Advancing the Management of Plasma Cell Dyscrasias

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Learning Objectives

• Interpret differential diagnoses of plasma cell dyscrasias
• Assess recent changes in clinical management of the spectrum of multiple myeloma (smoldering, monoclonal gammopathy of undetermined significance [MGUS])
• Evaluate the risks and benefits of early treatments for smoldering myeloma
• Plan management strategies for patients with solitary plasmacytomas and amyloidosis
Financial Disclosure

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All Blood Cells Begin as Hematopoietic Stem Cells

**Plasma Cell Disorders: Distribution of Plasma Cell Dyscrasias**

N = 1,296

- **MGUS** 62%
- **Myeloma** 15%
- **AL Amyloidosi** 10%
- **Lymphoproliferative** 2.5%
- **SMM** 3.5% (44)
- **Solitary or extramedullary** 1.5%
- **Macro** 3%
- **Other** 2.5%

AL = amyloidosis; MGUS = monoclonal gammopathy of uncertain significance; SMM = smoldering multiple myeloma.

Myeloma Is a Cancer of Plasma Cells

- Cancer of plasma cells
- Often preceded by nonmalignant state(s): MGUS or SMM
- Healthy plasma cells produce antibodies/immunoglobulins (Ig)
- Overproduction of a normal Ig “clone”
  - 65% IgG; 20% IgA, 20% light chain only
  - Baseline and ongoing monitoring of the disease is essential: CBC, CMP, SPEP, UPEP, serum free light chains

BM = bone marrow; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; CBC = complete blood count; CMP = complete metabolic panel.
Myeloma Disease Overview:
Case Presentation

• Bob is a 51-year-old accountant and avid runner who presents to the APP with complaints of back pain that had progressed from mild over 3 weeks.
• No significant medical history
• Routine labs

Complete Blood Count
- WBC count 3,300/μL
- Hemoglobin 10.3 g/dL
- Platelet count 138,000/μL

Complete Chemistry Panel
- Creatinine 1.7 g/dL
- Calcium 10.4 mg/dL
- Albumin 3.2 g/dL
- Total protein 10.9 g/dL
## Initial Evaluation Investigative Workup

<table>
<thead>
<tr>
<th>Test</th>
<th>Possible finding(s) with myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential counts</td>
<td>↓ Hgb, ↓ WBC, ↓ platelets</td>
</tr>
<tr>
<td>CMP and electrolytes</td>
<td>↑ Creat, ↑ Ca++, ↑ uric acid, ↓ Alb</td>
</tr>
<tr>
<td>Serum electrophoresis with quantitative immunoglobulins (SPEP)</td>
<td>↑ M protein in serum, may have ↓ levels of normal antibodies</td>
</tr>
<tr>
<td>Immunofixation of serum</td>
<td>Identifies light/heavy chain types M protein</td>
</tr>
<tr>
<td>α₂m and LDH</td>
<td>↑ Levels (measure of tumor burden)</td>
</tr>
<tr>
<td>24-hour urine protein electrophoresis with immunofixation (UPEP)</td>
<td>↑ Monoclonal protein (<em>Bence Jones</em>)</td>
</tr>
<tr>
<td>BM aspirate and biopsy, FISH and cytogenetics</td>
<td>≥ 10% clonal plasma cells, prognosis (FISH and cytogenetics) Congo red BM stain if amyloid suspected</td>
</tr>
<tr>
<td>Skeletal survey; low-dose whole-body CT or PET should be considered</td>
<td>Osteolytic lesions, osteoporosis, EM disease</td>
</tr>
<tr>
<td>MRI</td>
<td>Does not replace skeletal survey; consider w/SMM</td>
</tr>
</tbody>
</table>

α₂m = β₂ microglobulin; CT = computed tomography; EM = extramedullary; FISH = fluorescence in situ hybridization; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; sFLV = serum free light chain.

Myeloma Disease Overview

• Additional labs:
  • Monoclonal protein analysis (MPA): IgG 4,300 mg/dL and kappa 5,900 mg/dL
  • Serum protein electrophoresis (SPEP): Monoclonal “spike” 4.2 g/dL
  • 24-hour urine: normal < 0.16 g/24 hours
  • Beta2-microglobulin: elevated 2.6 mg/L
  • Anemia panel showed low B12, high MMA, suggestive of vitamin B12 deficiency
  • Bone marrow biopsy showed 40% kappa restricted “clonal” plasma cells; normal cytogenetics, no IgH translocations.
  • What is Bob’s diagnosis?

<table>
<thead>
<tr>
<th>M proteins: Lab/Normal Reference Range</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA serum IgG 717–1,411 mg/dL</td>
<td>4,300</td>
</tr>
<tr>
<td>MPA serum IgA 78–391 mg/dL</td>
<td>29</td>
</tr>
<tr>
<td>MPA serum IgM 53–334 mg/dL</td>
<td>24</td>
</tr>
<tr>
<td>MPA serum kappa 534–1,267 mg/dL</td>
<td>5,900</td>
</tr>
<tr>
<td>MPA serum lambda 253–653 mg/dL</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

MMA = methylmelonic acid

Baz et al; Cancer 101 (4):790-795, 2004
The Multiple Effects of Multiple Myeloma

## Differential Diagnosis of MM

<table>
<thead>
<tr>
<th>Condition</th>
<th>Premalignant</th>
<th>MGUS(^{1-4}) (Monoclonal Gammopathy of Undetermined Significance)</th>
<th>SMM(^{1-5,8}) (Smoldering Multiple Myeloma)</th>
<th>Active Multiple Myeloma(^{6-8})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonal plasma cells in bone marrow</td>
<td></td>
<td>&lt;10%</td>
<td>10%-60%</td>
<td>≥10%</td>
</tr>
<tr>
<td>Presence of myeloma-defining events (MDEs)</td>
<td></td>
<td>None</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Likelihood of progression</td>
<td></td>
<td>~1% per year</td>
<td>~10% per year x 5 years then 1%/year</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>No; observation</td>
<td>Yes for high risk*; No for others</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Clinical trial is preferred or offer treatment

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Diagnostic Criteria

Clonal bone marrow $\geq$ 10% or bony/extramedullary plasmacytoma
AND any one or more Myeloma Defining Events (MDE)

Calcium elevation
Renal complications
Anemia
Bone disease

Based on Bob’s high M protein, he agreed to enroll in a clinical trial for high-risk smoldering MM.
Is an Aggressive Approach to Treat Smoldering MM Recommended?

75% had an excellent response but at what cost?

Daratumumab Alone in Smoldering MM

CENTAURUS: PFS (Biochemical or Diagnostic)

PFS = progression-free survival

Extended daratumumab dosing prolongs biochemical/diagnostic PFS

### Pro and Cons of Early treatment for SMM

<table>
<thead>
<tr>
<th><strong>Pro</strong></th>
<th><strong>Cons</strong></th>
</tr>
</thead>
</table>
| Possible survival benefit in one study
| Methodologic flaws in the one study with survival benefit |
| Delay/prevent potentially irreversible complications (fractures/renal failure)
| Concern for long term toxicity / second malignancy |
| Contemporary therapy is better tolerated
| Not all patients require therapy and criteria to define risk are inconsistent |

QOL = quality of life

Is a cure for myeloma possible?
Minimal Residual Disease (MRD) and Transplant, Aiming for a “Cure”

Importance of MRD sensitivity in IFM 2009 Trial VRd ± ASCT

The lower the level of myeloma cells, the longer the response
While undergoing screening for a clinical trial, Bob developed acute back pain when lifting furniture. Based on the skeletal findings, Bob was admitted to the hospital for evaluation, management and pain control.
What Is Bob’s Diagnosis and Plan?

- Anemia, renal insufficiency, and osteopenia were not thought to be related to MM.
- With multiple lytic lesions and vertebral compression fractures, treatment for active MM is necessary.
- What are the next steps?
  - Treatment decision-making: clinical trial vs. standard care options
  - Supportive care (bisphosphonates, antiviral antibiotics)
  - Financial and social support services

Rajkumar et al., 2014, IMWG working group guidelines for MM diagnosis
# Drugs Used to Treat MM

<table>
<thead>
<tr>
<th>Immuno-modulatory Drugs</th>
<th>Proteasome Inhibitors</th>
<th>Chemotherapy Anthracyclines</th>
<th>Chemotherapy Alkylators</th>
<th>Steroids</th>
<th>Histone Deacetylase Inhibitors</th>
<th>Monoclonal Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (PO)</td>
<td>Bortezomib (IV/SC)</td>
<td>Doxorubicin (IV)</td>
<td>Cyclophosphamide (IV, PO)</td>
<td>Dexamethasone (IV, PO)</td>
<td>Panobinostat (PO)</td>
<td>Elotuzumab (IV)</td>
</tr>
<tr>
<td>Lenalidomide (PO)</td>
<td>Carfilzomib (IV)</td>
<td>Liposomal doxorubicin (IV)</td>
<td>Bendamustine (IV)</td>
<td>Prednisone (PO)</td>
<td></td>
<td>Daratumumab (IV)</td>
</tr>
<tr>
<td>Pomalidomide (PO)</td>
<td>Ixazomib (PO)</td>
<td></td>
<td>Melphalan (PO)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bortezomib +/- lenalidomide and dexamethasone is a common standard of care for newly diagnosed MM patients in the US +/- transplant if eligible, and desire.
## Side Effects of Common Myeloma Drugs (1)

<table>
<thead>
<tr>
<th></th>
<th>Thalidomide</th>
<th>Lenalidomide</th>
<th>Pomalidomide</th>
<th>Bortezomib</th>
<th>Carfilzomib</th>
<th>Ixazomib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathy (PN)</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Thrombosis (DVT, PE)</strong></td>
<td>✓ more with dex</td>
<td>✓ more with dex</td>
<td>✓ more with dex</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Myelosuppression</strong></td>
<td>✓ neutro</td>
<td>✓ anemia, thrombo, neutro</td>
<td>✓ neutron, anemia, thrombo</td>
<td>✓ thrombo</td>
<td>✓ neutro, thrombo</td>
<td>✓ thrombo</td>
</tr>
<tr>
<td><strong>Cardiopulmonary</strong></td>
<td>✓ slow heart rate</td>
<td>✓ slow heart rate</td>
<td>✓ shortness of breath</td>
<td>✓ hypotension</td>
<td>✓ shortness of breath, other</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Fatigue, weakness</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>GI disturbance</strong></td>
<td>✓ constipation</td>
<td>✓ diarrhea, constipation</td>
<td>✓ diarrhea, constipation</td>
<td>✓ nausea, vomiting, diarrhea</td>
<td>✓ nausea, vomiting, diarrhea, constipation</td>
<td>✓ nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td><strong>VZV</strong></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* Subcutaneous or weekly administration of bortezomib reduces risk of PN

PN = peripheral neuropathy; DVT = deep vein thrombosis; PE = pulmonary embolism; dex = dexamethasone; Neutro = neutropenia (low white blood cell) count; Thrombo = thrombocytopenia (low platelets); GI = gastrointestinal

Prescribing information: thalidomide, lenalidomide, pomalidomide, bortezomib, carfilzomib.
## Side Effects of Common Myeloma Drugs (2)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Panobinostat</th>
<th>Elotuzumab</th>
<th>Daratumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion reaction</td>
<td></td>
<td>✓ ~ 10%</td>
<td>✓ ~ 40%</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>✓ neutro, thrombo</td>
<td></td>
<td>✓ neutro, thrombo</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>✓QT↑, arrhythmias, ischemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI disturbance</td>
<td>✓diarrhea, nausea, vomiting</td>
<td>✓diarrhea, nausea</td>
<td>✓diarrhea</td>
</tr>
</tbody>
</table>
How old is too old? What determines “correct” treatment?

• Many studies define elderly as >65
• Age is just a number
• Geriatric Assessment and Frailty
  • http://www.myelomafrailtycorecalculator.net/
• The correct treatment balances:
  • Performance status
  • Comorbid conditions
  • Discuss treatment goals
  • Desire for aggressive treatment
• Mutual agreement between patient, treatment team is recommended
VRd vs Rd: SWOG S0777 Data
3 vs 2-Drug Regimen as Initial Induction

VRd: Bortezomib IV
Lenalidomide PO
Dexamethasone
(x8 cycles)
(n = 264)

Rd

Len: 25 mg PO
Until progression

Primary endpoint: PFS

<table>
<thead>
<tr>
<th>Median PFS, mo</th>
<th>VRd</th>
<th>Rd</th>
<th>HR; P</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td></td>
<td>30</td>
<td>0.712; .0018 (1-sided)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>75</td>
<td>64</td>
<td>0.709; .025 (2-sided)</td>
</tr>
</tbody>
</table>

VRd showed better PFS in patients with high- or standard-risk disease vs Rd‡

*All patients received aspirin (325 mg/d).
†Patients received VZ prophylaxis.
‡High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.

ASCT = autologous stem cell transplantation; CR = complete response; ISS = International Staging System; OS = overall survival; R = randomized; Rd = lenalidomide, dexamethasone; SWOG = Southwest Oncology Group; VRd = bortezomib, lenalidomide, dexamethasone.
IFM 2009 Study: ASCT vs. No ASCT

**Newly-Diagnosed MM ≤ 65 years**

- **VRd x 3**
  - PBSC Collection
  - Melphalan 200 mg/m² + ASCT
  - VRd x 5
  - Maintenance lenalidomide for 1 year

- **VRd x 3**
  - PBSC Collection
  - VRd x 2
  - Maintenance lenalidomide for 1 year

**VRd x 3**

**VRd x 5**

**VRd x 2**

**Primary endpoint: PFS; OS data not yet mature.**

- **Transplant-related mortality: 1.7%**
- **Regardless of MRD status, PFS was prolonged in the ASCT arm vs the VRd arm**
- **More MRD-negative patients in the ASCT arm**

<table>
<thead>
<tr>
<th></th>
<th>VRd</th>
<th>ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>CR,* %</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Median PFS,† mo</td>
<td>36</td>
<td>50</td>
</tr>
<tr>
<td>4-year OS, %</td>
<td>82</td>
<td>81</td>
</tr>
</tbody>
</table>

*P = .03, †P < .001.

IFM = Intergroupe Francophone du Myélome; PBSC = peripheral blood stem cell; R = randomized.

Maintenance Therapy w/wo Transplant, Relapsed Treatment

• Updated lenalidomide maintenance
• Elotuzumab + len/dex after transplant\(^1\)
• Ixazomib-based induction followed by long-term ixazomib maintenance (overall response rate of 94%, including a complete response of 35%)\(^2\)
• KRd (carfilzomib/lenalidomide/dexamethasone) vs Rd~ the ASPIRE trial\(^3\)
  • Pts stayed in remission longer with 3 vs 2 drugs
• Pom/cyclophosphamide/dex in relapsed myeloma w/wo transplant (IFM 2013)\(^4\)

3. Stewart et al., 2017
Multiple Myeloma Is a Clonal Disease; Clones Change Over Time

- Effective MM treatment reduces or eliminates the dominant clone
- Other clones can still exist.
- Ongoing treatment to suppress clones

Update on Bob:
After 5 years of remission, M spike rises from undetectable (0) to 1.36g/dL

### Monitoring MM is Essential: The IMWG Myeloma Response Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sCR, stringent complete response</strong></td>
<td>Normal free light chain (FLC); no clonal BM plasma cells</td>
</tr>
<tr>
<td><strong>CR, complete response</strong></td>
<td>Negative IFX and &lt; 5% BM plasma cells</td>
</tr>
<tr>
<td><strong>VGPR, very good partial response</strong></td>
<td>Positive IFX and negative SPEP; &gt; 90% urine protein decrease; urine M-protein level &lt; 100 mg per 24 h</td>
</tr>
<tr>
<td><strong>PR, partial response</strong></td>
<td>&gt; 50% decrease serum M-protein and &gt; 90% decrease in 24 h urinary M-protein</td>
</tr>
<tr>
<td><strong>SD, stable disease</strong></td>
<td>Not meeting criteria for CR, VGPR, PR, or PD</td>
</tr>
</tbody>
</table>

- sCR AND BM negative by next gen flow \((10^6)\)
- CR AND normal FLC ratio, BM negative by flow, 2 measures
- CR AND negative PCR \((10^5)\)
- CR: Negative immunofix; <5% PC in BM; 2 measures

sCR = stringent complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; MR = minimal response (only in relapsed); PD = progressive disease.
# Choices at Relapse/After 1+ Prior Myeloma Therapies

<table>
<thead>
<tr>
<th>Newer FDA-approved after 1+ myeloma therapies*</th>
<th>Comments</th>
<th>Combinations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib</td>
<td>IV</td>
<td>KRd, Kd</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>oral</td>
<td>Pd</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>IV</td>
<td>ERd</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>IV+ IMiD/PI</td>
<td>DRd, DVd</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>oral</td>
<td>IRd</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>oral/IV</td>
<td>Pano-Vd</td>
</tr>
</tbody>
</table>

*Lenalidomide (R) and/or bortezomib (V) are used in 2nd line combinations

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**Data and Experience**
- Disease genetics, prior Tx
- Efficacy of regimen
- Comorbid conditions

**Patient Preference**
- Chair time
- Finances/insurance
- Social status/support

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**Choices at Relapse/After 1+ Prior Myeloma Therapies**
Factors in Selecting Treatment for Relapsed/Refractory Myeloma

- **Disease-related factors**
  - Duration of response to initial therapy
  - High/low risk status
  - Biochemical disease progression, or symptomatic?
  - Other comorbid conditions

- **Treatment-related factors**
  - Previous therapy exposure (relapsed or refractory)
  - Toxicity of regimen (combination vs single agent)
  - Mode of administration (e.g., oral or IV)
  - Cost and convenience (out of pocket copays for IV/oral)
When to Initiate Therapy at Relapse

Not every relapse requires immediate therapy

- Asymptomatic biochemical relapse on 2 consecutive assessments
  - Consider observation
  - Monitor carefully

- Asymptomatic high-risk disease or rapid doubling time or extensive marrow involvement
  - Consider treatment
  - Patient-/disease-specific
  - Monitor carefully

- Symptomatic or extramedullary disease
  - Initiate treatment

Strategies at Relapse: Start low, go slow...or “Go for it”?

Slow-Growing Myeloma in First Relapse
- If initial treatment with bortezomib, lenalidomide repeat or change therapy
- Ixazomib, carfilzomib, daratumumab, and elotuzumab are all considerations with len/dex or pom/dex?
- Consider if high/low risk disease at diagnosis

Treating Relapsed-Refractory Myeloma
- Any peripheral neuropathy or renal dysfunction?
- What has been tried (protease inhibitor-based, immunomodulatory imide drug (IMiD)-based)
- Are clinical trials available?

Aggressive Myeloma With Rapid, Multiple Relapses
- Transplant if not done (allo, auto)
- Chemotherapy-based salvage with aggressive clones is often necessary
- Monoclonal antibodies (MoAb) candidates

Remember to discuss goals and costs of therapy
Encourage health maintenance to maintain “fitness” for next therapy
Suggested Preferred Treatment Options for RR Myeloma: An Example Decision Tree

First relapse

- Not refractory to lenalidomide
  - DRd
  - KRd (Frail: IRd, ERd)
- Refractory to lenalidomide†
  - DVD
  - VCD (Frail: Pd, IPd)

Second or higher relapse

Preferred options

- Any first relapse options not yet used Pom-based regimens (KPd, DPd, etc), preferably include Dara

Additional options

- VTD-PACE
- Bendamustine-based regimens, adding panobinostat

RR = relapsed/refractory; Pom = pomalidomide; Dara = daratumumab; KRd = carfilzomib-lenalidomide-dexamethasone; IRd = ixazomib-lenalidomide-dexamethasone; ERd = elotuzumab-lenalidomide-dexamethasone; IPd = ixazomib-pomalidomide-dexamethasone; VCD = bortezomib-cyclophosphamide-dexamethasone; VTD-PACE = bortezomib-thalidomide-dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide.

Relapsed/Refractory MM: General Considerations

**Disease-Related**
- DOR to initial therapy
- FISH/Cytogenetics
- Rate
- Active vs biochemical

**Regimen-Related**
- Prior drug exposure
- Toxicity of regimen
- Mode of administration
- Previous SCT

**Patient-Related**
- Pre-existing toxicity
- Co-morbidities
- Age
- Performance status
Traditional Approach to Relapsed Disease

- **Indolent**
  - First
  - Slow and asymptomatic
  - Low /standard risk

- **Aggressive**
  - Multiple
  - Fast or symptomatic
  - High risk

**Treatment implications**
- Single agent / doublet
- Sequential vs combination therapies
- Emphasis on patient preference and convenience

**Treatment implications**
- Triplet or combination therapies
- Emphasis on efficacy
Possible Change in Paradigm for RRMM

- Combination therapy (triplets) shown to outperform (doublets) in relapsed setting in terms of response and PFS: e.g., ASPIRE\textsuperscript{1}, IFM 2005-04\textsuperscript{2}
- QOL data favors triplets in some situations (ASPIRE)\textsuperscript{1}
- CR rates high with novel agent triplets (ASPIRE)\textsuperscript{1} and MRD- noted (POLLUX)\textsuperscript{4}
- The “new triplets” combinations with monoclonal antibodies don’t have overlapping toxicities (ELOQUENT2 and POLLUX)\textsuperscript{3,4}

- Not many trials have examined sequential vs combination therapy (CRD vs RD + CD)
- Limited QOL data
- Limited data on OS

# Regimens Studied in RRMM

<table>
<thead>
<tr>
<th>Pomalidomide</th>
<th>Carfilzomib</th>
<th>Daratumumab</th>
<th>Elotuzumab</th>
<th>Ixazomib</th>
<th>Panobinostat</th>
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Carfilzomib: Proteasome Inhibitor

Carfilzomib+Rd
FDA approved July 2015

Carfilzomib+d 56 mg/m²
FDA approved January 2016

KRd mg/m²
FDA approved January 2016

Overall Survival (OS)
24-month OS favored KRd
(24-mo OS 73.3% KRd vs 65.0% Rd; P=.04)

Clinical pearls
– Avoid starting first cycle at the end of the week – dyspnea
– Hydration but not over hydration
– Premedication (dex)
– Aspirin prophylaxis
– Monitor blood counts, response
– Monitor for infection
– Herpes virus prophylaxis
– Know cardiac and pulmonary status
– Diuretics
ARROW Study Design

1:1 Randomization
N = 478
- Relapsed and Refractory MM
- 2-3 prior lines
- Prior exposure to IMiD & PI (except carfilzomib or oprozomib)
- PS 0-1
- CrCl of ≥30 mL/min

Stratification:
- ISS stage
- Refractory to bortezomib
- Age (<65 vs. ≥65)

Arm A: Once-weekly carfilzomib + dex
(30 min infusion of K)
- Carfilzomib 20 mg/m² IV D1 (Cycle 1)
- Carfilzomib 70 mg/m² IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
- Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
- Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Arm B: Twice-weekly carfilzomib + dex
(10 min infusion of K)
- Carfilzomib 20 mg/m² IV D1, 2 (Cycle 1)
- Carfilzomib 27 mg/m² IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
- Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
- Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Primary end point: PFS

Follow-up for Disease Status until Confirmed PD
Long-term Follow-up for Survival

CrCl = creatinine clearance; K = carfilzomib; PI = proteasome inhibitor.

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ARROW: PFS

<table>
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<th>Twice-weekly (n=238)</th>
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<tr>
<td>Progression/Death, n (%)</td>
<td>126 (53%)</td>
<td>148 (62%)</td>
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<tr>
<td>Median PFS, months</td>
<td>11.2</td>
<td>7.6</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.693 (0.544, 0.883)</td>
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<td>p-value (2-sided)</td>
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Number of Patients at Risk:

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<td>Months from Randomization</td>
<td>240</td>
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<td>4</td>
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Mateos MV et al. ASCO 2018 abstract 8000
Oral immunomodulatory agent (IMiD)

Administration
- Oral; Recommended with low-dose dex, take without food

Monitor
- Blood counts: neutropenia most frequent GR 3/4 AE, liver function, response

Patient education
- Adherence and REMS, Infection prevention, protect renal health
  - Hydration
  - Avoid NSAIDs, IV contrast, other drugs with renal interactions

AE = adverse event; GR = grade; pom = pomalidomide; REMS = Risk Evaluation and Mitigation Strategies; NSAID = non-steroidal anti-inflammatory drug.

Pomalidomide ± dex
FDA approved
February 2013

Carfilzomib + Pomalidomide ± dex
FDA approved
2017

DARA + Pomalidomide + dex
FDA approved
2018
Ixazomib: Oral Proteasome Inhibitor

Ixazomib+Rd
FDA approved
November 2015

• Administration
  • Oral capsule 1x per week; do not crush or chew capsules or open capsule
  • Empty stomach: 1 hr before or 2 hr after food
  • Adherence, schedule, viral prophylaxis; Rapid response (1.1 months); fast absorption (if vomit, do NOT repeat dose)
  • Cyclic thrombocytopenia, peripheral neuropathy, peripheral edema

Ixazomib: PFS improvement added to Rd

Median PFS:
IRd: 20.6 mo
Placebo-Rd: 14.7 mo
Median follow up: ~15 mo

Log-rank P = .012
HR (95% CI): 0.742 (0.587-0.939)
Number of events:
IRD 129; placebo-Rd 157

35% improvement in PFS for IRd vs. Rd
Clinical Pearls for Elotuzumab

- Antibody administration: Risk of infusion reaction: 10%
  - 3-24 hr before = Dex 28 mg;
    45-90 min before = Dex 8 mg IV, H1, H2 and acetaminophen
  - Infuse at rate of 0.5 mL/min and escalate to 5 mL/min
  - Give weekly for 8 weeks then twice monthly until PD
- Prescribed w/ len-dex
  - DVT prophylaxis (for len), steroid side effects & schedule (am vs. pm), shingles prevention
- Monitoring
  - Blood counts (hold/adjust dose if needed)
  - Response assessment (monthly)
  - Glucose (dex can affect), renal, hepatic function


Double median PFS in Kd arm compared to Vd (18.7 vs 9.4 months)
Daratumumab Mechanism

Daratumumab
FDA approved
November 2015

Daratumumab combinations
DRd DVd and DPd
FDA approved
2016, 2018

Premeds: corticosteroids, antipyretics, and antihistamine
t蒙特鲁卡斯特 and loratadine?

Post med: oral corticosteroid for 2 days after infusion

- Educate patients/caregivers about infusion expectations
  (schedule, reactions, etc)
- Infection risk
  - Herpes prophylaxis (acyclovir)
  - INTERFERENCE WITH CR and type, cross-match

Schedule:

- Weeks 1-9 weekly
- Weeks 9-24 every 2 weeks
- Weeks 25 on every 4 weeks

ADCC = antibody-dependent cell-mediated cytotoxicity
ADCP = antibody-dependent cellular phagocytosis
CDC = complement-dependent cytotoxicity
MAC = membrane attack complex

Bone and Bone-modifying Agents (BMAs)

- ASCO Guidelines recommend BMAs for all MM patients to decrease SREs
  - IV: pamidronate or zoledronic acid, give every 3-4 wk for up to 2 yr
  - SC: Denosumab non-inferior to ZA, safe in kidney disease
  - Consider a 3-mo interval during maintenance or inactive disease periods
  - Resume treatment with relapse if stopped
  - Monitor calcium and replete calcium and vitamin D - especially w/ denosumab
- BMAs are not recommended in patients with solitary plasmacytoma, SMM, or indolent MM unless evidence of osteoporosis, osteopenia
- Good dental hygiene and routine monitoring to minimize risk of ONJ
  - Dental exam prior to starting (if possible)
  - Withhold BMAs for major dental procedures
- Renal disease
  - Pamidronate and zoledronic acid are not recommended if severe renal insufficiency (GFR <30 mL/min). Consider denosumab.
- Supportive care: surgical intervention, radiation, pain control if SRE


SRE = skeletal-related events; ONJ = osteonecrosis of the jaw; ZA = zoledronic acid.
Amyloidosis
Amyloidosis: Overview

- Amyloidosis: extracellular tissue deposition of fibrils
- Composed of low-molecular-weight subunits (most of which are in the molecular weight range of 5 to 25 kD) of a variety of proteins
- These proteins often circulate as constituents of plasma.
- Hereditary and nonhereditary types
- GOAL: Improve speed with which diagnosis is made
Amyloidosis: Types AL and AA

**AL amyloid:** Deposition of protein derived from Ig light chain fragments
- Detectable M protein in serum or urine or sFLC in 98% of patients
- Accounts for approximately 80% in developed countries

**AA amyloid:** Chronic diseases in which there is ongoing or recurring inflammation (i.e., RA or spondyloarthropathy)
- Fibrils are composed of fragments of the acute phase reactant serum amyloid A

Other types: Dialysis related, senile (WT transthyretin), hereditary (mutant transthyretin or fibrinogen)
Amyloid and LCDD: Therapy

Current Treatment Paradigm: Target the Plasma Cell Clone to Reduce Light Chain Production
Primary (AL) Amyloidosis and Light and Heavy Chain Deposition Diseases

- Amyloid fibrils misfolding of a number of different proteins that form beta-sheet fibrils which are deposited extracellularly in various organs
  - These proteins range from immunoglobulin (Ig) light chains in primary systemic amyloidosis (AL can be identified on biopsy specimens both by their characteristic appearance on electron microscopy,
  - Congo red (leading to green birefringence under polarized light)
  - Thioflavine T (producing an intense yellow-green fluorescence)
Symptoms of Amyloidosis

- Heart
  - Congestive heart failure
  - Palpitations / arrhythmia
- Nerve
  - Numbness / tingling or pain in fingers and toes
  - Weakness
  - Autonomic

- Kidney
  - Swelling
  - “Foamy” urine

- Skin
  - Easy bruising or bleeding or tongue enlargement, “geographic tongue”
Index of Suspicion

- Non DM nephrotic syndrome
- Non ischemic restrictive cardiomyopathy
- Non DM neuropathy
- Atypical myeloma presentation
- Macroglossia and raccoon eyes are often late presentations
AL Amyloidosis Diagnosis

- Consider screening patients with plasma cell dyscrasia
  - 24-hour UPEP – high % albuminuria
  - NT pro BNP, Troponin T
  - – possible cardiac involvement
  - Echocardiogram if NT pro BNP is abnormal
    - Look for decreased % global strain
AL Amyloidosis Diagnosis

- Bone marrow biopsy
  - Stain for kappa or lambda in blood vessels, Congo red stain not always +
- Fat biopsy: usually + late in the disease, some early
- Laser microdissection and tandem mass spectrometry of amyloid affected tissue
Tests Suggested for Primary (AL) Amyloidosis: Cardiac

Cardiac manifestations may be absent, minor
- In 1/3 of patients, disease manifested by cardiac events
- Most common ECG abnormality in cardiac amyloidosis is low voltage in the limb leads (50%)
  ECHO may show LV wall thickening with evidence of diastolic dysfunction, granular, “sparkling” appearance of the myocardium, IVS thickness in more advanced disease
  Global strain
  Cardiac MRI - global and subendocardial late enhancement of the myocardium
- Endomyocardial biopsy definitive diagnosis
- OS 6-9 mo if heart failure > years with treatment

ECG = electrocardiogram; ECHO = echocardiogram; LV = left ventricular; IVS = interventricular septum.
Diagnosis Clues: Heart and Nerve

- Longitudinal strain pattern shows “apical sparing” Phelan Heart 2012
- LVH (thickening) on echocardiogram without LVH on EKG, low voltage EKG

LVH = left ventricular hypertrophy

Amyloid fibrils stain blue, light pink and encircle each heart cell

Images used with permission from Dr. Elizabeth Sagatys, Moffitt Cancer Center.
Tests Suggested for the Diagnosis and Monitoring of Primary (AL) Amyloidosis

- Some have systemic MM as well as AL amyloid
- SPEP, UPEP
- B\(_2\)M, CBC diff, CMP, ALB
- Monoclonal protein, blood and urine
- 24-hr urine for protein
- Skeletal survey to r/o lesions
- High sensitivity TNT assay – improves detection of cardiac involvement and powerful diagnostic determinant
- Serum free light chain assay – more sensitive for organ response
- Echocardiography, fat-pad aspirate “congo red stain”
- Thioflavin if endomyocardial bx
Treatment of Amyloidosis: AL and AA

Treat to prevent complications and further organ damage
No drugs FDA approved to treat AL amyloid but lots of good options for many
- Corticosteroids such as dexamethasone, melphalan, cyclophosphamide or lenalidomide or bortezomib
- Clinical trials with transplant, daratumumab, carfilzomib

Secondary AA can lead to renal failure d/t high circulating levels of Serum Amyloid A
- Treatment aim is to control primary disease, such as RA, Crohn’s disease; colchicine in familial Mediterranean fever (FMF)
Amyloidosis Case Presentation

• 58-year-old schoolteacher with acute on chronic renal insufficiency
• Past history of hypertension x 5 years, type 2 diabetes (DM2), and hyperlipidemia
• Presents to PCP with progressive shortness of breath and bilateral LE edema
Physical Examination

- General: in no acute distress but visibly dyspneic after ambulating to exam room from lobby
- CV: diastolic murmur but heart rate regular at 118 BPM
- Lungs: Clear
- Abdominal: No HSM, soft
- Ext: 2+ pitting edema
Labs

- CBC: WBC 9.5, Hgb 11.4, platelets 152K
- Chemistry: Albumin 2.7, creatinine 1.9, calcium 9.2
- Troponin: <0.01; NT-pro-BNP: 3600 (normal <150)
- Serum free light chains: lambda 3250 mg/L (normal 3.0-19.4)
- 24-hr urine: 86% albumin, 11.2 g/24 hr (NORMAL <.16) lambda light chain protein on immunofixation
- Bone marrow: 10% clonal lambda plasma cells; Congo red stain positive
Cardiac and Renal

- Echocardiogram shows diastolic dysfunction, thickened IVS (2.1); enlarged wall motion abnormality, global strain 9.2%
- Baseline creatinine less than 1.6 mg/dL; currently 2.2 mg/dL
- Renal insufficiency previously attributed to 5-year history of hypertension, but kidney biopsy showed amyloid deposits
Diagnosis and Treatment

- Diagnosis: Systemic AL amyloidosis, lambda light chain type
- Cardiology referral
  - Started on torsemide and beta-blocker
- Nephrology referral
- Nurse education re: diuretic management, heart failure
- Bortezomib, cyclophosphamide and dexamethasone
  - Watch blood sugars w/ T2DM history
- Evaluation for HSCT
Exciting Updates on Amyloidosis

• Dr. Giampaolo Merlini gave a key lecture on AL amyloidosis – unprecedented!

• Abstracts 507 and 508 (ASH 2017): Daratumumab in Previously-Treated Systemic Light-Chain (AL) Amyloidosis (Sanchorawala and Roussel et al.)

• Abstract 1819 (ASH 2017) Daratumumab Is Safe and Highly Effective in AL Amyloidosis (Khourii et al)
  • DARA is generally safe, well tolerated

• Pooled analysis of “IMiD” drugs

• Ixazomib in relapsed amyloid: hematologic (52%) and organ (56%) response rates (Sanchorwala et al. Blood 2017)
Importance of a Collaborative Approach to Plasma Cell Dyscrasias
Conclusion

• Explosion of new therapies to treat MM and are used to treat amyloidosis
• APPs are positioned to educate patients, identify and intervene side effects
• Knowledge of the drugs and class effects allow for better education, surveillance and continued therapy
• Research is needed to inform sequencing of agents and use of drugs in amyloidosis
This has been a SMARTIE presentation.
SMARTIE participants, you can now go to smartie2018.com or visit the SMARTIE booth to answer the post-session questions for this presentation.

If you would like more information about this program, please ask a conference staff member or visit the SMARTIE booth.