Don’t Forget Multiple Myeloma
Activity Overview

This activity will give an overview of Myeloma, how to catch it early, characteristics that put patients at higher risk (age, race and gender) and treatment.

Target Audience

This activity is intended for primary care physicians.

Instructions to Receive Credit

To receive credit, read the introductory CME material, watch the webcast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Med-IQ and Roswell Park. Med-IQ is accredited by the ACCME to provide continuing medical education for physicians.

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Roswell Park Comprehensive Cancer Center
Chief of Myeloma
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Buffalo, NY
<table>
<thead>
<tr>
<th>Activity Planners</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ashley Snowden</strong></td>
</tr>
<tr>
<td>Director, Physician and Corporate Relations</td>
</tr>
<tr>
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</tr>
<tr>
<td>Elm &amp; Carlton Streets</td>
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<td>Roswell Park Cancer Institute</td>
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<td>Buffalo, NY</td>
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</tr>
<tr>
<td>Accreditation Manager</td>
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<tr>
<td>Med-IQ</td>
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<tr>
<td>Baltimore, MD</td>
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<tr>
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<tr>
<td>Director of CME</td>
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<tr>
<td>Med-IQ</td>
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<tr>
<td>Baltimore, MD</td>
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</tbody>
</table>
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Disclosure Statement

The content of this activity has been peer reviewed and has been approved for compliance. The faculty and contributors have indicated the following financial relationships, which have been resolved through an established COI resolution process, and have stated that these reported relationships will not have any impact on their ability to give an unbiased presentation.

Jens Hillengass, MD, PhD, has indicated no real or apparent conflicts.

The peer reviewers and activity planners have no financial relationships to disclose.
Don’t Forget Multiple Myeloma
Learning Objectives

Upon completion, participants should be able to:

• Review the characteristics that place patients in high risk for Multiple Myeloma

• Identification of the possible treatment paths for patients with Multiple Myeloma

• Identifying differences between common symptoms vs multiple myeloma
Multiple Myeloma

- **malignant** disease
- median age at diagnosis: **69 years**; M : F = 3 : 2
- proliferation of **plasma cells in bone marrow**
- **Incurable** in the vast majority of patients
- 5 year survival **50-75%** (SEER/ RPCCC)
- **30,000 new cases/year** (1.8% of cancers in the US)

Pathophysiology

- Replacement of physiological hematopoiesis
- Bone destruction
- Hypercalcemia
- Renal insufficiency
Patient reports that he felt very well until 04/2018. He is a Marathon runner and does exercise 4-5 times a week. In 04/18 he started to feel fatigued and experienced bone pain mostly in the thoracic spine, the lower back and the ribs. X-ray at that time didn't show any abnormalities. He also had an infection of the upper respiratory tract and an episode of diaphoresis. Further work-up because of increasing - now severe pain led to a CT chest/abdomen/pelvis revealed several small lytic lesions in the skeleton and compression fractures of T6, T9, L1 and L4 and a rib fracture.
Challenge: High Prevalence of Back Pain

- 15% to 20% of adults have back pain during a single year
- 50% to 80% of at least one episode of back pain during a lifetime
- 60% recover in 1 to 3 weeks;
- 90% recover in 6 to 8 weeks; and
- 95% recover in 12 weeks.
- **Serious** causes of low back pain (e.g. cancer) are **uncommon** (less than 1%)
Factors That Should Make a Provider Think of Myeloma

- Sudden onset, severe, persistent, exacerbating bone pain
- Additional symptoms:
  - Fatigue (anemia)
  - Frequent infections
  - Kidney issues
  - Neurological issues (hypercalcemia, peripheral Neuropathy)

=> Weight loss and B-symptoms are uncommon

---

Racial Differences

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Myeloma

- **MALE**
  - All Races: 8.3
  - White: 7.8
  - Black: 15.9
  - Asian / Pacific Islander: 4.7
  - American Indian / Alaska Native: 5.0
  - Hispanic: 7.7
  - Non-Hispanic: 8.4

- **FEMALE**
  - All Races: 5.2
  - White: 4.6
  - Black: 11.4
  - Asian / Pacific Islander: 3.2
  - American Indian / Alaska Native: 5.2
  - Hispanic: 4.9
  - Non-Hispanic: 5.3

SEER 18 2010-2014, Age-Adjusted

Age Distribution

Percent of New Cases by Age Group: Myeloma

Myeloma is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

69

SEER 18 2010-2014, All Races, Both Sexes

Racial Differences and Age

- White: Median = 71
- African American: Median = 66
- Asian: Median = 69
- Hispanic Median: = 65

N=37,963
p<0.001

Disease Presentation


Prevalence of MM-Related Complications by Race

At-Diagnosis

- Hypercalcemia: p<0.019
- Renal Dysfunction: p<0.001
- Anemia: p<0.001
- Fractures: p<0.001
- Dialysis: p<0.018

After-Diagnosis

- Hypercalcemia: p<0.001
- Renal Dysfunction: p<0.001
- Anemia: p<0.001
- Fractures: p<0.001
- Dialysis: p<0.001
Familial Risk

<table>
<thead>
<tr>
<th>Family History of Cancer</th>
<th>White Case, n (%)</th>
<th>White Control, n (%)</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>Black Case, n (%)</th>
<th>Black Control, n (%)</th>
<th>OR (95% CI)</th>
<th>p</th>
<th>Total Population OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Family History of Cancer</td>
<td>17 (11.1)</td>
<td>42 (16.1)</td>
<td>1.0 (reference)</td>
<td>0.062</td>
<td>20 (19.2)</td>
<td>61 (31.0)</td>
<td>1.0 (reference)</td>
<td>0.012</td>
<td>1.97 (1.28–3.04)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any Cancer</td>
<td>136 (88.9)</td>
<td>219 (83.9)</td>
<td>1.84 (0.97–3.48)</td>
<td>0.062</td>
<td>84 (80.8)</td>
<td>136 (69.0)</td>
<td>2.15 (1.18–3.90)</td>
<td>0.012</td>
<td>1.97 (1.28–3.04)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any Hematologic Malignancy</td>
<td>41 (26.8)</td>
<td>46 (17.6)</td>
<td>1.77 (1.08–2.91)</td>
<td>0.022</td>
<td>16 (15.4)</td>
<td>15 (7.6)</td>
<td>2.43 (1.13–5.22)</td>
<td>0.023</td>
<td>1.89 (1.25–2.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>11 (7.2)</td>
<td>10 (3.8)</td>
<td>2.04 (0.83–5.04)</td>
<td>0.120</td>
<td>9 (8.7)</td>
<td>1 (0.5)</td>
<td>20.9 (2.59–168)</td>
<td>0.004</td>
<td>3.75 (1.75–8.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematologic Malignancy Excluding Myeloma</td>
<td>34 (22.2)</td>
<td>38 (14.6)</td>
<td>1.71 (1.01–2.89)</td>
<td>0.047</td>
<td>8 (7.7)</td>
<td>15 (7.6)</td>
<td>1.09 (0.44–2.71)</td>
<td>0.855</td>
<td>1.48 (0.94–2.32)</td>
<td>0.090</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (NHL)</td>
<td>13 (8.5)</td>
<td>15 (5.8)</td>
<td>1.71 (0.78–3.76)</td>
<td>0.179</td>
<td>2 (1.9)</td>
<td>5 (2.5)</td>
<td>0.81 (0.15–4.33)</td>
<td>0.801</td>
<td>1.47 (0.73–2.97)</td>
<td>0.283</td>
</tr>
<tr>
<td>Hodgkin Lymphoma (HL)</td>
<td>3 (2.0)</td>
<td>3 (1.2)</td>
<td>1.81 (0.36–9.20)</td>
<td>0.474</td>
<td>2 (1.9)</td>
<td>3 (1.5)</td>
<td>1.53 (0.25–9.42)</td>
<td>0.647</td>
<td>1.65 (0.49–5.50)</td>
<td>0.418</td>
</tr>
<tr>
<td>Leukemia</td>
<td>20 (13.1)</td>
<td>23 (8.8)</td>
<td>1.52 (0.78–2.94)</td>
<td>0.218</td>
<td>4 (3.9)</td>
<td>9 (4.6)</td>
<td>0.84 (0.25–2.85)</td>
<td>0.777</td>
<td>1.26 (0.71–2.23)</td>
<td>0.427</td>
</tr>
<tr>
<td>Any Solid Tumor</td>
<td>127 (83.0)</td>
<td>207 (79.3)</td>
<td>1.56 (0.90–2.71)</td>
<td>0.112</td>
<td>74 (71.2)</td>
<td>127 (64.5)</td>
<td>1.55 (0.91–2.66)</td>
<td>0.107</td>
<td>1.55 (1.06–2.27)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Minimal diagnostic requirements to differentiate monoclonal plasma cell disorders?

Individual/ family **history** (hemato-oncological diseases in 1. degree relatives)

**Lab results**
- Differential **blood count**
- Biochemistry (liver/ **renal function**, electrolytes, albumin, beta2 MG, LDH, CRP)
- Monoclonal Protein in serum and urine (Gel **electrophoresis** + immunofixation)
- Nephelometric quantitation of immunoglobulins
- 24h urine collection (kappa/ lambda light chain concentration)
- **Serum free light chain** assay

### Stages of Monoclonal Plasma Cell Disease

<table>
<thead>
<tr>
<th></th>
<th>Monoclonal Gammopathy of Undetermined Significance</th>
<th>Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>clonal plasma cells in bone marrow</td>
<td>&lt;10%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>monoclonal protein</td>
<td>&lt;30g/l</td>
<td>&gt;30g/l</td>
</tr>
<tr>
<td>End organ damage</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>YES</td>
</tr>
</tbody>
</table>

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Incidences of MGUS

Figure 1. Prevalence of MGUS According to Age.
The I bars represent 95 percent confidence intervals. Years of age greater than 90 have been collapsed to 90 years of age.
Progression Risk

Kyle RA et al. NEJM. 2007; 356: 2582-2590
Course of Disease

Landgren O et al. JAMA. 2010; 304:2397-2404
### Table 11. Radiographic Findings in Patients With Multiple Myeloma (N=1005)

<table>
<thead>
<tr>
<th>Finding</th>
<th>% of patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lytic lesions</td>
<td>66</td>
</tr>
<tr>
<td>Pathologic fractures</td>
<td>26</td>
</tr>
<tr>
<td>Compression fracture</td>
<td>22</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>23</td>
</tr>
<tr>
<td>Osteosclerosis</td>
<td>0.5</td>
</tr>
<tr>
<td>Negative</td>
<td>21</td>
</tr>
</tbody>
</table>

*Total is more than 100% because many patients had more than 1 abnormality.

CT pos X-ray neg
**IMWG Criteria (2003)**

**MGUS**  
M-Protein < 30 g/l; clonal plasma cells < 10%; no „ROTI“*

**smoldering MM**  
M-Protein ≥ 30 g/l and/ or clonal plasma cell ≥ 10%; no „ROTI“*

**symptomatic MM**  
M-protein in serume and/ or urine; clonal plasma cells or plasmacytoma and ROTI* including bone lesions

**ROTI**  
1. Calcium level > 2.75 mmol/l  
2. Renal insufficiency (Kreatinin > 173 mmol/l oder 2.0 mg/dl)  
3. Anemia (hemoglobin < 10 g/dl)  
4. Bone lesions (lytic lesions or osteoporosis with fracture (CT or MRI)

**Others:** symptomatic hyperviscosity; amyloidosis; recurrent bacterial infections (> 2 episodes in 12 months)
IMWG Criteria (2014)

- Clonal bone marrow plasma cells ≥10% or biopsy proven plasmacytoma (not M-protein) and

ANY ONE OR MORE OF THE FOLLOWING MYELOMA DEFINING EVENTS (MDE)

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder. specifically
  - **Hypercalcemia:** Serum calcium >0.25 mmol/L above upper limit of normal or > 2.75 mmol/L (>1mg/dL above upper limit of normal)
  - **Renal insufficiency:** Creatinine Clearance <40 ml/min or Serum creatinine > 173 µmol/L (>2mg/dL)
  - **Anemia:** Normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL
  - **Bone lesions:** Lytic lesions, or osteoporosis with compression fractures detected by X-ray, CT or PET-CT

- Any one or more of the following biomarkers of malignancy
  - Clonal bone marrow plasma cell percentage ≥ 60% (IHC, Flow, Immunofluorescence)
  - Involved/uninvolved serum free light chain ratio ≥100 and involved FLC ≥100 mg/L
  - >1 focal lesions on magnetic resonance imaging studies

**SLIM-CRAB**
Plasma Cells in Bone marrow
Improvement of Overall Survival

Approved Treatments of Myeloma

1962
- Melphalan

1968
- Melphalan + Prednisone

1980
- High Dose Melphalan + BMT

1984
- VAD

1984
- Supportive Care

1990
- Single ASCT

1994
- Thalidomide

1999
- Single ASCT

2000
- Tandem ASCT

2002
- Bortezomib

2004
- Lenalidomide

2004
- Panobinostat

2005
- Ixazomib

2009
- Thalidomide

2013
- Pomalidomide

2014
- Carfilzomib

2015
- Daratumumab

2015
- Elotuzumab

2015
- Durvalumab

2020
- Brentuximab-Mafodotin

2020
- Isatuximab

2020
- Selinexor

2022
- Isatuximab - Mafodotin

Approved Treatments of Myeloma

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>Melphalan</td>
</tr>
<tr>
<td>1968</td>
<td>Melphalan + Prednisone</td>
</tr>
<tr>
<td>1980</td>
<td>High Dose Melphalan + BMT</td>
</tr>
<tr>
<td>1984</td>
<td>VAD</td>
</tr>
<tr>
<td>1984</td>
<td>Supportive Care</td>
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<tr>
<td>1990</td>
<td>Single ASCT</td>
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<td>2000</td>
<td>Tandem ASCT</td>
</tr>
<tr>
<td>2002</td>
<td>Bortezomib</td>
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<tr>
<td>2004</td>
<td>Lenalidomide</td>
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<tr>
<td>2013</td>
<td>Pomalidomide</td>
</tr>
<tr>
<td>2014</td>
<td>Carfilzomib</td>
</tr>
<tr>
<td>2015</td>
<td>Daratumumab</td>
</tr>
<tr>
<td>2015</td>
<td>Elotuzumab</td>
</tr>
<tr>
<td>2015</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>2020</td>
<td>Brentuximab-Mafodotin</td>
</tr>
<tr>
<td>2020</td>
<td>Isatuximab</td>
</tr>
<tr>
<td>2020</td>
<td>Selinexor</td>
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Package Inserts; NCI. Available at: https://www.cancer.gov/about-cancer/treatment/drugs/multiple-myeloma; Cancer.Net Multiple Myeloma: Latest Research
Newly Diagnose Myeloma

- Transplantation-eligible
  - age (?)
  - normal organ function
  - stem cells collected
  - patient choice

- Not transplant-eligible
  - age (?)
  - comorbidities
  - no stem cells
  - patient choice

UpToDate Available at: https://www.uptodate.com/contents/multiple-myeloma-treatment-beyond-the-basics#H5
First Line Treatment Transplant Eligible

- 4 x VRD or until best repose
- Stem cell collection
- 1-2 high dose melphalan + ASCT
- Lenalidomide Maintenance until Progression

**Alternatives:** VCD, PAD, KRD, IRD, VD, VTD, RD, VTD-PACE
First Line Treatment Transplant Ineligible

8 x VRD

Lenalidomide/ Dexamethasone until Progression

Daratumumab/ Lenalidomide/ Dexamethasone until Progression

Alternatives: Rd, VCD, KRD, KCD, IRD, VD

NCCN. Multiple Myeloma v3 2020
<table>
<thead>
<tr>
<th>Regimen/Trial</th>
<th>Patient characteristics</th>
<th>Best Response Post induction</th>
<th>Best Response on Study</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>ISS-3</td>
<td>High-risk</td>
</tr>
<tr>
<td>IFM2009 RVD-AHCT-RVD</td>
<td>350</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>FORTE KRD-AHCT-KRD</td>
<td>158</td>
<td>15%</td>
<td>33%</td>
</tr>
<tr>
<td>CASSIOPEIA DaraVTD-AHCT-DaraVTD</td>
<td>543</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>GRIFFIN DaraRVD-AHCT-DaraRVD</td>
<td>104</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>MASTER DaraK Rd-AHCT-DaraK Rd</td>
<td>81</td>
<td>20%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Risk and Safety Information

Adverse events experienced by more than 20% of participants in each study

IFM2009 RVD-AHCT-RVD: Neutropenia, thrombocytopenia, gastrointestinal disorders, infections
CASSIOPEIA DaraVDT-AHCT-DaraVDT: Neutropenia, thrombocytopenia, peripheral sensory neuropathy, constipation, asthenia, peripheral edema, nausea, pyrexia, paraesthesia

Grade 3 / 4 adverse events:

GRIFFIN DaraKVD-AHCT-DaraVDT: neutropenia, lymphopenia, thrombocytopenia, and leukopenia
MASTER DaraKRd-AHCT-DaraKRd: neutropenia, infection, insomnia, hyperglycemia, rash

Package Inserts Warnings:
Lenalidomide and thalidomide: embryo-fetal toxicity, hematologic toxicity, and venous thromboembolism

Lenalidomide and thalidomide Package Inserts
The Nasty Sibling: AL-Amyloidosis

Courtesy of S. Lentzsch; Mahmood S et al. Haematologica 2014; 99:

[Diagram showing the process of amyloid fibril formation and deposition in tissues, leading to organ damage and specific symptoms such as renal, periorbital, macroglossia, nail dystrophy, soft tissue, and heart involvement.]
The Nasty Sibling: AL Amyloidosis

Thank you

SDG
Instructions to Receive Credit

To receive credit, read the introductory CME material, watch the webcast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.

Contact Information

Call (toll-free) 866 858 7434
Email info@med-iq.com

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