Recent Advances in the Treatment of Newly Diagnosed Multiple Myeloma

Edward Libby, MD
Josh Epworth, ARNP
University of Washington Medical Center
Financial Disclosures

• Dr. Libby has no significant financial disclosures.
• Mr. Epworth has no significant financial disclosures.
Learning Objectives

1. Interpret data on current and novel treatments for multiple myeloma (MM)
2. Select initial therapy for MM based on patient risk and alignment with guidelines and best practices
3. Employ best strategies for management of adverse events associated with MM therapies
4. Evaluate recent advances related to use of minimal residual disease testing in patients with MM
What Is Multiple Myeloma?

A malignancy characterized by clonal proliferation of terminally differentiated plasma cells within the bone marrow
Multiple Myeloma Statistics

- Estimated new cases in 2019: 32,110 (1.8%)
- Estimated deaths in 2019: 12,960 (2.1%)
- Prevalence in 2016: 131,392 in US (18% of all hematologic malignancies)
- Percentage of patients surviving 5 years (2009-15): 52.2%

Signs and Symptoms at Presentation

**Subjective**
- Bone pain
- Frequent infections
- Fatigue
- Unintentional weight loss
- Foaming urine
- Easy bruising and bleeding

**Objective**
- Hypercalcemia
- Elevated creatinine
- Anemia
- Bone fractures, lesions, soft tissue masses
- Pancytopenia
- Elevated serum protein levels
How to Diagnose MM
Case Study 1

• TM is a 60-year-old highly active male who presented to OSH ED with dyspnea following minimal exertion, normally very active

• In ED exhibited the following:
  • Tachycardia and AFib
  • Volume overload
  • Elevated D dimer
Case Study 1

• TM is a 60-year-old highly active male who presented to OSH ED with dyspnea following minimal exertion, normally very active

• In ED exhibited the following:
  • Tachycardia and AFib
  • Volume overload
  • Elevated D dimer
  • CT angiogram of chest exhibited incidental finding of lytic lesions in T and L spine as well as ribs
Labs, Imaging, and Biopsy for NDMM Workup

**Labs**
- Serum protein electrophoresis
- Urine protein electrophoresis
- Serum immunofixation
- Serum free light chains
- Complete blood count
- Comprehensive metabolic panel
- Lactate dehydrogenase
- Beta 2 microglobulin

**Imaging**
- Whole body low-dose CT
- or
- FDG PET/CT
- or
- Bone marrow MRI*

**Bone Marrow Biopsy**
- Morphology
- Flow cytometry
- Cytogenetics
- FISH array
- Molecular testing
Monoclonal Protein/M-Spike

- Present in approximately 85% of patients
- Made by abnormal plasma cells and detected in serum and/or 24-hour urine. Also referred to as a paraprotein.
- Testing: SPEP or UPEP
- No detectable M-spike 15% (non-secretory)
- Can detect by serum free light chains in these cases

SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis
Bone Marrow Biopsy
<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osseous (Skeletal) Survey</td>
<td>A patient-friendly, fast, low radiation scan without IV contrast that depicts bone damage. Excellent for radiation therapy planning and <strong>evaluation of the stability of bony structures and fractures</strong>.</td>
</tr>
<tr>
<td>MRI Bone Marrow</td>
<td>Not very patient friendly; long time on scanner required, <strong>highly sensitive for early bone damage</strong> without radiation. Detects pathological fractures and cord compression. Per NCCN guidelines if the whole body low-dose CT or PET/CT is negative, consider this modality to discern smoldering multiple myeloma from multiple myeloma.</td>
</tr>
<tr>
<td>PET/CT Whole Body</td>
<td>A critical tool for <strong>assessing for the presence of extramedullary disease</strong>. Detects active bone lesions and measures level of disease metabolic activity.</td>
</tr>
<tr>
<td>Whole Body Low-Dose CT</td>
<td>A head-to-toe group of x-rays. Inexpensive and widely available. Has a 30% failure rate of detecting lesions that can be found on bone marrow MRI.</td>
</tr>
</tbody>
</table>

Precursors to Symptomatic Multiple Myeloma

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Serum M protein < 3 g/dL and clonal bone marrow plasma cells < 10% and no myeloma defining events or amyloidosis

Progression rate to MM in 5 years: 1% per year

Smoldering Multiple Myeloma

- Serum protein ≥ 3 g/dL or urinary protein ≥ 500 mg/24 hours and/or clonal bone marrow plasma cells 10%-59% and no myeloma defining events

Progression rate to MM in 5 years: 10% per year

Myeloma Defining Events

Any one of the following creates a diagnosis of multiple myeloma

- BM biopsy > 60% (Y/N)
- Involved vs. uninvolved free light chain ratio ≥ 100:1 (Y/N)
- > 1 focal lesion by MRI ≥ 5 mm (Y/N)

CRAB Criteria

≥ 10% clonal cells in bone marrow or biopsy proven plasmacytoma PLUS one or more of the following creates a diagnosis of multiple myeloma

Ca: 1 mg/dL over ULN or > 11 mg/dL
Cr: > 2 mg/dL or CrCl < 40 mL/min
Hgb: > 2 g/dL below LLN or < 10 g/dL
Bone lesions (Y/N)

Bone Marrow Biopsy: Diagnosis

Hematopathology

Detects the level of plasma cell neoplasm in bone marrow. Presents the percentage of marrow cellularity occupied by disease. Percentage of plasma cells: Normal range is 1%-2%.
A Positive Diagnosis of Multiple Myeloma, by Either CRAB Criteria or a Myeloma Defining Event, Is the Trigger to Start Treatment
Newly Diagnosed Multiple Myeloma: Case Study

• TM is a 60-year-old highly active male who presented to OSH ED with dyspnea following minimal exertion, normally very active.

• In ED exhibited the following:
  • Tachycardia and AFib
  • Volume overload
  • Elevated D dimer
  • CT scan exhibits lytic lesions
Newly Diagnosed Multiple Myeloma: Case Study

MDE
BM: 30%
FLCR: 67.66
Lesions: No

CRAB
Ca: 9.5 (C: 8.86)
Cr: 1.25
Hb: 14.7
Lesions: Yes

Immunology
M-spike: 1.6 g/dL
KFLC: 39.24 mg/dL
Immunofixation: IgG
Ratio: 67.7

Bone Marrow
30% abnormal plasma
Normal cytogenetics

Imaging
Osseous Survey: Multiple lytic lesions in thoracic and cervical spine. Lytic lesions throughout bilateral femur including a 2.3 x 7.5 cm lytic lesion in right proximal diaphysis with greater than 50% thinning of medial femoral cortex.
Staging and Prognosis in Multiple Myeloma

Beta 2 Microglobulin
Albumin
LDH
Genetics
# Staging and Prognosis in Multiple Myeloma

<table>
<thead>
<tr>
<th>Revised International Staging System (R-ISS)</th>
<th>Similar to ISS but incorporates factors including serum LDH and the high-risk chromosomal abnormalities del(17p), t(4;14) and/or t(14;16) by FISH</th>
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<td>Utilizes data from the serum beta-2 microglobulin and serum albumin to determine three stages with prognostic significance</td>
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<td>Durie-Salmon</td>
<td>Staging determined by measurements of tumor cell density in bone marrow combined with assessments of renal function, serum calcium levels, anemia, and presence of bony lesions. Questionable as a method of predicting prognosis.</td>
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Revised International Staging System (R-ISS)

Similar to ISS but incorporates factors including serum LDH and the high-risk chromosomal abnormalities del(17p), t(4;14) or t(14;16) by FISH

**R-ISS I:** B2M < 3.5 mg/L and serum albumin ≥ 3.5 g/dL, normal LDH and the absence of del(17p), t(4;14) or t(14;16) by FISH on BM. Estimated PFS at 5 years 55% and OS at 5 years 82%

**R-ISS II:** Neither stage I or III. Estimated PFS 42 months, estimated OS 83 months.

**R-ISS III:** B2M ≥ 5.5 mg/L and LDH is greater than normal limits and or the detection of del(17p), t(4;14) or t(14;16) by FISH on BM. Estimated PFS 29 months, estimated OS 43 months.

**mSMART 3.0: Classification of Active MM**

**High-Risk**
- High Risk genetic Abnormalities
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High Plasma Cell S-phase
- GEP: High risk signature

**Standard-Risk**
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)

**Double Hit Myeloma:** Any 2 high risk genetic abnormalities

**Triple Hit Myeloma:** 3 or more high risk genetic abnormalities

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www.msmart.org
Survival by R-ISS of NDMM Patients

Treating Newly Diagnosed Multiple Myeloma
Treating Multiple Myeloma

“The significant challenge of current myeloma management is matching the progress made in improved survival through disease control while optimizing quality of life with effective supportive care from initial diagnosis to end-of-life care.”

Front-Line Treatment

- RVd
- DRd
- KRd
- DVMP
- RVd Lite
- Studies
- Transplant
- Radiation
<table>
<thead>
<tr>
<th>R</th>
<th>Lenalidomide: 25 mg PO on days 1-14</th>
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<tbody>
<tr>
<td>V</td>
<td>Bortezomib: 1.3 mg/m² SC on days 1, 4, 8, 11</td>
</tr>
<tr>
<td>D</td>
<td>Dexamethasone: 20 mg PO on days 1, 2, 4, 5, 8, 9, 11, 12 OR 40 mg PO on days 1, 8, 15</td>
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</tbody>
</table>

**Maintenance**: Bortezomib 1.3 mg/m² SC every other week OR Lenalidomide 10 to 15 mg days 1-21 of 28 days

Carfilzomib, Lenalidomide, and Dexamethasone (KRd) for High-Risk NDMM 28-Day Cycle (Transplant Eligible)

**K**
Carfilzomib: Once or twice weekly dosing starting on C1 days 1&2, 20 mg/m², then increasing up to 27 mg/m² or 70 mg/m² respectively.

**R**
Lenalidomide: 25 mg PO on days 1-21

**D**
Dexamethasone: 40 mg PO on days 1, 8, 15, 22

**Maintenance**: Carfilzomib once or twice weekly every other week or consider KRd maintenance

### Lenalidomide, Bortezomib, Dexamethasone (RVd-Lite) 35-Day Cycle (Transplant Ineligible)

**R**
- Lenalidomide: 15 mg PO on days 1-21

**V**
- Bortezomib: 1.3 mg/m² SC on days 1, 8, 15, 22

**D**
- Dexamethasone: 20 mg PO on days 1, 8, 15, 22

**Maintenance**: Bortezomib 1.3 mg/m² SC every other week OR Lenalidomide 1-21 of 28 days

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# Daratumumab, Lenalidomide, Dexamethasone (DRd) 28-Day Cycle (Transplant Ineligible)

<table>
<thead>
<tr>
<th></th>
<th>Daratumumab: 16 mg/kg (Cycles 1-2) weekly, (C 3-6) EOW, (C7+) monthly</th>
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<tbody>
<tr>
<td>D</td>
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</tbody>
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Continue treatment until toxicity or progression of disease

## Daratumumab, Bortezomib, Melphalan, Prednisone (DVMP) 42-Day Cycle (Transplant Ineligible)

| D | Daratumumab: 16 mg/kg (Cycle 1-6) weekly, (C 2-9) EOW, (C10+) monthly |
| V | Bortezomib: 1.3 mg/m² SC: (C1) twice weekly weeks 1, 2, 4, 5, (C2-9) once weekly 1, 2, 4, 5 |
| M | Melphalan: 9 mg/m² PO days 1-4 of each cycle |
| P | Prednisone: 60 mg/m² PO days 1-4 of each cycle |

VMP stops after Cycle 9, daratumumab continues treatment until toxicity or progression of disease

Transplant: Autologous

- Factors for eligibility: age, performance status, comorbidities
- Transplant pathway
  - 4-6 cycles of induction therapy
  - High-dose melphalan conditioning
  - Transplant
  - Maintenance
- Patients who had upfront ASCT had a greater PFS and response rate compared with those who deferred transplant—no change in OS

Managing Side Effects
Managing Side Effects

- Bone disease
- Hypercalcemia
- Pain
- Anemia
- Coagulation/Thrombosis
- Infection
<table>
<thead>
<tr>
<th>Bone Disease</th>
<th><strong>Strengthening</strong></th>
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<tbody>
<tr>
<td></td>
<td>• Zoledronic acid</td>
</tr>
<tr>
<td></td>
<td>• Pamidronate</td>
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<tr>
<td></td>
<td>• Denosumab</td>
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<table>
<thead>
<tr>
<th>Assessments</th>
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<tbody>
<tr>
<td>Dental exam (monitor for ONJ)</td>
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<table>
<thead>
<tr>
<th>Orthopedic consult</th>
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<tbody>
<tr>
<td>• Impending or actual bone fractures</td>
</tr>
<tr>
<td>• Spinal cord compression</td>
</tr>
<tr>
<td>• Vertebral column instability</td>
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<table>
<thead>
<tr>
<th>Hypercalcemia</th>
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</thead>
<tbody>
<tr>
<td>• Hydration</td>
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<tr>
<td>• Bisphosphonates</td>
</tr>
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<table>
<thead>
<tr>
<th>Pain</th>
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<tbody>
<tr>
<td>• Short/long-acting opioids</td>
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<tr>
<td>• Radiation</td>
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<table>
<thead>
<tr>
<th>Anemia</th>
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<tbody>
<tr>
<td>• Transfusions</td>
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<tr>
<td>• Erythropoietin</td>
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<table>
<thead>
<tr>
<th>Coagulation/Thrombosis</th>
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<tbody>
<tr>
<td>• ASA (81-325 mg)</td>
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<td>• DOAC</td>
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<table>
<thead>
<tr>
<th>Peripheral Neuropathy</th>
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<tr>
<td>Monitor, dose change</td>
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<table>
<thead>
<tr>
<th>Infection</th>
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<tbody>
<tr>
<td>• Monitoring of CBC with neutrophils</td>
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<p>| |</p>
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<tbody>
<tr>
<td>• Review infection risk reduction</td>
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<tr>
<td>• Test for hepatitis B prior to start of daratumumab</td>
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<tbody>
<tr>
<td>• Herpes zoster prophylaxis with use of proteasome inhibitor or daratumumab/elotuzumab</td>
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<tbody>
<tr>
<td>• Re-vaccinate ASCT 6-12 months post-transplant</td>
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</tbody>
</table>
Case Study: X-Ray of Right Femur
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Treatment</th>
<th>SE Management</th>
</tr>
</thead>
</table>
| **Diagnosis**  
IgG Kappa multiple myeloma with lytic lesions | **Prognosis**  
- R-ISS Stage I  
- B2M: 1.8  
- Albumin: 4.8  
- LDH: 242  
- No high-risk genetics  
- Median OS 62 months | **Treatment**  
- RVd 6 cycles to VGPR  
- VRD-PACE  
- (melphalan) ASCT  
- Lenalidomide maintenance | **SE Management**  
- Zoledronic acid 2 years  
- Ortho consult with rod stabilization  
- Radiation  
- Opioid pain meds  
- ASA 81 mg  
- Acyclovir with PI  
- Mild paresthesia tips of toes |
Case Study (cont.)

- Patient is currently 2 years status post ASCT, receiving lenalidomide 15 mg days 1-21/28. Mild fatigue, no other significant maintenance related side effects. Will continue maintenance until progression of disease or toxicity.

- Continues in his VGPR, he is assessed with monthly labs and clinical assessment and continues to exhibit disease stability with no indications of progression of disease by labs, ROS, or physical exam.

- Has returned to his active lifestyle with modifications in weight training.
Suggested Reading

• Induction Therapy for Newly Diagnosed Multiple Myeloma, DOI: 10.1200/EDBK_238527 American Society of Clinical Oncology Education Book.

Response in Myeloma: Current Definitions and Future Trends

- Partial response (PR)
  - ≥ 50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h
  - If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.
  - If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%.
  - In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
Response in Myeloma: Current Definitions and Future Trends (cont.)

• Very good partial response (VGPR): ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h.

• Complete response (CR): Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates.

• Stringent complete response (sCR): Complete response plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells).
Minimal Residual Disease (MRD) Testing

• New concept in myeloma
• Measurement of residual myeloma cells in marrow after chemotherapy and/or transplant
• Can be done by flow cytometry or using next-generation sequencing (genetic testing)
• Sensitivity between 10^-5 and 10^-6
• Most sensitive technology (NGS) can detect one cancer cell out of 1,000,000 normal cells
• Goal is for patient to be **MRD negative or no residual disease**
Depth of Response Matters

Start of chemo
Multiple Myeloma Treatment: The Foreseeable Future
Belantamab Mafodotin (GSK 2857916)

- Antibody drug conjugate
- Many similarities to brentuximab vedotin for Hodgkin disease
- 60% response rate in heavily pretreated patients with RRMM
- 30% response rate in penta-refractory patients (daratumumab refractory)
- IV every 3 weeks
- Thrombocytopenia and keratitis
Belantamab mafodotin (GSK 2857916)
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GSK 2857916
Belantamab mafodotin
antibody drug conjugate

Monomethyl auristatin F (MMAF)
(microtubule-disrupting agent)
New Drugs

- BiTEs – bispecific antibodies
- Early in development
- Can be administered over and over
- Blinatumomab, approved for acute lymphoblastic leukemia, is a BiTE
- Many companies are developing BiTEs
New “Living” Drug

- CAR T cells
- Possibly will be approved for myeloma in 2020
- Administered once only at this time
- Many companies are developing CAR T cells
bb2121

- 33 patients
- Hematologic toxic effects were the most common events of grade 3 or higher, neutropenia (85%), leukopenia (58%), anemia (45%), thrombocytopenia (45%)
- 25 patients (76%) had cytokine release syndrome, grade 1-2 in 23 patients (70%) and grade 3 in 2 patients (6%)
- Neurologic toxic effects occurred in 14 patients (42%) and were of grade 1 or 2 in 13 patients (39%)
- One patient (3%) had a reversible grade 4 neurologic toxic effect
- Response rate 85%, 15 patients (45%) had complete responses
- Six of the 15 patients who had a complete response have relapsed
- Median PFS 11.8 months
- CAR T-cell expansion was associated with responses, and CAR T cells persisted up to 1 year after the infusion

Next-Generation Immunomodulatory (IMiD) Drugs

- First generation: thalidomide; second generation: lenalidomide; third generation: pomalidomide
- **Iberdomide** under study
- Cereblon E3 ligase modulator
- Phase 1/2 study presented at the IMW in Boston in Sept. 2019 of 27 patients with RRMM (all RR to daratumumab and pomalidomide), ORR was 29.6%, comprising a 3.7% VGPR and a 25.9% PR
More Questions?

Come see us at Booth #829 (next to the APSHO Booth) in the Exhibit Hall from 12:10 to 1:00 today
This has been a SMARTIE presentation.

To access your post-session questions, you can:

- Click on the link that was sent to you via email
- Visit the SMARTIE station
- Go to jadprolive.com/smartie2019