Managing Toxicities of Myeloma Therapy

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Quick review of important updates and implication for practice:
- Definition of myeloma
- Staging system
- Guiding principles of MM therapy - preventing relapse

Toxicities of currently used agents in MM
- IMiDs: Thalidomide, Lenalidomide, Pomalidomide
- PIs: Bortezomib, Carfilzomib, Ixazomib
- Monoclonal Antibodies: Elotuzumab, Daratumumab
- Adjuncts: Dexamethasone, Zoledronic acid

Toxicities from autologous stem cell harvest and transplantation
Common patient and caregiver questions
Last-minute pearls
Natural History of MM

Asymptomatic

MGUS* or Smoldering Myeloma

Active Myeloma

Plateau Remission

Relapse

Symptomatic

Therapy

Therapy

Therapy

Refractory Relapse

M Protein (g/l)

~90,000

~30,000

~11,000

New cases in U.S.²

Prevalence in the U.S.³

Annual deaths in U.S.²

*Monoclonal gammopathy of uncertain significance

~90,000

~11,000

~30,000

~11,000
# Outcomes in Relapsed and Refractory Multiple Myeloma

## Frontline Treatment

<table>
<thead>
<tr>
<th>Expected survival (months)</th>
<th>20-50</th>
<th>14-16</th>
<th>6-10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity to therapy</strong></td>
<td>Sensitive</td>
<td>Less Sensitive/Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td><strong>Treatment limitations/comorbidities</strong></td>
<td>Peripheral neuropathy (~15% at diagnosis)</td>
<td>&gt;80% incidence of peripheral neuropathy Compromised marrow reserve Cytopenia</td>
<td>Intolerant to or ineligible for available therapy</td>
</tr>
</tbody>
</table>

Elderly population (↑ risk for heart, lung, renal, liver dysfunction, diabetes)

Drugs for MM: Many Choices for Your Patient

- Thalidomide 1999
- Lenalidomide 2003
- Bortezomib 2006
- Liposomal Doxorubicin 2007
- Carfilzomib 2012
- Pomalidomide 2013
- Panobinostat, Daratumumab, Elotuzumab, Ixazomib 2015
Here’s a List of Options from NCCN:

### Preferred Regimens

<table>
<thead>
<tr>
<th>Therapy for Previously Treated Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Regimens</td>
</tr>
<tr>
<td>• Repeat primary induction therapy (if relapse at &gt;6 mo)</td>
</tr>
<tr>
<td>• Bortezomib (category 1)</td>
</tr>
<tr>
<td>• Bortezomib/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/liposomal doxorubicin (category 1)</td>
</tr>
<tr>
<td>• Bortezomib/thalidomide/dexamethasone</td>
</tr>
<tr>
<td>• Carfilzomib</td>
</tr>
<tr>
<td>• Carfilzomib/dexamethasone</td>
</tr>
<tr>
<td>• Carfilzomib/lenalidomide/dexamethasone (category 1)</td>
</tr>
<tr>
<td>• Cyclophosphamide/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>• Daratumumab&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</td>
</tr>
</tbody>
</table>

| Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) |
| Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE) |
| Elotuzumab<sup>11</sup>/lenalidomide/dexamethasone (category 1) |
| Ixazomib<sup>12</sup> |
| Ixazomib<sup>12</sup>/dexamethasone |
| Ixazomib<sup>12</sup>/lenalidomide/dexamethasone (category 1) |
| High-dose cyclophosphamide |
| Lenalidomide/dexamethasone<sup>13</sup> (category 1) |
| Panobinostat/bortezomib/dexamethasone<sup>14</sup> (category 1) |
| Pomalidomide<sup>15</sup>/dexamethasone<sup>13</sup> (category 1) |
| Thalidomide/dexamethasone<sup>13</sup> |

### Other Regimens

<table>
<thead>
<tr>
<th>Therapy for Previously Treated Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Regimens</td>
</tr>
<tr>
<td>• Bendamustine</td>
</tr>
<tr>
<td>• Bortezomib/vorinostat</td>
</tr>
</tbody>
</table>

| Lenalidomide/bendamustine/dexamethasone         |
| Panobinostat<sup>14</sup>/carfilzomib           |
MYELOMA DIAGNOSTIC CRITERIA
“Old” Diagnostic Criteria for MM

• Presence of M protein in serum or urine
• Identification of >10% monoclonal plasma cells in bone marrow and/or plasmacytoma
• Evidence of end-organ damage: CRAB(I) criteria
  • Calcium Elevation: Ca++ ≥ 11 mg/dL
  • Renal Failure: SCr ≥ 2 mg/dL
  • Anemia: Hb < 12 g/dL
  • Bone: Lytic lesions, pathologic fracture
  • Infections: Recurrent, due to hypogammaglobulinemia

**Revised International Myeloma Working Group**

**Myeloma Diagnostic Criteria**

**Definition of MM**

Clonal bone marrow plasma cells ≥10% OR biopsy-proven bony or extramedullary plasmacytoma

The above, plus any 1 or more of the following myeloma-defining events

<table>
<thead>
<tr>
<th>Biomarkers of malignancy</th>
<th>Evidence of end organ damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clonal bone marrow plasma cell percentage ≥60%</td>
<td>• Calcium elevation (&gt;1 mg/dL higher than the upper limit of normal or &gt;11 mg/dL)</td>
</tr>
<tr>
<td>• Involved:uninvolved serum free light chain ratio ≥100</td>
<td>• Renal insufficiency (creatinine clearance &lt;40 mL/min or serum creatinine &gt;2 mg/dL)</td>
</tr>
<tr>
<td>• &gt;1 focal lesion on MRI studies</td>
<td>• Anemia (Hb &lt;10 g/dL or &gt;2 g/dL below the lower limit of normal)</td>
</tr>
<tr>
<td></td>
<td>• Bone lesions (1 or more osteolytic lesions on skeletal radiography, CT, or PET-CT)</td>
</tr>
</tbody>
</table>

The presence or absence of monoclonal protein is used to divide MM into secretory and nonsecretory types

MYELOMA STAGING
## Durie-Salmon Staging for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Myeloma cell mass ( \times 10^{12} \text{ cells/m}^2 )</th>
<th>Median OS</th>
</tr>
</thead>
</table>
| I     | All of the following:  
Hemoglobin >10 g/dL  
Serum calcium level \( \leq 12 \text{ mg/dL} \) (normal)  
Normal bone or solitary plasmacytoma on x-ray  
Low M component production rate:  
   IgG <5 g/dL; IgA <3 g/dL  
   Bence Jones protein <4 g/24 hr | <0.6 (low) | 1a: 191 m  
                                      |           | 1b: N/A |
| II    | Not fitting stage I or III | 0.6–12 (intermediate) | 2a: 54 m  
                                      |           | 2b: 11m |
| III   | One or more of the following:  
Hemoglobin <8.5 g/dL  
Serum calcium level >12 mg/dL  
Multiple lytic bone lesions on x-ray  
High M-component production rate:  
   IgG >7 g/dL; IgA >5 g/dL  
   Bence Jones protein >12 g/24 hr | >1.2 (high) | 3a: 34m  
                                      |           | 3b: 5m |

### Subclassification |
- **A**: Normal renal function (serum creatinine level \( <2.0 \text{ mg/dL} \))  
- **B**: Abnormal renal function (serum creatinine level \( \geq 2.0 \text{ mg/dL} \))

Durie B, Salmon S. Cancer. 1975;36:842; Multiple Myeloma Research Foundation. Available at: www.multiplemyeloma.org
International Staging System (ISS) for MM

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>ALB &gt; 3.5 and $\beta_2$M &lt; 3.5</th>
<th>62m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>ALB &lt; 3.5 and $\beta_2$M &lt; 3.5 OR $\beta_2$M 3.5 – 5.5</td>
<td>44m</td>
</tr>
<tr>
<td>Stage 3</td>
<td>$\beta_2$M &gt; 5.5</td>
<td>29m</td>
</tr>
</tbody>
</table>

$\beta_2$M=serum $\beta_2$ microglobulin in mg/dL; ALB=serum albumin in g/dL

### Revised International Staging System (ISS) for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>ALB &gt; 3.5 and $\beta_2$M &lt; 3.5 + Absence of high risk CA AND LDH wnl</td>
<td>NR</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Neither stage 1 or 3</td>
<td>83m</td>
</tr>
<tr>
<td>Stage 3</td>
<td>$\beta_2$M &gt; 5.5 + High risk CA OR LDH &gt; ULN</td>
<td>43m</td>
</tr>
</tbody>
</table>

$\beta_2$M = serum $\beta_2$ microglobulin in mg/dL; ALB = serum albumin in g/dL; CA = cytogenetic abnormalities (del 17p, t(4;14), t(14;16))

LENGTH OF THERAPY
What Is the Goal of Maintenance?

- Tumor Volume → Time
- Ineffective treatment
- High-Dose Therapy
- Alkylators
- Dexamethasone

Goal of newer therapy options

Ultimate goal: Cure

Limit of detection
Responses Deepen with Length of Therapy

Mayo Phase II
- Stringent complete response: 53%
- Completed response: 32%
- Very good partial response: 6%
- Partial response: 24%

BiRd Phase II
- Stringent complete response: 43%
- Completed response: 19%

MM-009/MM-010 Phase III
- 46% of CR/VGPR achievers started with a PR and achieved a CR/VGPR with further treatment cycles

Number of responders
- CR/VGPR
- PR
The Importance of Continuous Therapy

Continuous therapy may be associated with significant improvement in patient outcomes

Pooled analysis of 3 phase 3 trials analyzing continuous therapy vs fixed-duration therapy in 1218 patients with newly diagnosed multiple myeloma. Primary endpoints were PFS1, PFS2, and OS. Median follow-up was 52 months.

OS=overall survival.
Treatment Discontinuation Can Adversely Impact Outcomes

- Drug discontinuation due to AEs was correlated with increased risk of death within the first 6 months (HR: 1.67; 95% CI, 1.12-2.51; P=0.01)


**AE** = adverse event; **CI** = confidence interval; **HR** = hazard ratio.
Treatments Are Discontinued in the Real World for Many Different Reasons\textsuperscript{1}

- Stable disease/ remission
- Progression
- Toxicity
- Poor PS
- As planned
- Patient refusal

Guiding Principles:

• Patients who are now asymptomatic may have active myeloma and require treatment

• Continuous combination therapy provides best outcomes
  – Stopping treatment for ANY reason leads to relapse and potentially inferior survival
  – We have to learn how to safely treat through AEs
Treatment Decision in Older Patients

Patients
- ADL
- Comorbidities
- Hospitalization
- Medications
- Social Support

Multiple Myeloma
- Cytogenetics
- Stage
- Tumor Burden
- Optimal Chemo
- Supportive Meds

Goals of Care (CR vs. Disease Control?)
- Expectations
- Understanding
- Life Expectancy
Efficacy and Safety of Three Bortezomib-Based Induction and Maintenance Regimens in Previously Untreated, Transplant-Ineligible Multiple Myeloma Patients: Final Results from the Randomized, Phase 3b, US Community-Based UPFRONT Study

**Induction: 8 x 21-day cycles**

**Cycles 1-4**
- **VD**
  - V: 1.3 mg/m², days 1, 4, 8, 11
  - D: 20 mg, days 1, 2, 4, 5, 8, 9, 11, 12

**Cycles 5-8**
- **V: 1.3 mg/m², days 1, 4, 8, 11**
- **D: 20 mg, days 1, 2, 4, 5**

**Cycles 9-13**
- **V: 1.6 mg/m², days 1, 8, 15, 22**
- **Rest period: days 23-35**

**Maintenance: 5 x 35-day cycles**

**Randomize 1:1:1**

**VTD**
- V: 1.3 mg/m², days 1, 4, 8, 11
- T: 100 mg, days 1-21
- D: 20 mg, days 1, 2, 4, 5, 8, 9, 11, 12

**VMP**
- V: 1.3 mg/m², days 1, 4, 8, 11
- M: 9 mg/m², days 1, 2, 3, 4 of every other cycle
- P: 60 mg/m², days 1, 2, 3, 4 of every other cycle

Patients in the VTD arm received concomitant prophylaxis with aspirin, full-dose warfarin, or low-molecular weight heparin unless medically contraindicated.* In all treatment arms, prophylaxis for herpes zoster was recommended. *Palumbo A, et al. Leukemia 2008;22:414-23.
RESULTS

• 502 patients were randomized to
  – VD (n=168)
  – VTD (n=167)
  – VMP (n=167)

• Baseline characteristics were well-balanced across the treatment arms
  – Median age was 73 years (range 38-91)
  – 48% of patients had comorbidities at baseline
    • The most common were diabetes mellitus (21%), renal disease (15%), and chronic pulmonary disease (8%)
ORRs after 13 cycles were 73% (VD), 80% (VTD), and 70% (VMP) including:

- 30%, 40%, and 32% CR/nCR, respectively
- 37%, 51%, and 41% ≥VGPR, respectively

*Response- evaluable population (n=425 patients who received at least one dose of study drug, had measurable disease at baseline, and had at least one post-baseline M-protein measurement)
After a median follow-up of 42.7 months, 265 (53%) patients had progressed and/or died.

Median PFS (95% CI) was 14.7 months (12.0, 18.6), 15.4 months (12.6, 24.2), and 17.3 months (14.8, 20.3), for VD, VTD, and VMP, respectively, with no global difference among arms (p=0.458).
Median OS (95% CI) was 49.8 months (35.7, not estimable [NE]), 51.5 months (38.5, NE), and 53.1 months (41.1, NE) for VD, VTD, and VMP, respectively, with no global difference among arms ($p=0.789$).
MANAGING SIDE EFFECTS WITH COMMONLY USED ANTI-MM AGENTS
Immunomodulatory Agents

- Thalidomide
- Lenalidomide
- Pomalidomide
IMiDs Alter the Bone Marrow Microenvironment

MM cells

Bone Marrow Stromal Cells

IL-6

TNFα

IL-1β

Bone Marrow Stromal Cells

ICAM-1

VEGF

bFGF

Bone Marrow Vessels

PBMC

CD8+ T Cells

NK Cells


# Thalidomide (Thalomid): Immunomodulatory Agent

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of blood clot</td>
<td>23%</td>
<td>Aspirin; if higher risk, need heparin or other anticoagulation</td>
</tr>
<tr>
<td>Fatigue</td>
<td>80%</td>
<td>Exercise, limit carbohydrates, coffee, other stimulants, taking thalidomide at night; dose reduction</td>
</tr>
<tr>
<td>Constipation</td>
<td>55%</td>
<td>Stool softeners, laxatives</td>
</tr>
<tr>
<td>Rash</td>
<td>30%</td>
<td>Common at beginning of therapy; treat through. Can apply topical hydrocortisone if itchy</td>
</tr>
<tr>
<td>Brain fog</td>
<td>28%</td>
<td>Exercise, dose reduction</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>55%</td>
<td>*** CAN BE PERMANENT ***&lt;br&gt;Dose effect threshold: ~60 grams = 100% neuropathy rate (approx. 1 year of thal treatment)</td>
</tr>
</tbody>
</table>
# Lenalidomide (Revlimid): Immunomodulatory Agent

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood counts, esp. neutropenia</td>
<td>40%</td>
<td>Transfusions, G-CSF (neupogen, neulasta), erythropoietin (procrit/aranesp); <strong>OK to give G-CSF and lenalidomide at the same time</strong></td>
</tr>
<tr>
<td>Increased risk of blood clot</td>
<td>22%</td>
<td>Aspirin; if higher risk, need heparin or other anticoagulation</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
<td>Exercise, limit carbohydrates, coffee, other stimulants</td>
</tr>
<tr>
<td>Muscle cramping</td>
<td>21%</td>
<td>Pickle juice, apple cider vinegar</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46%</td>
<td>Cholestyramine, colestipol; **there is lactose in the LEN cap</td>
</tr>
<tr>
<td>Rash</td>
<td>28%</td>
<td>Common at beginning of therapy; treat through. Can apply topical hydrocortisone if itchy</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7%</td>
<td>**high index of suspicion; treat as per standard of care; be wary of amyloidosis</td>
</tr>
</tbody>
</table>
Managing Cytopenias with Lenalidomide

- Prior PI had G-CSF and lenalidomide concomitantly
- PI changed to reflect practice of clinical trials, no scientific basis
- JUST LIKE MDS: blood counts get worse before better on lenalidomide – TREAT THROUGH CYTOPENIAS!!!
Perfectly safe to give lenalidomide to patients with renal insufficiency, even with ESRD!

The recommendations for initial starting doses for patients with MM are as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Renal Function (Cockcroft-Gault)</th>
<th>Dose in Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal / mild renal impairment</td>
<td>CLcr &gt;50 mL/min</td>
<td>25 mg every 24 hours</td>
</tr>
<tr>
<td>Moderate renal impairment</td>
<td>CLcr 30-50 mL/min</td>
<td>10 mg every 24 hours</td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td>CLcr &lt;30 mL/min (not requiring dialysis)</td>
<td>15 mg every 48 hours</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>CLcr &lt;30 mL/min (requiring dialysis)</td>
<td>5 mg once daily; on dialysis days, administer the dose following dialysis</td>
</tr>
</tbody>
</table>

• Lenalidomide is NOT nephrotoxic, it is cleared by the kidney
• No excess harm to patients if started at correct dose, just as effective as standard dose LEN¹

# Pomalidomide (Pomalyst): Immunomodulatory Agent

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood counts, esp neutropenia</td>
<td>50%</td>
<td>Transfusions, G-CSF (neupogen, neulasta), erythropoietin (procrit/aranesp); <strong>OK to give G-CSF and pomalyst at the same time</strong></td>
</tr>
<tr>
<td>Increased risk of blood clot</td>
<td>8%</td>
<td>Aspirin; if higher risk, need heparin or other anticoagulation</td>
</tr>
<tr>
<td>Fatigue and asthenia</td>
<td>55%</td>
<td>Exercise, limit carbohydrates, coffee, other stimulants</td>
</tr>
</tbody>
</table>
Pomalidomide (Pomalyst): Immunomodulatory Agent

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>35%</td>
<td>Often subjective and passes with time. R/o PE, infection</td>
</tr>
<tr>
<td>URI/Pneumonia</td>
<td>23%</td>
<td>* Similar to rates of URI in other late-line MM txs</td>
</tr>
<tr>
<td>Dizziness/Confusion</td>
<td>20%</td>
<td>** Be careful about co-metabolism of narcotics and other CYP inhibitors/inducers</td>
</tr>
<tr>
<td>Fever</td>
<td>20%</td>
<td>Rule out infection; antipyretics</td>
</tr>
</tbody>
</table>
Pomalidomide (Pomalyst): Special Considerations

- Pomalyst is metabolized hepatically via CYP3A4 and CYP1A2
- This means:
  - Do not give with strong CYP inducers/inhibitors (i.e., narcotics)
  - Cigarette smoking can induce CYP1A2. Tell your patients to stop smoking
  - Teas (with exception of black tea) should be avoided
  - Take on EMPTY stomach (Cmax is 30% lower when taken with food)
  - Older patients tolerate pomalyst well! No dose reduction needed except for HD patients
# Bortezomib (Velcade): Proteasome Inhibitor

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low platelet count</td>
<td>50%</td>
<td>Transfusions, dose reduction</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>46%</td>
<td>Lower the velcade dose, *happens early, risk reduced with subcutaneous administration</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25%</td>
<td>Exercise, limit carbohydrates, coffee, other stimulants</td>
</tr>
<tr>
<td>Increased risk for shingles</td>
<td>11%</td>
<td>Acyclovir/Valacyclovir</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35%</td>
<td>Imodium, lomotil, kaopectate</td>
</tr>
<tr>
<td>Boron allergy</td>
<td>???</td>
<td></td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>reported</td>
<td></td>
</tr>
</tbody>
</table>
Give Bortezomib Subcutaneously!

In a study of patients with relapsed MM, ORR* at 12 weeks: 43% with subcutaneous VELCADE and 42% with IV VELCADE

— The study met its primary non-inferiority objective that single-agent subcutaneous VELCADE retained at least 60% of the ORR after 4 cycles relative to single-agent IV VELCADE

The peripheral neuropathy from bortezomib happens EARLY

- In patients treated with VELCADE (bortezomib)+MP, 47% experienced treatment-emergent PN, including 13% with grade ≥3
- 11% of patients discontinued treatment with VELCADE due to PN and continued MP; 3% of patients discontinued treatment with VELCADE+MP due to PN
- Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment

* A cumulative VELCADE dose of approximately 45 mg/m² is equivalent to approximately four 6-week cycles of VELCADE+MP.

- Treatment with VELCADE may cause PN that is predominantly sensory. However, cases of severe sensory and motor PN have been reported. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain, or weakness

Carfilzomib (Kyprolis): Proteasome Inhibitor

- Irreversible inhibitor of the 26S proteasome
- Has been shown to overcome bortezomib resistance
- ORR in phase 2 trial of CRD: 100%, >VGPR: 100% (in patients treated with >11 cycles)

Jakubowiak et al. ASH 2011
# Carfilzomib (Kyprolis): Toxicities

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>47%</td>
<td>Transfusions, dose reduction</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>35%</td>
<td>Tends to be transient, like pomalidomide</td>
</tr>
<tr>
<td>Fatigue</td>
<td>56%</td>
<td>Exercise, limit carbohydrates, coffee, other stimulants</td>
</tr>
<tr>
<td>URI</td>
<td>28%</td>
<td>Also very similar to pomalidomide</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33%</td>
<td>Imodium, lomotil, kapectate</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>24%</td>
<td>1 of 3 patterns emerges</td>
</tr>
<tr>
<td>Fever</td>
<td>30%</td>
<td>Antipyretics, rule out infection</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>reported</td>
<td>Premedicate with allopurinol and IVF**</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>2%</td>
<td>Monitor carefully for emergence of sx, hold dosing</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>reported</td>
<td>Monitor carefully</td>
</tr>
</tbody>
</table>
## Carfilzomib (Kyprolis): Cardiac Toxicities

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>18-30%</td>
<td>antihypertensives</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>12%</td>
<td>Early identification; stop carfilzomib, reversible; biggest risk factor is prior cardiac disease</td>
</tr>
</tbody>
</table>


Figure 1. Incidence of cardiac events in patients treated with carfilzomib. Cumulative incidence function estimates of cardiac events and discontinuation because of progressive disease or for other (nontoxicity) reasons.

60 consecutive myeloma patients treated with carfilzomib-based regimens who were thoroughly evaluated for cardiovascular risk factors, 12% experienced a reversible reduction of left ventricular ejection fraction (LVEF) by ≥20%. The incidence of LVEF reduction was 5% at 3m, 8% at 6m, 10% at 12m, and 12% at 15m
Ixazomib (Ninlaro): Oral Proteasome Inhibitor

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>78%</td>
<td>Similar pattern to bortezomib</td>
</tr>
<tr>
<td>URI</td>
<td>19%</td>
<td>Similar to other agents in relapsed setting</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42%</td>
<td>Imodium, lomotil, kaopectate</td>
</tr>
<tr>
<td>Constipation</td>
<td>34%</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>22%</td>
<td>Consider premedication</td>
</tr>
<tr>
<td>Rash</td>
<td>19%</td>
<td>Treat through if not severe</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>19%</td>
<td>Placebo + Rd comparator was 14%</td>
</tr>
</tbody>
</table>
Elotuzumab: CS1, SLAMF7m CRACC, CD319

- Elotuzumab (HuLuc63) is a humanized monoclonal IgG1 antibody targeting human CS1, a cell surface glycoprotein

- CS1 is highly and uniformly expressed on >95% of primary MM cells
  - Restricted expression on NK cells
  - Little to no expression on normal tissues
  - May promote adhesion to bone marrow stroma

- Acts primarily through NK cell-mediated ADCC

Hsi et al, 2008; Tai et al, 2008;
Elotuzumab works via a dual mechanism of action
- By directly activating natural killer cells
- And through antibody-dependent cell-mediated cytotoxicity (ADCC) to cause targeted myeloma cell death

Collins et al, 2013.
# Elotuzumab (Empliciti): Toxicities

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>27%</td>
<td>Slow infusion, antihistamines, APAP, and steroid, premedication</td>
</tr>
<tr>
<td>Cough</td>
<td>34%</td>
<td>Rule out URI, slow rate, antitussives, 1g magnesium, pretreatment montelukast</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62%</td>
<td>Exercise, limit carbohydrates, coffee, other stimulants</td>
</tr>
<tr>
<td>URI</td>
<td>23%</td>
<td>Also very similar to pomalidomide and carfilzomib</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47%</td>
<td>Imodium, lomotil, kapectate</td>
</tr>
<tr>
<td>Constipation</td>
<td>36%</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Fever</td>
<td>37%</td>
<td>Antipyretics, rule out infection</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13.2%</td>
<td>Anti-VZV prophylaxis</td>
</tr>
</tbody>
</table>
Daratumumab (Darzalex): Monoclonal Antibody Anti-CD38

• Binds to CD38 and elicits signaling cascade and immune effector function engagement, leading to
  – Complement-dependent cytotoxicity (CDC)
  – Antibody-dependent cell-mediated cytotoxicity (ADCC)
  – Antibody-dependent cell-mediated phagocytosis (ADCP)
  – Induction of apoptosis
  – Modulation of cellular enzymatic activities associated with calcium mobilization and signaling
  – Combination of these activities leads to elimination of plasma cells from bone marrow in MM patients

• CD38 is ALSO found on rbcs, HPSCs, smooth muscle (bronchioles)
## Daratumumab (Darzalex): Monoclonal Antibody Against CD38

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>17%</td>
<td>Slow infusion, antihistamines, APAP, and steroid, premedication</td>
</tr>
<tr>
<td>Cough</td>
<td>20%</td>
<td>Rule out URI, slow rate, antitussives, 1g magnesium, pretreatment montelukast</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39%</td>
<td>Exercise, limit carbohydrates, coffee, other stimulants</td>
</tr>
<tr>
<td>URI</td>
<td>23%</td>
<td>Also very similar to pomalidomide, carfilzomib, elotuzumab</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16%</td>
<td>Imodium, lomotil, kaopectate</td>
</tr>
<tr>
<td>Constipation</td>
<td>15%</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Fever</td>
<td>21%</td>
<td>Antipyretics, rule out infection</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>72%</td>
<td>Anti-VZV prophylaxis, suspect CMV</td>
</tr>
</tbody>
</table>
# MoAb-Related Adverse Events

## Infusion-Related Reactions (IRRs)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Grade 1-2</th>
<th>Grade 3-4</th>
<th>Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elotuzumab + Rd&lt;sup&gt;1&lt;/sup&gt;</td>
<td>9%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Elotuzumab + Vd&lt;sup&gt;2&lt;/sup&gt;</td>
<td>5%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Daratumumab + Rd&lt;sup&gt;3&lt;/sup&gt;</td>
<td>43%</td>
<td>5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Daratumumab + Vd&lt;sup&gt;4&lt;/sup&gt;</td>
<td>36%</td>
<td>9%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

MoAb, monoclonal antibody; Rd, lenalidomide-dexamethasone; Vd, bortezomib-dexamethasone

Challenges with MoAbs

• Interference RBC compatibility testing
• Interference CD38 detection by flow cytometry
• Interference IFX and SPEP testing
Daratumumab Interferes with Blood Compatibility Testing


©2016 by American Society of Hematology
Elotuzumab can be detected in SPEP and IFE in samples from patients treated with elotuzumab

©2016 by American Society of Hematology
## Dexamethasone

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactivity/Insomnia</td>
<td>Benzodiazepines (valium, ativan, etc.), ambien, Tylenol-PM; split dexamethasone dosing; switch to IV form; can try prednisone</td>
</tr>
<tr>
<td>Fluid retention (ankle/face swelling)</td>
<td>Diuretics, limit salt intake on dexamethasone days</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Limit carbohydrates on dexamethasone days</td>
</tr>
<tr>
<td>Increased risk for infection</td>
<td>Prophylactic antibiotics (bactrim, dapsone, etc.)</td>
</tr>
<tr>
<td>Proximal muscle loss</td>
<td>Exercise</td>
</tr>
<tr>
<td>Cataracts</td>
<td>*** Incidence ~ 10% after 2 years</td>
</tr>
</tbody>
</table>
### Zoledronic Acid (Zometa): Bisphosphonate

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone ache, low grade fever</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; infusion only, acetaminophen (Tylenol)</td>
</tr>
<tr>
<td>Kidney toxicity</td>
<td>Ensure infusion is given over 30 minutes (package insert says 15).</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>Keep teeth in good repair; follow up with dentist before and during zometa therapy; DO NOT ALLOW DENTAL EXTRACATIONS OR IMPLANTS.</td>
</tr>
</tbody>
</table>
# Autologous Stem Cell Transplant Toxicities

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Rate</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>100%</td>
<td>Patients recover at a rate of 1%/day</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>100%</td>
<td>Lemon drops, tart food, time</td>
</tr>
<tr>
<td>Migratory myalgias/arthralgias</td>
<td>50%</td>
<td>Acetaminophen, loratadine</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>75%</td>
<td>Time; encourage fluid intake, grazing</td>
</tr>
<tr>
<td>Loose bowel movements</td>
<td>50%</td>
<td>Imodium, lomotil, kaopectate</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>75%</td>
<td>Time</td>
</tr>
<tr>
<td>Failure to recover counts</td>
<td>1%</td>
<td>Consider stem cell boost</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>100%</td>
<td>Time, IVIG</td>
</tr>
</tbody>
</table>

It’s mostly hand-holding.
COMMON PATIENT AND CAREGIVER QUESTIONS (WITH ANSWERS)
Should I take any supplements?

• OK to take calcium 500-1500mg/day + vitamin D 1000-2000 i.u./ day
• OK to take a centrum silver (or similar multivitamin) daily
• AVOID:
  – Antioxidants: Green tea, acai berries, etc.
  – Excess vitamin C (extra supplements; vit C in food is ok)
• Best supplement is water:
  – Adequate hydration flushes chemotherapy and excess light chains through the kidneys
Are there any medications to avoid?

• Never take NSAIDS:
  – Ibuprofen, Aleve, Motrin, Advil, naproxen, etc. → can lead to kidney damage

• Never get IV contrast (iodine) for CT scan:
  – Can also cause kidney damage
  – Includes CT angiograms
  – MRI/PET-CT generally ok

• Ask your myeloma doctor about safety before starting IV antibiotics:
  – Certain antibiotics that are IV (like gentamycin) can also lead to renal failure in multiple myeloma
Are there any lifestyle changes that I should make?

• Try to get 20 minutes of cardiovascular exercise most days of the week
  – Reduces inflammation in the body
  – Better control of blood sugar
  – Get rid of excess weight
  – Tolerate chemo better

• Take care of your teeth!
  – See the dentist regularly to avoid osteonecrosis of the jaw
Last-Minute Pearls and Reminders

- Thalidomide is the only agent that is NOT myelosuppressive
- Only three drugs have been shown to mitigate del17p: pomalidomide, ixazomib, daratumumab
- Neuropathy with bortezomib occurs within first 4 cycles. If PN develops later in course, suspect MM relapse
- Diarrhea from IMiDs is due to bile acid salt malabsorption: use sequestrants
- PN from bortezomib is reversible; thalidomide generally is not
- Cardiac and renal toxicity from carfilzomib is reversible
- Do not stop treatment, even for patients in CR
THANK YOU!

You can contact me at: tomer.mark@ucdenver.edu
ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY MULTIPLE MYELOMA CARE

Education Project
Project Goals and Objectives

Greatly enhance the education of community providers and adoption of effective practices, including incorporation of the latest and best treatment options for patients diagnosed with multiple myeloma.

I. Raise awareness about education needs of healthcare providers in the community setting related to the management of multiple myeloma patients.

II. Educate the multidisciplinary healthcare team on how to implement effective practices in the treatment of multiple myeloma in community-based programs.

III. Establish vetted and designated resources for multiple myeloma that will be an enduring source of information for providers.

IV. Convene a strong network of advocacy and professional partners to increase peer-to-peer learning and adoption of effective practices.
Site Visits

- Yuma Regional Medical Center Cancer Center
  - Yuma, Arizona
  - Comprehensive Community Cancer Program
- John Theurer Cancer Center at Hackensack University Medical Center
  - Hackensack, New Jersey
  - Academic Comprehensive Cancer Program
- Moffitt Cancer Center
  - Tampa, Florida
  - NCI-Designated Comprehensive Cancer Program
International Myeloma Working Group (IMWG)

• Incorporating the latest guidance from the International Myeloma Working Group (IMWG) to improve diagnosis, assess prognosis, and develop tailored treatment plans
  
  • Diagnostic workup that includes flow cytometry, immunohistochemistry, cytogenetics, and molecular diagnostics
  • Revised International Staging System (R-ISS)
  • Assess risk profiles and engage in shared decision-making conversations with each patient
  • Refer patients who are eligible candidates for transplant evaluation

imwg.myeloma.org
Skeletal-Related Events (SREs)

- Many patients with multiple myeloma have bony lesions and are often treated with either zoledronic acid (infusion) or denosumab (injection)
  - Monitor for side effects such as osteonecrosis of the jaw (ONJ)
  - Assess patient preferences
- Incorporating the 2018 ASCO Clinical Practice Guideline Update: Role of Bone-Modifying Agents in Multiple Myeloma
  - Key clinical question: “What is the role of bone-modifying agents in patients with multiple myeloma?”
- Severe SREs such as spinal cord compression or vertebral compression fractures may occur
  - Often requires surgical management to prevent permanent paralysis
Advancing Research to Improve Care

• John Theurer Cancer Center has been involved with the Multiple Myeloma Research Foundation (MMRF) CoMMpass (Relating Clinical Outcomes in MM to Personal Assessment of Genetic Profile) Study
  • Discovery of 12 different molecular types of multiple myeloma, each with its own level of risk

• Moffitt Cancer Center is a founding member of Oncology Research Information Exchange Network (ORIEN), a cross-institutional research partnership
  • Includes a longitudinal study called Total Cancer Care, which examines the effects of different cancers, treatment choices, and lifestyle so that physicians can have a better understanding of patient outcomes and treatment options
Project Webpage

- Advisory Committee
- Educational Resources
  - Regional lecture series
  - Resource Portal for HCPs
- Journal Supplement -
  - Released October 2018 – *Print and Web*

accc-cancer.org/multiple-myeloma-care
Models of Effective Care Delivery

- *Multidisciplinary Multiple Myeloma Care: Models of Effective Care Delivery* offers a convenient summary of recent updates in the management of this heterogeneous disease, including information on:
  - Diagnostic Criteria by the International Myeloma Working Group
  - Revised International Staging System
  - ASCO Clinical Practice Guideline Update: Role of Bone Modifying Agents in Multiple Myeloma

- Plus, read how three cancer programs—a community-based comprehensive program, an academic medical center, and an NCI-designed program—are delivering multidisciplinary care to this patient population.

[Download Online]
Models of Effective Care Delivery -

- Yuma Regional Medical Center Cancer Center
- John Theurer Cancer Center at Hackensack University Medical Center
- Moffitt Cancer Center
Questions?
Thank You!