td>
</tr>
<tr>
<td>Free light chains</td>
<td>Elevation of the involved light chain</td>
</tr>
<tr>
<td>- Radiologic imaging</td>
<td>MM is like a puzzle. It's hard to put all the pieces together</td>
</tr>
<tr>
<td>- (Skeletal survey, MRI/CT, PET)</td>
<td>Bone marrow biopsy</td>
</tr>
</tbody>
</table>

Clinical Presentation (cont.)

<table>
<thead>
<tr>
<th>Disease Process</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency (20%–25%) light chain</td>
<td>Serum creatinine ≥2 mg/dL or greater</td>
</tr>
<tr>
<td>Calcium, &lt; 7 mg/dL (13%–30%)</td>
<td>Anemia, nausea, lethargy, polydipsia (excessive thirst), constipation, confusion</td>
</tr>
<tr>
<td>Nephropathy (20%)</td>
<td>Numbness, tingling, carpal tunnel syndrome neuropathy?</td>
</tr>
<tr>
<td>Immune function deficiency (0.8–4.4 infections per patient-year)</td>
<td>Recurrent infections, bacteremia, pneumonia, &quot;tumor licker&quot; in 1%</td>
</tr>
</tbody>
</table>

Multiple Myeloma Disease Continuum

- MGUS
  - (Monoclonal Gammapathy of Undetermined Significance)
  - Smoldering Multiple Myeloma
  - Multiple Myeloma

- M protein (per dL)
  - <5 g
  - ≥5 g

- Smoldering
  - Multiple Myeloma
  - ≥10%

- Multiple Myeloma
  - M-spike or plasmacytoma

- Clonal PC in bone marrow
  - ≤10%

- End-organ damage
  - None

- Likelihood of progression
  - 1% per year
  - 10% per year for 5 years: 75% by 15 years

- Symptoms
  - Asymptomatic
  - Asymptomatic

- Active treatment
  - No
  - No
  - Yes

20,000 Diagnosed With Multiple Myeloma Annually in United States; 10,000 Deaths

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank</td>
<td>Cancer Type</td>
</tr>
<tr>
<td>1</td>
<td>Lung</td>
</tr>
<tr>
<td>2</td>
<td>Breast</td>
</tr>
<tr>
<td>3</td>
<td>Colorectal</td>
</tr>
<tr>
<td>4</td>
<td>Prostate</td>
</tr>
<tr>
<td>5</td>
<td>Leukemia</td>
</tr>
<tr>
<td>6</td>
<td>Pancreatic</td>
</tr>
<tr>
<td>7</td>
<td>Melanoma</td>
</tr>
<tr>
<td>8</td>
<td>Brain</td>
</tr>
<tr>
<td>9</td>
<td>Thyroid</td>
</tr>
<tr>
<td>10</td>
<td>Leukemia</td>
</tr>
<tr>
<td>11</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td>12</td>
<td>Myeloma</td>
</tr>
<tr>
<td>13</td>
<td>All Other Cancers</td>
</tr>
<tr>
<td>14</td>
<td>Thyroid</td>
</tr>
</tbody>
</table>

Asymptomatic multiple myeloma patients with no disease activity, but still present at risk for end-organ damage, infection, or other complications. MGUS = monoclonal gammopathy of undetermined significance. CRAB = hypercalcemia, renal impairment, anemia, bone lesions. MM = multiple myeloma.
Disease Progression in Smoldering Multiple Myeloma and MGUS Patients

ARS Question

Which is NOT one of the "CRAB" criteria for diagnosis of myeloma?

1. Calcium elevation
2. Anemia
3. Bone lesions
4. Renal insufficiency or renal failure
5. Blood monoclonal proteins

New Criteria "CRAB" Criteria: Myeloma Defining Event (MDE)

Multiple Myeloma Disease Staging: Two Systems

Jane is Stage II (D2M 3.9)

Multiple Myeloma Disease Staging: Two Systems

MM Treatment Options Have Expanded

Advancements in HSCT
Primary Therapy for MM Differs Between Transplant Eligible and Ineligible

Newly Diagnosed MM Patient

Think: Induction, Consolidation, Maintenance

Transplant Eligible

Induction Therapy (Initial treatment) Non-alkylator based

Early Autologous Transplant

Delayed Autologous Transplant

Extended Induction

Relapsed or Refractory

Transplant Ineligible

Bortezomib
Lenalidomide
Melphalan
Thalidomide
Other

Candidate for Transplantation Depends on Many Factors

Myeloma/Related Factors
- Type of myeloma
- Disease stage
- Disease aggressiveness
- Responsiveness to treatment
- Serum albumin
- Beta-2 microglobulin
- Chromosomal analysis

Patient-Related Factors
- Age
- Health/performance status
- Kidney, heart, lung, & liver function
- Serum albumin
- Beta-2 microglobulin
- Chromosomal analysis

Transplant recommendations: IMWG guidelines
- Autologous: self-donation
- Syngeneic: identical sibling
- Allogeneic: related or unrelated donor, includes cord blood
- Reduced intensity ("mini") transplant: non-myeloablative
- Tandem transplants

Questions Surround ASCT in the Era of Novel Agents

- Can we cure MM with transplant?
- Is sequential therapy better than transplant?
- Responses to treatment (similar to transplant) have been observed in the non-transplant setting
- The depth of response to treatment is important. CR: the single most important surrogate for long-term disease control and overall survival ….. But is a CR with standard therapy different in quality from CR following transplant?
- Will we have a "BCR-ABL" test such as in CML to assess burden??

**What is the best way to treat MM in 2013?**
A Few Induction Regimens for MM......

- Bortezomib/Dexamethasone
  - Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11
  - Dexamethasone 40 mg po Days 1–4, 9–12
  - Repeat every 3 weeks for 2-4 cycles

- Bortezomib/Thalidomide/Dexamethasone (VTD)
  - Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11
  - Thalidomide 200 mg po Days 1–21
  - Dexamethasone 20 mg on the day of and on the day after bortezomib
  - Repeat every 3 weeks ± 3 cycles

- Lenalidomide/Dexamethasone
  - Lenalidomide 25 mg po Days 1–21 every 28 days
  - Dexamethasone 40 mg po Days 1, 8, 15, 22 every 28 days
  - Repeat every 4 weeks for 2 cycles

Modern therapy for MM requires various parts
Supportive care integral and will be discussed later.

Cooke et al, 2009;
HLA = human leukocyte antigen; RIC = reduced-intensity conditioning.

4) RIC Allo-SCT
3) Myeloablative Allo-SCT
2) Tandem Transplant
1) Myeloablative Single ASCT

SCT Options in Patients With MM

1) Myeloablative Single ASCT
   - Double Myeloablative ASCT
   - Myeloablative ASCT: Myeloablative HLA-Matched Allo-SCT
   - Myeloablative ASCT: Myeloablative HLA-Matched MUD SCT
   - Myeloablative ASCT: HLA-Matched Allotype SCT
   - Myeloablative ASCT: HLA Mismatched Allo-SCT

2) Myeloablative Allo-SCT

3) Auto- and Auto-Allo Transplant BMT CTN 0102

Risk Stratification Strategy

- At diagnosis, risk stratification helps guide the initial treatment
- Risk stratification may or may not lead to a better outcome (RR, PFS, and OS)
- Bortezomib and/or lenalidomide in patients with high-risk features such as high β2m, del(13), t(4;14) could overcome poor outcomes compared with conventional chemotherapy
Transplant Studies in Multiple Myeloma

Matt E. Kalaycio, MD, FACP
Chairman, Department of Hematologic Oncology and Blood Disorders
Director, Bone Marrow Transplant Program
Taussig Cancer Institute

Autologous Transplantation vs Conventional Chemotherapy For Newly Diagnosed Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>CR (median months)</th>
<th>EFS (median months)</th>
<th>OS (median months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attal et al (2003)</td>
<td>22</td>
<td>28**</td>
<td>57**</td>
</tr>
<tr>
<td>Fermand et al (1996)</td>
<td>18.7</td>
<td>50.4 ST</td>
<td>59.3</td>
</tr>
<tr>
<td>*Blade et al (1996)</td>
<td>24.3**</td>
<td>66.9</td>
<td></td>
</tr>
<tr>
<td>Child et al (2003)</td>
<td>44</td>
<td>42.3</td>
<td>67.4</td>
</tr>
<tr>
<td>*Barlogie et al (1996)</td>
<td>51</td>
<td>31.6**</td>
<td>54.8**</td>
</tr>
</tbody>
</table>

Single vs. Double Transplant

- A second transplant within a short time frame (~4 months)
- May only benefit patients not achieving very good partial response (VGPR; i.e., 90% reduction in M protein)
- Not all trials show improved survival
- Melphalan should be avoided prior to stem cell harvest
- Patients don’t like second transplants

The goal of HD MEL with ASCT is CR

- CR correlates with PFS
- Definition of CR
  - Immunofixation vs Immunophenotypic vs Molecular
  - "Stringent" CR = normalization of the FLC ratio
- Duration of CR
- Newer treatment regimens achieve CR as often as ASCT
CR rates with ASCT and newer regimens

<table>
<thead>
<tr>
<th>CR %</th>
<th>After Induction</th>
<th>After ASCT #1</th>
<th>After ASCT #2</th>
<th>After Post-ASCT Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>29-37%</td>
<td>VTD</td>
<td>22</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>35%</td>
<td>Rosinol et al</td>
<td>42</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>67%</td>
<td>Jakubowiak et al</td>
<td>17</td>
<td>33</td>
<td>47</td>
</tr>
<tr>
<td>17</td>
<td>Barlogie et al</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

CR rates improve with ASCT

<table>
<thead>
<tr>
<th>CR %</th>
<th>After Induction</th>
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<th>After ASCT #2</th>
<th>After Post-ASCT Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>35%</td>
<td>VTD</td>
<td>19</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>67%</td>
<td>Rosinol et al</td>
<td>5</td>
<td>23</td>
<td>30</td>
</tr>
</tbody>
</table>

PFS with novel induction followed by ASCT

ASCT vs Novel Agents

<table>
<thead>
<tr>
<th>Palumbo et al, ASCO 2010, Abs 8015</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ld x 4 cycles for induction</td>
</tr>
<tr>
<td>• Cytoxan + G mobilization</td>
</tr>
<tr>
<td>• Randomize</td>
</tr>
<tr>
<td>– Mel/Pred/Len x6</td>
</tr>
<tr>
<td>– Mel 200 x 2</td>
</tr>
<tr>
<td>• No maintenance</td>
</tr>
<tr>
<td>• Median F/U 12 months</td>
</tr>
</tbody>
</table>

ASCT vs Novel Agents

<table>
<thead>
<tr>
<th>Palumbo et al, ASCO 2010, Abs 8015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Therapy</td>
</tr>
<tr>
<td>• Maintenance therapy is the use of ongoing low intensity chemotherapy to eliminate or suppress the minimal residual tumor clone over a prolonged period of time</td>
</tr>
<tr>
<td>• Maintenance therapy is administered when the disease is in remission, either undetectable or at a low level</td>
</tr>
<tr>
<td>• The purpose of maintenance therapy is to prolong remission duration and thereby, life expectancy</td>
</tr>
<tr>
<td>• Immunomodulatory molecules are well suited for maintenance therapy, as they can be administered orally at low doses for a prolonged period of time</td>
</tr>
</tbody>
</table>
Thalidomide Maintenance After ASCT

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>N</th>
<th>Thalidomide Dose (mg) / Duration</th>
<th>PFS / EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attal et al, 2006</td>
<td>597</td>
<td>Thalidomide 200 (median dose) vs. observation / progression</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spencer et al, 2006</td>
<td>252</td>
<td>Thalidomide 200 + prednisone vs. prednisone / 12 months</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Marchis et al, 2008</td>
<td>212</td>
<td>Thalidomide 200 + dexamethasone vs. dexamethasone / 12 months</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Bataille et al, 2008</td>
<td>139</td>
<td>Thalidomide 200 + prednisone vs. observation / 12 months</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Stagner et al, 2012a</td>
<td>136</td>
<td>Thalidomide 150 + prednisone vs. prednisone / 12 months</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Maiolino et al, 2008</td>
<td>212</td>
<td>Thalidomide 200 + dexamethasone vs. dexamethasone / 12 months</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Barlogie et al, 2006*</td>
<td>668</td>
<td>Thalidomide 400 / progression</td>
<td>+</td>
<td>NS</td>
</tr>
<tr>
<td>Morgan et al, 2010a*</td>
<td>820</td>
<td>Thalidomide 100 / progression vs. observation / 48 months</td>
<td>+ / -</td>
<td>NS</td>
</tr>
<tr>
<td>Lokhorst et al, 2010*</td>
<td>550</td>
<td>Thalidomide 50 / progression</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Stewart et al, 2010</td>
<td>332</td>
<td>Thalidomide 200 + prednisone vs. observation / 48 months</td>
<td>+</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Thalidomide also given as part of induction therapy.

PFS = progression-free survival; EFS = event-free survival; OS = overall survival; NS = not significant.

Thalidomide Maintenance: MRC Trial

At Median Follow-Up From Randomization of 38 Months

HR [95% CI] = 1.45 [1.22, 1.73], p = .0003

Maintenance, N = 407
No maintenance, N = 410

20  40  60  80  100
12  24  36  48  60  72
Patients (%)
PFS (months)

HR [95% CI] = 0.91 [0.72, 1.17], p = 0.40

Maintenance, N = 408
No maintenance, N = 410

20  40  60  80  100
12  24  36  48  60  72
Patients (%)
OS (months)

Thalidomide maintenance improves PFS but without an OS advantage

Lenalidomide Maintenance: CALGB 100104 Schema

CALGB, ECOG, BMT-CTN

Registration

Restaging Days 90–100

Placebo

Lenalidomide* 10 mg/d until relapse

Patient stratification based on diagnostic β2m level and prior thalidomide and lenalidomide use during induction

Consolidation: Lenalidomide alone 25 mg/day po Days 1–21 q28days for 2 months

Randomization: Stratified According to β2m, del(13), VGPR

0.00 0.25 0.50 0.75 1.00
0 6 12 18 24 30 36 42 48
Placebo Revlimid

p < .001

p = .027

Lenalidomide Maintenance Post-Transplant: The IFM 2005-02: Study Design

Phase III Randomized, Placebo-Controlled Trial

N = 614 Patients, From 78 Centers, Enrolled Between 7/2006 and 8/2008

Patients < 65 Years, With Non-Progressive Disease, ≤ 6 Months After ASCT in First-Line

Randomization: Stratified According to β2m, del(13), VGPR

Consolidation: Lenalidomide alone 25 mg/d po Days 1–21 q28days for 2 months

Arm A

Placebo (n = 307) until relapse

Arm B

Lenalidomide (n = 307) 10–15 mg/d until relapse

p = 10⁻⁹

p = .79

Placebo (n = 307)

Len (n = 307)


Median F/U: 36 months post-random, 46 months post-diagnosis

p < 10⁻⁹

p = .79

p = .027

Cleveland Clinic

McCarthy et al, 2011.
ASCT Summary

- New drugs have CR rates approaching ASCT
- CR increased further by ASCT
- CR increased further by Post-transplant therapy
  - Is prolonged therapy as good as intensive, short course treatment?
- IMiD maintenance: Possible increase in 2° malignancies
  OS benefit so far in 1 study
  PFS benefit in all 3 studies

Auto-Allo Tandem?

Late relapses

Stem cell transplant for myeloma

- Single ASCT current standard of care
  - Tandem ASCT in select patients
  - Timing uncertain
- Post ASCT treatment SOC
  - Consolidation vs maintenance
  - No standard role for Allogeneic transplant

International Myeloma Working Group Consensus Statement Regarding the Current Status of Allogeneic Stem-Cell Transplantation for Multiple Myeloma

Nursing Considerations and Supportive Care in Myeloma
Remember Jane?

- Diagnosed with IgG Kappa Multiple Myeloma, ISS stage II.
- Kappa free-serum is also significantly elevated at diagnosis, m spike
- Goals: Control disease, prevent treatment or disease-related complications
- Wants to undergo Autologous transplant upfront as part of clinical trial
- Induction regimen
  - Bortezomib 1.3 mg/m² IV Day 1, 4, 8, 11 q21days
  - Dexamethasone 40 mg Day 1, 2, 4, 5, 8, 9, 11, 12 q21days
  - Lenalidomide 15 mg PO d 1-14, q21 days

ARS Case Study

You are the nurse caring for Jane prior to transplantation.

What supportive care therapy would you consider to be important to start prior to C1?

1) Granulocyte stimulating factor (GCSF)
2) Platelet transfusions
3) Bone marrow transplant
4) Bisphosphonates, acyclovir
5) None of the above

ARS Case Study: Question 1

Jane complains of numbness and pain in her feet after cycle 1 of bortezomib, lenalidomide and dexamethasone. What would you anticipate to be the correct intervention?

1. Continue bortezomib. She needs to go to transplant.
2. Hold Bortezomib until pain resolves. Then continue at full dose.
3. Hold Bortezomib until pain resolves. Then reduce the dose of bortezomib to 1.0mg/m² days 1, 4 and 11 IV.
4. Hold bortezomib until pain resolves. Then reduce the dose of bortezomib 1.0mg/m² days 1, 4, 8 and 11 and give SC.
5. Either 3 or 4.

Peripheral Neuropathy (PN)

- Damage to the peripheral nervous system caused by injury, inflammation, or degeneration of peripheral nerve fibers
  - Can affect QOL, compromise optimal treatments
- Incidence of PN is increasing
- More neurotoxic drugs have been developed
- Patients are living longer, multiple treatment regimens
- Multifactoral
  - Older age, chemotherapy dose/duration
  - Prior cisplatin or vinca alkaloids
  - Co-administration with other neurotoxic agents
  - Pre-existing conditions such as DM, ETOH, HIV positive, female gender, Vit B12 deficiency/B6 toxicity

Peripheral Nervous System

PN: Management Strategies

- Regular monitoring at each treatment visit and neurotoxicity assessment using a well-established PN assessment tool preferably at the beginning of each treatment cycle
- Treatment dose and schedule modifications
- Pharmacologic and non-pharmacologic interventions
- Patient education
Disease and Treatment Related Side Effects:

Infections in MM

- A leading cause of death in myeloma patients
  - Risk further increased by cytotoxic therapy, transplant, and glucocorticoids
- Immunoglobulin levels decreased
- Hyporesponsive to antigen stimulation
- Deficient antibody production
- Infection of bone marrow by plasma cells
- Interventions
  - Prompt reporting of symptoms
  - IV Ig prophylaxis
  - Poor response to pneumococcal and influenza vaccines (STILL GIVE)
  - No ZOSTAVAX; give herpes zoster oral prophylaxis (bortezomib, carfilzomib)

Bone Disease in MM

- Malignant cells produce osteoclast-activating factors that destroy bone cells
  - Leads to osteolysis, bone pain, and pathologic fracture
- Bisphosphonates inhibit bone destruction
  - Monitor patients for:
    - Acute phase reactions
    - Renal dysfunction
    - Osteonecrosis of the jaw

Renal Complications in MM Patients

- 25% to 50% have renal impairment at ANY TIME during disease
- 30% to 40% have elevated serum creatinine at presentation
- Treat: Hydrate, avoid dehydration, correct hypercalcemia, NO NSAIDs, dyes

Management of Musculoskeletal System: Bone

- Osteonecrosis
  - Evaluation with x-rays (panoramic) or MRI
  - Prompt orthopedic referral for evaluation
  - Pain assessment with appropriate pharmacological interventions
    - Discontinue steroid use
    - Avascular necrosis (3%)
- Osteoporosis
  - Bone density
  - Consider supplementation with calcium 1,000 mg/day and vitamin D 400 IU/day
  - IV/PO bisphosphonates
Bone Complications: A Result of Disease and Treatment

- Compression fractures
  - Vertebroplasty, kyphoplasty
  - Radiation (if plasmacytoma) but avoid to protect bone marrow
  - Bisphosphonates

General Disease, and Treatment Related Side Effects:

- MM is intrinsically hypercoagulable disease associated with a higher risk of thromboembolic events
- This may lead to DVT or PE
- Higher risk for DVT/PE in patients treated with conventional chemotherapies plus novel therapies such as
  - Thalidomide, lenalidomide or pomalidomide
  - Doxorubicin, high-dose corticosteroids

DVT/PE: Signs and Symptoms

**DVT**
- Slight fever, Tachycardia
- Unilateral swelling, erythemia, warm extremity
- Cyanosis/cold skin if venous obstruction
- Dull ache, pain, tight feeling over area and palpation
- Homans’ Sign not always positive
- Distension superficial venous collateral vessels

**ULTRASOUND**

**PE**
- Anxiety
- Sudden shortness of breath
- Worsening chest discomfort
- Rapid pulse and heart rate
- Low grade fever
- Pleural friction rub, crackles followed by diminished breath sounds, wheezing

**SPIRAL CT/VQ SCAN**

Thalidomide and Lenalidomide: Thromboembolic Event Management

- Symptom assessment at baseline and each visit
- Thromboembolic event: Prophylaxis
  - Full-dose warfarin
  - LMWH or full-dose heparin for high-dose dexamethasone, doxorubicin, or multagent chemotherapy independent of risk factors
  - LMWH or full-dose heparin for patients with ≥2 risk factors
  - Aspirin for low-risk patients only
- Risk factors include
  - Drugs (EPO)
  - History of thromboembolic events
  - Obesity
  - Concurrent cardiac or renal disease, diabetes, acute infection
  - Surgery

General prophylactic strategies- all novel agents
- Monitor signs and symptoms
- Monitor CBC and differential
- Educate on signs and symptoms of neutropenic fever, anemia, thrombocytopenia

Myelosuppression management
- Growth factor therapy
- Dose reduction as appropriate
- Transfusion as indicated

VTE: Signs and Symptoms

**Thromboembolic Events: Prophylaxis**

- Mechanical
  - Ambulation, Exercise is the most effective prophylactic strategy
  - Sequential compression devices
  - Antiembolism stockings- questionable
- Steroid dose reduction
  - Decreased risk of VTE in ECOG trial
  - Dexamethasone reduced dosing 40mg weekly
    - DVT: 26% Rd vs 12% Rd (p=0.0003)
    - Infection/Pneumonia: 16% vs 9% (p=0.04)

LMWH = low molecular weight heparin; EPO = erythropoietin.
Overview of GI Side Effects

- Novel therapeutics can cause serious GI side effects
  - Constipation: stool softeners, laxatives
  - Diarrhea: loperamide, diet (cdiff, stool culture)
  - Nausea and/or Vomiting: Ginger, peppermint, small meals, 5ht3 receptor antagonist, motility agents
  - Weight loss – small meals, secondary causes??
- Onset, duration, aggravating/alleviating factors

Diarrhea common in lenalidomide maintenance post transplant


Overall Recommendations

- Effective management includes
  - Monitoring patients carefully
  - Educating patients and caregivers about what to expect during treatment
  - Appropriate prophylaxis
  - Pharmacologic and non-pharmacologic interventions
  - Effective management leads to
  - Increased adherence to therapy
  - Improved QOL
  - Prevention of serious adverse events

Effective management leads to increased adherence to therapy, improved QOL, and prevention of serious adverse events. Effective management includes monitoring patients carefully, educating patients and caregivers about what to expect during treatment, and using appropriate prophylaxis and pharmacologic or non-pharmacologic interventions.

New "New Drugs": Relapsed MM

- Carfilzomib, no significant PNP, appears at least as effective as bortezomib; FDA Approved June, 2012 for RRMM failed bortezomib, imid
- Pomalidomide, tolerated about as lenalidomide, but more effective; FDA Approved February, 2013 for RRMM failed bortezomib, rev
- Elotuzumab, humanized antibody against CS1, promising in Ph2 with Rd
- Azacitidine, DNA methylation inhibitor, OS benefit in MDS
- Panobinostat, histone deacetylase inhibitor, promising in Ph1/2 with Bort/Dex

Conclusions

- The landscape of MM continues to change
- Nurses are critical in the management of MM related side effects
- There is no clear consensus but guidelines exist to help “guide” our decisions regarding transplantation and side effect management
- Future research will aim at providing clarity and best management strategies
  - Optimal induction, consolidation, maintenance