Dr. Reeder has received research funding from Celgene, Millennium, and Novartis.

Ms. Mayo has received honoraria from Celgene, Millennium, and Novartis and has served on the Advanced Practice Provider Steering Committee for Celgene.
Learning Objectives

1. Discuss agents for treatment of multiple myeloma (MM) and their side effects/management
2. Understand and discuss the heterogeneous genetic nature of MM
3. Learn the basic prognostic factors and how they impact treatment choices and outcomes
4. Understand the role of stem cell transplantation
5. Implement effective clinical strategies for minimizing toxicity
6. Utilize practical strategies for enhancing patients’ adherence to treatment
Multiple Myeloma Statistics at a Glance

- Estimated new cases (2015): 26,850
- Estimated deaths (2015): 11,240
- Percentage of patients surviving 5 years: 46.6% (2005–2011)
- Estimated number of people living with myeloma in US: 89,658
- Percentage of all cancer diagnoses: 1.6%
- Percentage of all cancer deaths: 1.9%

Risk Factors for Multiple Myeloma

- Age (average age at diagnosis: 72)
- Male sex (58% vs. 42%)
- Family history
- African-American race
- Monoclonal gammopathy

Most patients who are diagnosed have NO known risk factors!

Bone marrow

For example, pelvis bone with bone marrow

Myeloma cells (plasma cells)

Blood stream (and urine)

Intact immunoglobulins
- heavy chains + light chains

Immunoglobulin free light chains
Presenting Signs and Symptoms

Patient-reported symptoms
- Fatigue
- Back/bone pain
- Weight loss
- Frequent infections
- Bruising/bleeding
- Foam in urine

Objective findings
- Anemia
- Lytic lesions on imaging
- Compression fractures
- Unexplained osteoporosis
- Pancytopenia
- Renal failure
- Hypercalcemia

However, many patients are asymptomatic!
Making a Diagnosis

Blood tests
- CBC with differential
- CMP
- Serum protein electrophoresis
- Serum immunoglobulins (IgA, IgG, IgM)
- Serum free light chains (kappa FLC, lambda FLC)
- Beta-2 microglobulin ($\beta_2$M)

Urine tests
- 24-hr urine for protein electrophoresis

CBC = complete blood cell count; CMP = comprehensive metabolic panel.
Serum Protein Electrophoresis

Imaging

- **Skeletal survey**: Standard at diagnosis, x-rays of entire skeleton looking for lytic lesions
- **PET/CT**: Radioactive glucose is given, then CT scan is performed. Cells that are dividing rapidly (active cancer) show up bright on PET/CT. Can help to distinguish between active disease and old bone damage
- **MRI**: Generally performed on areas of concern to take closer look at bone where it is painful
Skeletal Survey

This image of a patient’s skull shows lytic (“punched out”) lesions due to multiple myeloma.

Image courtesy of Dr. Craig Reeder.
This patient has extensive, avid disease from multiple myeloma.

Image courtesy of Dr. Craig Reeder.
Monoclonal gammopathy of unknown significance (MGUS)

- Less than 10% monoclonal plasma cells
- Precursor to myeloma
- However, NOT all MGUS progresses to myeloma; rate of about 1% to 2% per year, varies depending upon risk

Multiple myeloma

- Greater than 10% monoclonal plasma cells
- Not all multiple myeloma requires therapy! “Smoldering” vs. active disease
- “Active” (end organ damage) vs. “smoldering” (no end organ damage, no treatment)
### Diagnostic Criteria for Symptomatic MM

<table>
<thead>
<tr>
<th>C</th>
<th>Calcium elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum calcium ≥ 11 mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>Renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CrCl &lt; 40 mL/min&lt;sup&gt;a&lt;/sup&gt; or serum creatinine &gt; 2 mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemoglobin &lt; 10 g/dL or &gt; 2 g/dL below lower limit of normal</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 1 osteolytic lesion&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Measured or estimated by validated equations.

<sup>b</sup>As determined by skeletal radiography, CT, or PET-CT. If bone marrow has < 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

2014 Update

- “High-risk” smoldering myeloma is now classified as active
- Nearly all patients with these features progress to active disease within 1 year
- Sixty percent or more plasma cells on bone marrow biopsy
- Light chain ratio > 100
- MRI evidence of lesions
# International Staging System (ISS) for Multiple Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum $\beta_2M &lt; 3.5$ mg/L, Serum albumin $\geq 3.5$ g/dL</td>
<td>62 mo</td>
</tr>
<tr>
<td>II</td>
<td>Serum $\beta_2M &lt; 3.5$ mg/L, Serum albumin $&lt; 3.5$ g/dL OR Serum $\beta_2M$ 3.5 to $&lt; 5.5$ mg/L*</td>
<td>44 mo</td>
</tr>
<tr>
<td>III</td>
<td>Serum $\beta_2M \geq 5.5$ mg/L</td>
<td>29 mo</td>
</tr>
</tbody>
</table>

*Irrespective of serum albumin level.

ISS: Survival

MM Characterized by Periods of Relapse and Remission

Goals of Myeloma Therapy

- Immediate goals
  - Gain rapid control of disease
  - Reverse toxicities disease has caused (bone pain, renal dysfunction, cytopenias)
  - Allow for stem cell collection if transplant candidate

- Long-term goals
  - Help patient to live longer
  - Prevent further organ damage by disease
  - Delay relapse
  - MULTIPLE MYELOMA IS STILL NOT CONSIDERED “CURABLE”
Phases of Therapy

- Induction
- Transplant for appropriate patients after induction has been successful (greater than 50% reduction in myeloma)
- Maintenance
- Relapse treatment
Long-Term Survival With CyBorD Induction Therapy in Newly Diagnosed Multiple Myeloma

CB Reeder,¹ DE Reece,² V Kukreti,² JR Mikhael,¹ C Chen,² S Trudel,² K Laumann,³ J Hentz,³ JG Piza,² R Fonseca,¹ PL Bergsagel,¹ JF Leis,¹ R Tiedemann,² J Spong,¹, A Mayo, PA-C,¹ AK Stewart¹

¹Hematology/Oncology, Mayo Clinic, Scottsdale, Arizona
²Hematology/Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada
³Mayo Cancer Center Statistics

CyBorD: Introduction

- Triplet therapy commonly used in both standard- and high-risk multiple myeloma
- Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) produces rapid and deep responses in newly diagnosed multiple myeloma
- CyBorD is one of the most active induction regimens and is cost-effective

## CyBorD: Details

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>300 mg/m² po or 500 mg po</td>
<td>Days 1, 8, 15, 22</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.5 mg/m² SC or IV</td>
<td>Days 1, 8, 15, 22</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg po</td>
<td>Days 1, 8, 15, 22</td>
</tr>
</tbody>
</table>

## CyBorD Results

<table>
<thead>
<tr>
<th></th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL (n = 63)</td>
<td>42% (95% CI, 31%–57%)</td>
<td>70% (95% CI, 59%–82%)</td>
</tr>
<tr>
<td>Standard risk (n = 39)</td>
<td>48% (95% CI, 33%–69%)</td>
<td>81% (95% CI, 69%–95%)</td>
</tr>
<tr>
<td>High risk (n = 24)</td>
<td>33% (95% CI, 19%–59%)</td>
<td>54% (95% CI, 37%–78%)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

Other Induction Regimens

- Combination such as VRD (bortezomib, lenalidomide, dexamethasone)
- Combinations with carfilzomib are promising; FDA guidelines have not yet moved this drug into routine front-line therapy, but research is underway
- Lenalidomide/dexamethasone may be used (all oral regimen)
- Clinical trials to examine other effective combinations
The Role of Transplant in Myeloma

AUTOLOGOUS stem cell transplant

- Performance status
- Age is one factor, but there is not a strict cutoff, and we consider “physiologic” age
- Comorbidities (physical, psychiatric)
- Response to induction therapy
- Social/financial support

No transplant

- Often age/performance status related but may also be related to social situation, finances, or simply patient’s desire not to have the transplant
- Many other effective therapies that can be used, even when transplant is not possible
Maintenance Therapy

- Once patients have maximized response to induction therapy, they may or may not go on to transplant.
- Those who do not go on to transplant will likely be maintained on the same drug combination that worked for them, perhaps less often/lower dosage.
- Following transplant, it is now increasingly common to use maintenance regimens to increase the amount of time in remission.
Major Classes of Myeloma Therapy

Proteasome inhibitors
- Bortezomib
- Carfilzomib
- Oral proteasome inhibitors in clinical trial

IMiDs (immune-modulating drugs)
- Thalidomide
- Lenalidomide
- Pomalidomide
Bortezomib

- Initial FDA approval 2003
- Revolutionized treatment of myeloma; prior to its approval, we had only a few, rather toxic drugs with limited efficacy
- Data after the mid-2000s showed a large increase in survival for patients with multiple myeloma because of this and other “novel” agents
Bortezomib Side Effects

- Sensory neuropathy: Lessened by subcutaneous administration, weekly administration
- Nausea/vomiting
- Diarrhea
- Fatigue
How Does Neuropathy Present?

- Numbness and/or tingling, starts distally and moves proximally as it progresses
- May or may not be associated with pain
- Interferes with function as it progresses (fine-motor skills, balance)
- May also be described as cold sensation in extremities, burning
Alternative Presentations of Neuropathy

- Intermittent sharp or shooting pains
- Autonomic dysfunction/hypotension
- Predominantly sensory but may contain a motor component for some patients (muscle weakness, generalized lack of coordination)
- Allodynia
Risk Factors for Neuropathy

- Older age
- Diabetes
- Prior chemotherapy exposure
- Amyloidosis and/or paraprotein-related neuropathy prior to therapy
- Spinal stenosis
Treatment of Peripheral Neuropathy

- Duloxetine is the only medication with American Society of Clinical Oncology (ASCO) recommendations, and those are moderate

- Other agents with potential beneficial effects
  - Gabapentin/pregabalin
  - Venlafaxine
  - Desipramine
  - Topiramate
  - Baclofen
  - Lidocaine dermal patch
  - Narcotic pain medications
Nonprescription Medications/Treatments

Potentially useful interventions

- Alpha-lipoic acid
- Omega-3 fatty acids
- Vitamin B\textsubscript{6}
- Acupuncture
- Physical therapy
- Modification of environment
Carfilzomib

- FDA approved 2012
- Clinical trial for approval (PX-171-003), 22.9% overall response rate
- Initial approval for patients with relapsed/refractory disease who had previously received bortezomib and an IMiD (lenalidomide/thalidomide)
- Now also approved in combination with lenalidomide and dexamethasone in any relapsed setting

Carfilzomib Side Effects

- Fatigue (54%)
- Anemia (47%)
- Nausea (45%)
- Thrombocytopenia (36%)
- Dyspnea (35%)
- Pyrexia (30%)

Carfilzomib Warnings

- Cardiac events: Worsening congestive heart failure, ischemia
- Tumor lysis syndrome
Thalidomide

- Used for morning sickness for pregnant women in 1960s and caused severe birth defects (limb deformities); later found to work against myeloma
- Approved on limited basis in 1998, with special risk management program; FDA approval for myeloma in 2006
- Oral, effective, great improvement over other therapies available at the time!
Thalidomide (cont)

- Benefits: Oral therapy, effective, tolerable even in older patients, little effect on blood counts
- Black box warning: Fetal toxicity, thrombosis, cytopenias
- Other side effects: Neuropathy, dizziness, fatigue, constipation… COST!
- Often a useful adjunct to other therapies
Lenalidomide

- Analog of thalidomide, FDA approved in 2005 for relapsed/refractory disease, initial therapy in 2015
- Oral, often well tolerated, may maintain patients for years with good quality of life!
- Often induction therapy of choice in older patients, younger alone, or in combination
- Same black box warning as thalidomide (fetal toxicity, thromboembolism, cytopenias)

Lenalidomide (cont)

- Common side effects: Cytopenias (especially neutropenia), diarrhea, muscle cramps, fatigue
- Can impair ability to collect stem cells, so want to collect after limited therapy rather than years if you may want to transplant
- Question about increased risk of secondary malignancies, especially hematologic (myelodysplastic syndrome, acute leukemias) in patients who also had high-dose melphalan (transplant)

Pomalidomide

- Third-generation “IMiD” drug
- Still effective in people who failed other IMiDs
- FDA approved for relapsed/refractory, post lenalidomide, post bortezomib in 2013, given with dexamethasone
- Appears promising in combination with proteasome inhibitors as well

Celgene 2013. Pomalyst (pomalidomide) package insert.
Pomalidomide (cont)

- Same black box warning as all IMiDs and REMS program (fetal toxicity, thromboembolism, cytopenias)
- Side effects seem to be a cross between those with thalidomide and lenalidomide

REMS = Risk Evaluation and Mitigation Strategy.
Celgene 2013. Pomalyst (pomalidomide) package insert.
Other Myeloma Drugs in Use

- Cyclophosphamide, melphalan
- STEROIDS! (dexamethasone, prednisone)
- Liposomal doxorubicin
- Panobinostat (approved March 2015)
Clinical Trials

- Monoclonal antibodies (anti-CD38)
- Immune system
- Oral forms of proteasome inhibition
- Novel agents
- Genetic sequencing
- Right now, there are 13 open trials for myeloma at Mayo Clinic Arizona and 7 pending
Acute Leukemia

Myeloma

Hyperdiploidy

t(11;14)

t(4;14)

t(14;16)

t(6;14)

3 decades
Multiple Myeloma Cytogenetics
FISH

CCND1/IgH Rearrangement
Molecular Prognostic Model

Survival probability

- Poor: 24.7 mo
- Intermediate: 42.3 mo
- Good: 51.0 mo

-$t(11;14)$
-$t(4;14)$
-$t(14;16)$
-$\Delta 13$
-$-17p13$

$P < .001$

Progression-Free Survival: High Risk

SCT and PFS in Patients With t(4;14)

Genetic Classification

Hyperdiploid (h) MM
- 45% of all MM
- Numerous chromosome trisomies
- More favorable outcome
- Slightly more common in males
- More common in elderly

Nonhyperdiploid (nh) MM
- 40% of all MM
- Highly enriched for IgH translocations
- Overall less-favorable outcome
- Examples include t(11;14), t(4;14), t(14;16), del(17p)

Remaining 15% of MM is either with overlap or unclassified in the two major genetic categories

Multiple Myeloma: Nonhyperdiploid

- t(11;14)(q13;q32): 15%–20%
  - "Good" prognosis with HDT/SCT (but, no enrichment in long-term survivors)
  - Associated with
    - IgM myeloma (90%)
    - AL amyloidosis (50%)
    - Light chain multiple myeloma
    - CD20+
    - Lymphoplasmacytic morphology
    - PC leukemia

- t(4;14)(p16;q32): 14%
  - Poor prognosis
  - FGFR3 overexpression

- t(14;16)(q32;q23): 5%
  - Poor prognosis

Nonhyperdiploid

- t(14;20): Uncommon
  - Poor prognosis, MAFB expression
- Del 17p (p53): 11%
  - Very poor prognosis
- Del 13, 13q: 50%
  - Surrogate for nonhyperdiploid myeloma

Other mutations

- RAS-activating mutations: 30%-50% multiple myeloma
- p53 (17p13)
  - 5% at diagnosis, 30% in advanced disease
- c-myc, late event
- PTEN, leads to PI-3K, AKT activation
- Tumor suppressors p16, p18
- 1q21, overexpression/gains

Myeloma Prognosis

- Host factors: Age, performance status, comorbidities
- Stage: Durie-Salmon, ISS
- Disease aggressiveness: FISH, LDH, circulating PCs
- Response to therapy

*Disease characteristics help in counseling and in choosing therapy.*

ISS = International Staging System; FISH = fluorescence in situ hybridization; LDH = lactate dehydrogenase; PC = plasma cell.
Defining High Risk

- FISH
- Metaphase cytogenetics abnormality
- PCLI > 3%
- PC leukemia
- High LDH, $\beta_2$M, and low albumin
- Failure to respond to novel agent
- Early relapse after HDT
- Gene-expression profile (GEP) signature

PC = plasma cell; PCLI = plasma cell-labeling index; HDT = high-dose therapy.
Failure to Respond to Induction With Novel Agent

PFS post SCT

OS post SCT

PFS = progression-free survival; OS = overall survival.

Gene-Expression Profiling

- University of Arkansas and IFM (Intergroupe Francophone du Myélome) have identified gene signatures that can provide prognostic discrimination
- There is minimal overlap between these two signatures, and both will need validation
- It is conceivable that gene signatures may become predictive markers in the future

Gene-Expression Profile Signatures

mSMART

*Mayo Stratification for Myeloma and Risk-Adapted Therapy*

Newly Diagnosed Myeloma
Multiple myeloma is increasingly recognized as more than one disease, characterized by marked cytogenetic, molecular, and proliferative heterogeneity. The result is a widely varied outcome, ranging from low to very high risk. Treatment is evolving rapidly as more effective agents and combinations become available.

mSMART (Mayo Stratification for Myeloma and Risk-Adapted Therapy) is a consensus opinion that takes into account genetically determined risk status and the various treatment strategies currently available.

Risk stratification and individualizing treatment options are complex and based not just on the cytogenetic classification presented here, but also on various host factors, disease stage, and a variety of other prognostic factors.

Therefore, we recommend all patients with newly diagnosed myeloma be seen at least once at a referral center with expertise in the disease.

mSMART (cont)

- The general approach is presented here (mSMART: off study). However, clinical trials must be considered and are preferred at every level (mSMART: on study).
- Management decisions are also varied depending on renal function and the presence or absence of coexisting amyloidosis.

# mSMART 2.0: Classification of Active MM

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Standard risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| ▪ FISH<sup>c</sup>  
  - Del 17p  
  - t(14;16)  
  - t(14;20)  
| ▪ FISH  
  - t(4;14)<sup>d</sup>  
  - 1q gain  
  - Complex karyotype  
  - Metaphase Deletion 13 or hypodiploidy  
  - High PC S-phase<sup>f</sup>  
| All others, including:  
  ▪ Trisomies  
  ▪ t(11;14)<sup>e</sup>  
  ▪ t(6;14)  

<sup>a</sup>Note that a subset of patients with these factors will be classified as high risk by GEP.

<sup>b</sup>LDH > ULN and β<sub>2</sub>M > 5.5 may indicate worse prognosis.

<sup>c</sup>Trisomies may ameliorate.

<sup>d</sup>Prognosis is worse when associated with high β<sub>2</sub>M and anemia.

<sup>e</sup>t(11;14) may be associated with plasma cell leukemia.

<sup>f</sup>Cutoffs vary.

Impact of 4;14 and ISS Staging on Survival Outcomes in MM

# mSMART: Off-Study

## Transplant Eligible

<table>
<thead>
<tr>
<th>Standard risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trisomies only</strong></td>
<td><strong>t(11;14), t(6;14), trisomies + IgH</strong></td>
<td><strong>Del 17p, t(14;16), t(14;20)</strong></td>
</tr>
<tr>
<td>4 cycles of Rd&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 cycles CyBorD</td>
<td>4 cycles of VRd</td>
</tr>
<tr>
<td>Collect stem cells&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous stem cell transplant</td>
<td>Autologous stem cell transplant</td>
<td></td>
</tr>
<tr>
<td>Continue Rd&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 cycles of Rd consolidation; then Len maintenance if not in VGPR but Len responsive&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Bor or CyBorD for minimum of 1 year</td>
</tr>
</tbody>
</table>

<sup>a</sup>Bortezomib-containing regimens preferred in renal failure or if rapid response needed.

<sup>b</sup>If age > 65 or > 4 cycles of Rd, consider G-CSF plus cyclophosphamide or plerixafor.

<sup>c</sup>Continuing Rd for patients responding to Rd and with low toxicities; dex is usually discontinued after 1st year.

*Consider risks and benefits; if used, consider limited duration 12–24 months.

In patients treated with Rd, continuing treatment is an option for patients responding well with low toxicities; dex is usually discontinued after 1st year.

Bortezomib containing regimens preferred in renal failure or if rapid response needed.

CyBorD is considered a less toxic variation of VMP; VMP can be used as alternative.

Continuing Rd for patients responding to Rd and with low toxicities; dex is usually discontinued after 1st year.

Clinical trials strongly recommended as the first option.

High-Risk Myeloma

- Need complete response for long-term disease control (overall survival)
  - Aggressive therapy: All drugs up front
  - Triplet regimens
    - VRD, VTD (PI + IMiD + steroid)
    - KRD? (ENDURANCE trial underway)

- Intermediate risk: Need proteasome inhibitor
  - CyBorD (VCD) (alkylator + proteasome inhibitor + steroid), VRD
Standard-Risk Myeloma

- Overall survival similar whether or not complete response is achieved
  - Option for less-aggressive therapy
  - *Sequential* agents vs. all up front
  - *Control* vs. cure approach

- CyBorD
- Rd
- MPT
Kaplan-Meier Survival Curves for All Patients

Kaplan-Meier Survival Curves by mSMART Risk

Multiple Myeloma Treatment Paradigm

- Induction
- Stem cell harvest
- Transplant
- Continue induction
- Relapse 2
- Salvage
- Salvage/SCT
- Relapse 1
Autologous Stem Cell Transplant

- Most studies show improved progression-free survival and some overall survival compared with standard therapy
- Low mortality in young patients
- High-dose therapy increases depth of response
  - Depth correlates with survival
- Second stem cell transplant
  - Beneficial if < VGPR after SCT #1
  - Rarely needed in era of novel agents
  - May not be needed if maintenance utilized
  - Can be used as salvage if first SCT remission > 2 years
- Stem cell harvest, after 4–6 cycles of therapy
Stem Cell Transplant: Process

- Precollection evaluation
- Stem cell mobilization
- Stem cell harvest
- Cryopreservation
- Conditioning (high-dose melphalan)
- Stem cell infusion
- Supportive measures
- Engraftment
Stem Cell Harvesting After Novel Agents

- **Thalidomide**
  - Probably no impact (or minimal) on yield or engraftment

- **Lenalidomide**
  - Reduces stem cell yield
    - Duration of therapy > 4–6 cycles
    - Age of patient
    - Mobilization techniques: G-CSF vs. chemotherapy + G-CSF
  - No effect on engraftment

- **Bortezomib**
  - Probably no impact on yield or engraftment

- **Chemotherapy**
  - Melphalan: Significant impact (stem cell toxic)
  - Cyclophosphamide: No impact
Stem Cell Collection Guidelines

- Harvest early, after 3–4 cycles of induction
  - G-CSF alone usually adequate
  - If > 4 cycles of lenalidomide-based therapy
    - G-CSF + cyclophosphamide, or
    - G-CSF + plerixafor
  - If > 65 years old
    - G-CSF + reduced dose cyclophosphamide
    - Add plerixafor day 2 if needed

Maintenance Therapy

- **Thalidomide**
  - All maintenance studies show improvement in event-free survival
  - Three show improvement in overall survival
  - The benefits seem to be for those having less-than-maximal response from primary therapy
  - Toxicity and intolerance limit usefulness

- **Lenalidomide**
  - Less toxic than thalidomide
  - Two trials now show prolonged event-free survival/progression-free survival compared with placebo; one shows overall survival benefit
  - Second primary cancers a concern

- **Bortezomib**
  - Early data are promising, but optimal dose/schedule unclear
mSMART
Mayo Stratification for Myeloma and Risk-Adapted Therapy

Relapsed Myeloma
mSMART 2.0: Classification of Relapsed Multiple Myeloma

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Standard risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Relapse &lt;12 mo from transplant or progression within 1st year of diagnosis&lt;br&gt;- FISH&lt;br&gt;  - Del 17p&lt;br&gt;  - t(14;16)&lt;br&gt;  - t(14;20)&lt;br&gt;- High-risk GEP</td>
<td>- FISH&lt;br&gt;  - t(4;14)&lt;br&gt;  - 1q gain&lt;br&gt;  - Complex karyotype&lt;br&gt;  - Metaphase&lt;br&gt;  - Deletion 13 or hypodiploidy&lt;br&gt;  - High PC S-phase</td>
<td>- All others, including:&lt;br&gt;  - Trisomies&lt;br&gt;  - t(11;14)&lt;br&gt;  - t(6;14)</td>
</tr>
</tbody>
</table>

First Relapse: Off Study

Relapsing after auto transplant

On maintenance → CyBorD if Rev maintenance*; Rd, or KRd if Vel maintenance*

Off therapy/unmaintained → Rd or CyBorD if standard-risk*; CyBorD or VRd if high risk*

Relapsing after nontransplant therapy

On therapy/maintenance → Not eligible for ASCT

Off therapy/unmaintained → Transplant eligible

On therapy/maintenance → CyBorD if Rev maintenance; Rd, or KRd if Vel maintenance

Off therapy/unmaintained → Repeat first-line Rx if remission off therapy is > 12 mo; If not, CyBorD if relapsing after ImiD based Rx; otherwise Pom/dex or KRd

*Consider 2nd auto if eligible and > 18 months unmaintained or > 36 months maintained response to first auto.

Second or Later Relapse*
Off Study

Not plasma cell leukemia (PCL) or similar extramedullary disease (EMD)

Dual-refractory
(bortezomib and lenalidomide)**

KRd or Pom/dex to maximum response or 18 months, then Rd

Triple-refractory
(bortezomib, lenalidomide, and carfilzomib)**

PCD, PVD, or Car-Pom-Dex to maximum response or 18 months, then Pom/dex

Triple-refractory
(bortezomib, lenalidomide, and pomalidomide)**

KRd or Car-Pom-Dex to maximum response or 18 months, then Rd or Pom/dex

* If single refractory, refer to first-relapse algorithm.

**Auto transplant is an option if transplant candidate and feasible; doublets such as Cyclo-Pred, Pd or Kd could be considered in patients with indolent disease.
Second or Higher Relapse: Off Study

**Secondary PCL or extensive EMD**

- VDT-PACE x 2 cycles*
  - Auto transplant if transplant candidate; if not, maintain with one of the regimens listed that the patient is not known to be refractory to (VRd, VCd, KRd, PVd, or Car-Pom-Dex)

**Quadruple-refractory (lenalidomide, pomalidomide, bortezomib, and carfilzomib)**

- VDT-PACE* x 2 cycles if possible.*
  - Auto transplant if transplant candidate; if not, consider alkylator-containing combination if not alkylator refractory or treat with anthracyclin-containing regimen such as RAD, VDD, PAD, or CHOP**

*CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status.

**Other options to consider in fit patients: bendamustine- or panobinostat-containing regimens.

Risk Status and Relapse

- Recall the importance of risk stratification in myeloma and its varied presentation
- Relapse occurs more quickly and aggressively in high-risk patients
- Close monitoring and rapid institution of therapy are critical
- Risk factors can change since time of first diagnosis; reevaluate at time of relapse
- More likely require longer-term (if not indefinite) therapy
- Standard-risk patients may not need rapid intervention; fewer drugs at once, more likely sequential

Second Transplants

Three requirements should be met:

1. Did the patient benefit from the first ASCT? (i.e., response deepened)
2. Did the patient tolerate the first ASCT well?
3. Did the patient have a minimum 2-year progression-free survival after the first ASCT?¹,²

Expect 50%–70% of progression-free survival with second ASCT

Re-treatment in Combination

- Even if a patient has become resistant to a certain agent, may become sensitive
  - Due to clonal evolution
  - When combined with another agent (e.g., VRD 30% response in V- and D-resistant disease)\(^1\)

- Other combinations include:
  - VDT-PACE\(^2\), DCEP, melphalan + … tend to be a bridge to more definitive therapy

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Future Therapies

Classes of Agents in Development for Myeloma

- Oral proteasome inhibitors: Ixazomib (MLN 9708), oprozomib
- Monoclonal antibodies
  - SLAMF7 (signaling lymphocytic activation molecule F7): elotuzumab (formerly CS-1)
  - Anti-CD38: Daratumumab, SAR650984
  - Anti-CD138: Indatuximab, ravatansine
- KSP inhibitors: Filanesib
- Histone deacetylase inhibitors: Panobinostat, ACY-1215
- Akt inhibitors: Afuresertib
- BCL family inhibitors: ABT-199
Future Therapies (cont)

- CDK inhibitors: Dinaciclib
- Nuclear transport: CRM/XPO1, selinexor
- IAP antagonists: LCL161
- PIM kinase inhibitors: LGH447
- Bromodomain and extraterminal (BET) inhibitors: GSK525762
- Immune therapies: Programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1)
Anti-CD38 Monoclonal Antibodies

- Most promising agents for myeloma (according to 80% vote at International Myeloma Working Group)
- Two currently in later development: Daratumumab and SAR650984
- Both have significant single-agent activity and can be combined
- Will this be the “rituximab” of myeloma?
Daratumumab: Response

RR=35%

RR=10%

IMWG Criteria

Summary and Recommendations

- Baseline genetic information should be obtained in all cases of multiple myeloma.
- Minimal testing required for prognostication should include FISH, LDH, $\beta_2$M, albumin.
- Gene-expression signatures should be incorporated in all clinical trials.
- Multiple tools are available for risk stratification.
- Risk determination can help guide therapy and counseling.
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MSMART.org
RISK STRATIFICATION IN MULTIPLE MYELOMA: PUTTING THE PIECES TOGETHER

ANGELA MAYO, MS, PA-C Good afternoon. We have some financial disclosures. Dr. Reeder has received research funding from Celgene, Millennium, and Novartis. And I've received honoraria from Celgene, Millennium and actually Amgen, and I'm on the Advanced Practice Provider Steering Committee for Celgene. Our objectives for today are we’re going to start by talking about some of the agents for treatment of multiple myeloma and some of the basics of diagnosis for multiple myeloma, to understand and discuss the heterogeneous genetic nature of multiple myeloma, to learn about the basic prognostic factors and how they impact treatment choices and outcomes, to understand the role of stem cell transplantation, implement effective clinical strategies for minimizing toxicity, and to utilize some practical strategies for enhancing patients' adherence to treatment.

To start, just a little background, a few multiple myeloma statistics. This is the second most common hematologic malignancy in the United States. It’s far behind non-Hodgkin’s lymphoma, which is the first by far. It’s about 1.6 percent of all cancer diagnoses. So if you’re working in the community where you see everything that comes in, this may be a relatively small percentage of what you see, but you will see it. It’s almost two percent of all cancer deaths. There are over 20,000 new cases in the United States estimated in 2015. And the percentage of patients surviving is getting greater and greater, thanks to a lot of
new therapies and a lot of research being done in the area. But it’s still not a curable malignancy.

Some of the risk factors for multiple myeloma: first of all, keep in mind most of your patients will not have any risk factors. They won’t have any known predisposition. But men tend to get this a little more often than women. It congregates in elderly patients; the average age at diagnosis is 72. Also, preexisting monoclonal gammopathy: we now know that everyone has preexisting MGUS before they develop myeloma. Whether or not that’s detected is a different story. So if your patient’s been detected with monoclonal gammopathy then you’re surveying them and making sure they’re not showing you any signs of progression. African Americans tend to have multiple myeloma at higher percentages than other ethnic groups. And while this is certainly a minority, there are some people with family history. We do have some brother and sister teams that both have multiple myeloma, so there is the potential for family history.

Multiple myeloma and where we’re going to find it: you’ll find some plasma cells in the bone marrow when you do a bone marrow biopsy. In the blood you’ll be able to see intact immunoglobulins—IgA, IgG, IgM—with the light chains, and you’ll also be able to detect free light chains. Presenting signs and symptoms. Probably the two biggest ways that I hear patients tell me they were diagnosed, one is anemia. They were having a workup for anemia and this is discovered. The other one is pain, particularly things like back pain. People think, “Oh, I shouldn’t have lifted that refrigerator,” and they don’t get better and they don’t get
better and they go to their primary doctor and they don’t get better and someone x-rays and says, “Eww, what’s going on here?”

Some people are identified when they’re acutely ill. So if you do inpatient work, you may find a patient in renal failure. You might find a hypercalcemic patient and that’s their first presenting symptom, those people having pretty aggressive disease at that point. Many patients are asymptomatic. I’ve had patients come in to me, they’re diagnosed with a hemoglobin of 6.8 and said, “I felt pretty good. I was working. Now that I think about it, I guess I didn’t feel that great,” but you kind of become used to it when your hemoglobin gradually goes down over time.

Making a diagnosis: many of the patients will probably come to you with a diagnosis already made. But if you’re working inpatient in particular, you may be the one making this diagnosis. We need a CBC and a CMP panel. We need to check the immunoglobulins in the serum. We need to do a serum protein electrophoresis, check for free light chains in the serum, and beta-2 microglobulin we’ll talk about as a part of the staging. Urine: you want to get a 24-hour urine for protein electrophoresis on all your newly-diagnosed patients. So this is a protein electrophoresis if these have ever come to you and you said, “What is all that squiggly stuff?” If we look at the blue, that tells what a normal protein electrophoresis looks like. The predominant protein is albumin. If we see that kind of green color in the background, there is a spike in the gamma region. That’s the M spike.
Imaging is somewhat of a topic of discussion in multiple myeloma. People are saying, “What test should I get?” Not things such as a bone scan. These are lytic lesions. They’re going to show up better on x-ray. Skeletal survey is always the gold standard, and skeletal survey is good because it’s relatively inexpensive, you could get it done quickly, and you can survey the whole body. However, nowadays sometimes we’re using other methods of detecting too; PET/CT for people with avid disease on PET/CT. I have seen avid disease on PET/CT that did not show up on skeletal surveys at times. And then MRI: we’ll talk a little bit about high-risk smoldering myeloma and how we use MRI to determine if those people are actually progressive to active myeloma. We also use MRI if your patient complains to you of a specific painful area. We want to evaluate a certain area in the spine. Sometimes MRI is very helpful at taking a real close look.

Here’s an example of a skeletal survey. This is a patient’s skull. The patient has punched out lytic lesions, which you can see. Surprisingly, most of these patients with the lytic lesions in the skull are relatively asymptomatic from this. And this is a PET/CT of a very nice individual that I had the privilege to care for. Unfortunately, at this stage in his PET/CT, he had very avid disease and even extramedullary presentation of myeloma, which is something that we do sometimes see. Myeloma doesn’t have to be confined to the bone. Sometimes we can see it in soft tissue and organ involvement, which usually portends a very poor prognosis.

Do we have to do a bone marrow biopsy? What if you know what your patient has? You’re doing a workup, they have an M spike, everything is clear,
they have anemia. Do you have to do a bone marrow biopsy? Absolutely yes. You’re going to get a lot more information from the bone marrow biopsy which we’ll talk about, and Dr. Reeder will be talking about the risk factors and how we can identify some of those, and it’s definitely a part of the workup that we can’t eliminate. When you do your bone marrow biopsy, if they have less than 10 percent monoclonal plasma cells and they’re asymptomatic, they have monoclonal gammopathy of unknown significance. You’re going to follow those patients. You’re going to see them on your calendar and say, “Oh, I probably have an easy day. I just have to talk to this person about their M spike.” Not all monoclonal gammopathy progresses to myeloma. It’s a relatively small percent per year depending upon the type and depending upon how it’s behaving, risk of about one to two percent per year. But it is cumulative so you do want to follow your patients.

Multiple myeloma, greater than 10 percent monoclonal plasma cells: within that category you’re going to say, “Are they smoldering or are they active?” If they don’t have any evidence of end organ disease then they’re smoldering. If they are active, which we’ll get to in a minute, those are people that are being harmed by their disease and those are people that do require therapy. Here’s the diagnostic criteria for symptomatic myeloma which many of you probably are familiar with: CRAB. So you have elevated calcium, renal insufficiency, anemia or other cytopenias, and bone lesions. So that’s traditionally how we differentiate it. You don’t have any CRAB, I don’t care how many plasma cells are in your bone
marrow, you don’t have active myeloma, you don’t require therapy. If the patient does have one or more of these symptoms then they are in need of therapy.

This has changed a little bit in recent times. So in 2014 we have an update for high-risk smoldering myeloma. It’s always rather uncomfortable to know that someone has pretty significant smoldering myeloma and you don’t want to sit and wait for them to break a bone. So now we’re looking at some of the indications for therapy, even in the absence of the strict CRAB criteria. So this includes things like 60 percent plasma cells on bone marrow biopsy. Those patients, nearly all of them progressed within a year in a study. So we just kind of consider those active myeloma now. We’re going to go ahead and treat them. Also, patients that have a light chain ratio of over 100 from the involved over the uninvolved, whether it’s kappa or lambda. Ratio over 100, those people require therapy because they’re at high risk. And then MRI: we sometimes use MRI of the patient’s spine to identify lesions that may be subtle that maybe we didn’t know were there previously. So this is a way that we can kind of get a step ahead of severe damage for our patients.

The ISS staging system: A lot of your patients will probably ask you, “What stage am I?” And it’s going to radically different than when we stage something like colon cancer, for example. We stage a stage I colon cancer, they have surgery and they’re done. They have a stage IV colon cancer, then they have metastatic disease and they require palliative chemotherapy if they’re going to proceed with that. Myeloma is a little different because we’re going to use the
same treatment whether they’re stage I, stage II, or stage III. We’ll talk about some subtleties of which treatments to pick.

There’s only two pieces of information that we need in order to decide what stage a patient is in. They can both be obtained from the blood work. It’s the beta-2 microglobulin and the serum albumin. If the beta-2 microglobulin is high, that’s an indicator of high tumor burden, and beta-2 over 5.5 puts them into stage III disease. If a patient has an adequate albumin and a low beta-2 microglobulin, then they’re a lower risk. They’re a stage I patient. And then stage II is kind of the catch all for everybody else. It doesn’t fit into those two criteria. So it’s a little bit of a strange stage that you can get from two pieces of blood information. You don’t have to check the beta-2 microglobulin month after month after month. You need it for staging upfront. And the staging does make a difference because as you can see, the stage I patients had a median survival of over five years whereas the stage III were roughly around two and a half years.

We’re talking about modifying the staging system too to include some of those high-risk factors, some of the high-risk genetics that we’re going to discuss later today. ISS does correlate with survival, the staging. And myeloma in general is characterized by periods of relapse and remission. So the place where we’ve made the most progress in the world of myeloma is in this middle area. We have many, many new agents. I heard somebody yesterday refer to people who had been in the field in the while as “seasoned.” Well, I guess I’m seasoned. I don’t know if that’s a good thing or not. But we’ve come up with many, many drugs. When I first started out, we had very few drugs. We had VAD, which was toxic
and it didn’t work very well and we had transplant for a select few patients, and we had oral melphalan, and then we had, “Sorry, I can’t do anything else for you.”

Now we have agents that are more effective, more tolerable, and there are more of them. We’re going to talk about some of those agents and we’re going to use all of them or many of them throughout the treatment process of many of our patients. And so now what we have is a lot more of those relapse and remissions. So the time that the patient is alive is extended. The quality of their life hopefully is extended because the agents are more tolerable. So that’s why I think that we have reasons for optimism. However, over on that end of the chart where it says refractory and relapse, we definitely still see this. We still see people that have become resistant to all of their therapy and succumb to their disease. And generally speaking, we still call multiple myeloma an incurable disease, although we do have a few wonderful and fortunate people out there that are a couple decades from their diagnosis that seem to be cruising along just fine. Hopefully we’ll have more in the future.

So when we talk about giving someone myeloma therapy, this is one thing where you don’t necessarily want to say, “Oh, I’m not going to treat you because you’re kind of fragile or because you’re anemic or you’re not feel—I’m not going to treat you,” because if you don’t treat people they’re not going to feel well for the most part. So one of your immediate goals is we want to gain rapid control of the disease. We want to reverse some of the toxicities. If we give someone effective therapy, a lot of times we restage the patients after the first month of
therapy and sometimes before that point I'll be seeing the patient to check on them and they’ll say, “My pain is so much better. I’m not needing those pain pills anymore and I feel pretty good about that.” Most of the time when we restage them, at a month they’re making some improvements.

Renal: if you’re in the hospital or if you’re in the outpatient setting and you see someone in renal failure from myeloma, effective, prompt therapy can reverse that process. People can come off of dialysis and can make a huge difference, so that’s something you really want to get on top of right away. And then we also want to allow for stem cell collection if the patient is a candidate for an autologous transplant. Our long-term goals: we want the patient to live longer. We want to prevent them from having more toxicities. We want to prevent relapse. So those are some of the things that we’re looking at long term. So we want to talk about getting control right now but we also want to remind our patients that it’s kind of a marathon and not a sprint and it’s going to be a disease that requires long-term therapy.

So our phases of therapy: we have induction, then we have transplant for our transplant-eligible patient, which we want to do after induction. If you’re seeing this patient in the clinic and you’re not at a transplant center and you think they might be a candidate, send them for an evaluation. We don’t have a hard and fast age cutoff. We do consider things like that. We consider co-morbidities, but there are some people in their 70s that are transplant candidates. There are some people who are in their 50s who are not. And the best thing to do is to kind of give them that option to talk to a transplanter upfront. Then we want to do
maintenance therapy. We no longer just treat people for a few months and say, “All right, your numbers look good. Let’s see what happens.” We know now that if we maintain people on therapy, they will often stay in remission for longer. And then eventually, unfortunately, most of them will relapse and will have to do some treatment there.

This I’m going to skip over. We have lots of information so this is for your future information. It’s one of the induction therapies. Dr. Reeder will talk a little more about how we choose an induction therapy based on the individual patient. If you’ve seen myeloma patients, you probably know that there are some that just seem to keep cruising along and coming in and they’re taking the wrong medication for years and they’re good, and there’s other people that holy cow, it blows up and they get sick. So we’re going to talk a little bit about who is who and how we treat them differently.

Role of transplant: we had a good talk on transplant earlier this morning, so the bottom line is that it’s an autologous transplant for myeloma. Age is one but not the only factor that we consider. We want them to respond to induction therapy first. Unfortunately, one of the sad things that we sometimes do see is that social and financial reasons do play into whether people get transplanted or not. You need a caregiver and that’s problematic for some folks. There are people that can’t be out of work to do their transplant so we definitely try to work with those people as much as we can but sometimes it is a decision that’s made not just based on medical situation. So maintenance therapy: after their induction
therapy or their transplant, we may possibly put them on some maintenance regimens.

I’m going to talk a little bit for the remainder of my time up here about some of the major drugs that you’re going to see in the myeloma world, couple of the side effects to look out for, and some of the practical things when you’re managing those patients. So two major classes of myeloma therapy, we’re coming up with more and more drugs. We have other classes of therapy, but we’ve got proteasome inhibitors and we’ve got IMiDs, and those two families of drugs have really revolutionized the way we treat myeloma today. So we’ll start with the proteasome inhibitors. One thing I want to throw out, for all the proteasome inhibitors as class, which is bortezomib or Velcade and carfilzomib or Kyprolis, there are others up and coming, oral formulations of these drugs that we’re looking at in clinical trials, one of the risk that we have is the risk of shingles. So we put everyone on some antiviral therapy, some prophylaxis antiviral therapy because otherwise you will be seeing shingles.

I remember when bortezomib was approved, and again that’s making me feel kind of old, but it was 2003, and it really changed the way we treat multiple myeloma. After this point we saw the data showing a lot longer survival for our patients because this is a pretty well-tolerated drug. It’s a very effective drug. If we’re talking about side effects, one of the really basic things that you should really assess is for sensory neuropathy. Sensory neuropathy is less now than it was when this drug first came out. Now we’re administering subcutaneously instead of IV and that reduces the risk. Now we’re often administering weekly
instead of twice weekly, and that reduces the risk. But when we have our patients that are living ten years or more, you don’t want to give them the gift that keeps giving which is terrible neuropathy.

So you want to assess it, not necessarily stop the drug at the first twinge in their feet but you definitely want to continue to ask those questions. You may need to dose reduce. It’s better to dose reduce someone and keep them on therapy than to cause them significant toxicity sometimes. Again, there’s always a balancing act. If your patient is acutely ill, you may be willing to take a little more risk here than if someone is not that ill from their disease or if someone has a number of other therapeutic options. GI toxicity is relatively minor, but it is something that you’ll hear about—nausea, vomiting, diarrhea, and then fatigue like all of our chemotherapy drugs. Traditionally we don’t routinely pre-medicate people with antiemetic that are getting bortezomib. If they have nausea, then certainly we can but it’s not reflexively something we do. I always send them home with something for nausea.

Neuropathy: again, we won’t have time to probably address all of this, but the way that neuropathy presents and what are patients going to tell you. They’ll say it’s numb or tingly. It usually starts distally, usually feet first, and it may or may not be associated with pain. It’s a big distinction to make. If their feet feel like they’re falling asleep it might be okay. If their feet hurt, that’s not okay. That causes them a lot of problems. It can interfere with function as it progresses. It can interfere with fine motor skills and balance. Sometimes they’ll describe it a
little differently. It could be a cold sensation in the extremities, a burning feeling, sharp, shooting pains. So those are questions that you really want to ask.

Allodynia: sometimes people just get exquisitely sensitive to all sort of sensation. The thing to keep in mind about neuropathy is that there’s some risk factors, older age, diabetes, prior chemotherapy, spinal stenosis. If you have an amyloid patient, they may already have neuropathy as part of their disease. Sometimes the paraprotein itself, the myeloma protein can cause neuropathy before we even treat folks.

Treatment: what you want to keep in mind is that treatment is not that effective overall. So if we’re waiting until we’re treating something that’s very painful, we might have a hard time. So the best thing is to kind of prevent and minimize, but I have included some things here. ASCO recommendations: duloxetine is the only thing that’s officially on their recommendations and that’s for moderate. People will try some nonprescription things such as alpha-lipoic acid, B vitamins, acupuncture and physical therapy, and sometimes just things like modification of environment. Like I had a patient who was going for a hike and said, “Now I have to take my hiking stick ’cause I don’t always know where my feet are in space.” So those are all things to advise your patients on as well.

We have carfilzomib, which is the next generation, a proteasome inhibitor. This drug was FDA approved in 2012, so relatively recently. The clinical trial that approved this drug had a 22.9 percent overall response rate. You might think that’s not that stellar. I actually participated in this trial and the patients were very, very heavily pretreated. So for people that had a lot of prior therapy, for almost a
quarter of them to respond was a big improvement. So initially this drug was approved for relapsed and refractory disease as a single agent, and more recently it has obtained a new FDA indication where we can give it with lenalidomide and dexamethasone in any relapsed setting. Before, it was initially approved for people who had already received bortezomib, already received an IMiD, usually lenalidomide, and then they could go on carfilzomib. Now it’s approved at first relapse and it’s with lenalidomide and dexamethasone in combination. Very powerful combination, so very nice response rates to that drug.

Side effects: fatigue, cytopenias, some nausea. Some of the things that are a little bit different is that your patients might have kind of a flu-like reaction, usually the evening that they get their carfilzomib. You can often make this less severe by pre-medicating them with a little bit of dexamethasone. The standard premedication is 4 mg. If they’re receiving it with Revlimid and dexamethasone in combination, they may get more of a therapeutic dose of dexamethasone. But if you give a little bit of dex before the carfilzomib goes in, we tend to see less of that. Dyspnea is reported by a third of patients. You want to look at the fluid balance. Traditionally when we start giving this drug, we give it with kind of a lot of fluid, and from there we can give less if the patient tolerates it. You may want to watch that if you have a patient with some congestive heart failure. If you have a patient that’s already edematous, you may want to cut back on that fluid and you may be able to help their dyspnea that way. But those are things that your patients may tell you. Those are things that you want to look out for.
Warnings: if someone already had pretty significant congestive heart failure or ischemia, you may want to watch them relatively closely. And another warning is that in the clinical trial, some tumor lysis syndrome did occur. Particularly when we think of tumor lysis, we usually think of lymphoma. So if you have someone that has lymphoma-like presentation, if they have extramedullary disease, if they have big, bulky soft tissue tumors, they’re kind of at risk for tumor lysis. If you have patients with plasma cell leukemia where if you see the plasma cells in their peripheral blood, that’s a very aggressive disease. That’s also a risk factor for tumor lysis.

Now we’re going to talk about the IMiDs, the immune modulating drugs, and we’ll start with the oldest IMiD, thalidomide. So thalidomide in the 1960s was used for morning sickness in pregnant women and many of you probably know the outcome of that. It was not good. Babies had severe birth defects. So they shelved thalidomide for a long time, and lo and behold it worked for multiple myeloma. So back in 1998 it was approved on a limited basis and they have a special risk management program that you’re probably familiar with if you prescribe any of these IMiDs. I used to have to actually call this and help my patients with it and I can still hear the lady’s voice in my head. But that’s to try to protect. We don’t want any women who are pregnant or who could become pregnant to be exposed to this drug, which is very important. It’s an oral drug, and when it first came out in the late 1990s it was a great improvement over the other therapies that were available.
With thalidomide you want to watch out. There’s a black box warning, so the fetal toxicity, also thrombosis which is a class effect. So thalidomide, lenalidomide, pomalidomide, increased risk of thrombosis. You’re going to look at your patient and make an individual decision, but most of our patients are at the minimum on an aspirin, an 81 mg aspirin. People who’ve had prior thrombotic events may be on full anticoagulation either with warfarin or one of the newer anticoagulants. That’s something that you want to prevent. They didn’t prevent it upfront when this drug first came out and we saw a lot of clots.

Cytopenia is probably less with thalidomide than many of our drugs. It tends to be well tolerated in terms of blood count. Neuropathy: neuropathy with this drug does occur. It tends to be progressive. It tends to be the longer you’ve been on it, the more likely someone is to get it. It tends to not be reversible so you really want to stay on guard with patients who’ve been on thalidomide for a while. Thalidomide, often we think of it as being a little less used these days with some of the newer IMiDs, but it is actually still used and it’s also useful as an adjunct therapy. So we do use it.

Then we have lenalidomide, which was FDA approved in 2005 for relapsed and refractory disease, and then just this year it was approved for initial therapy in patients. This is an oral therapy. Your patients may really like that. It’s well tolerated. I had a wonderful woman who went and tended a lighthouse, and the only way you could get to this lighthouse was by a ferry and she was going to stay there for a month and that was just one of her dreams and she got to do this. And guess what? She took her lenalidomide with her and she took it and
she was able to stay on myeloma therapy and enjoy that experience. Often we use this as induction therapy for older patients and it has the same black box warning as thalidomide regarding the fetal toxicity, the clot risk, and the cytopenias.

When my patients are on IMiDs I always tell them what the signs are of a blood clot, and I explain to them, “If one of your legs is red, we need to know right away. If you’re short of breath and we don’t understand why, we need to know right away,” and teach them what to look for. Also if they’re going on a long trip, I tell them to move around. I try to give them a little preventative coaching there without scaring them like crazy, hopefully. Common side effect of lenalidomide: cytopenias. So when you have a new patient on this drug you want to check their CBC fairly often. We often check weekly for the first month or two to make sure that they’re not going to become neutropenic. Diarrhea also can occur. And muscle cramps. People tend to have these charley horse kind of sharp, shooting pains. Usually those are managed. We can use things like, I’ve told people to drink tonic water. One of our doctors tells people to drink pickle juice if you can stomach pickle juice. Apparently it helps. And fatigue, like all our drugs.

And now, one thing to keep in mind with lenalidomide, we sometimes use it for induction but it can impair our ability to collect stem cells. So you don’t want your patient on lenalidomide for two years and then say, “I think I’m going to try to collect some stem cells.” If you think you might transplant this person ever, you’re going to treat them first up front for, I don’t know, maybe four months or so, then you’re going to collect their cells. And if you decide to go back to
lenalidomide and not transplant them, then you’ve got your cells and you can go back without worry about impairment. There’s some question regarding the increased risk of secondary malignancies, hematologic malignancies which seems to be in association with patients who’ve also been transplanted and who are on lenalidomide. So we want to watch for cytopenias, we want to watch of MDS or AML type symptoms that are not extremely common but could definitely be serious if they did occur.

And then we have pomalidomide which is the third generation IMiD drug and this was approved just back in 2013. And so this can still be an effective drug even if your patients failed the other IMiDs. It was originally approved in 2013 for relapsed and refractory patients who have already had lenalidomide who have already had bortezomib because those were our two gold standards. We give it with dexamethasone. It definitely seems to work better with dexamethasone. We had done a trial where they had some people with dexamethasone and some without and I remember quite clearly someone who wasn’t responding, we added a little bit of dex and it turned out to be a pretty good drug for him. And pomalidomide also appears promising in combination with proteasome inhibitors.

For pomalidomide there is the same black box warning: fetal toxicity, thromboembolism, particularly DVT and PE, cytopenias. The side effects seem to be a little more of a cross, a little more neuropathy than lenalidomide, a little more low blood counts than thalidomide. So it seems to be a little bit of a hybrid but you want to look for all those things. But often for patients, again, a well-tolerated oral therapy for their myeloma. Other drugs in use: we definitely use
alkylating agents. Cyclophosphamide. Often we use oral cyclophosphamide in combination, and there’s some data on there about cyclophosphamide, bortezomib, and dexamethasone. We use melphalan oral and we use melphalan IV as our conditioning for transplant. Steroids, which everybody knows and hates: dexamethasone and prednisone. Your patients will be on them for most of the myeloma therapies. Liposomal doxorubicin is also approved, and panobinostat is the newest drug to be FDA approved March of 2015 for relapsed refractory disease.

Clinical trials: Dr. Reeder has some information about that as well but I just really have to put in a plug for clinical trials. A lot of these drugs were recently clinical trials. We did clinical trials with pomalidomide. We did clinical trials with carfilzomib. This is how we’re making that survival better. The hot drug that you will probably be hearing from in the very near future, monoclonal antibodies, anti-CD38 antibodies. To be really quick and dirty, it’s kind of like the myeloma equivalent of rituximab. These drugs are in late phase clinical trials and will be looking at the FDA for approval in the near future for some of these medications.

We’re looking at ways to help the immune system be involved. We’re looking at oral forms of some of our drugs like oral proteasome inhibitors. We’re looking at genetic sequencing. We’re looking at gene profiling to try to tell us more about what people going to respond to, what’s their risk status. And so as of the time that I wrote this, there were 13 open trials for multiple myeloma at our center and seven that were pending. So if you ever feel like you’re stumped with
a patient, you don’t have to wait until their very end stage to talk about a clinical trial. So feel free to call us or feel free to call your local center that has a lot of clinical trials and see if there’s anything that might be of benefit to your patients. And with that, I’m going to turn it over to one of my wonderful supervising physicians, Dr. Reeder.

CRAID REEDER, MD Thank you, Angela. A very nice introduction. I thank the organizers for inviting us to talk to today. It’s always hard to follow Angela. She’s a great speaker and did a great job, although pickle juice doesn’t work in my experience for muscle cramps but we’ve all tried it.

We’ve made a lot of progress over the last three decades in learning about myeloma, and one thing we know is it’s not one disease. It’s really many diseases, and just analogous to what we’ve learned in acute leukemia over the last few years; the chromosome abnormalities often predict what the disease is going to do and what drugs might work for the disease, and the same thing is true now for multiple myeloma. When we first started looking at myeloma genetics—the chromosome makeup—metaphase chromosomes are often normal in multiple myeloma because the cells aren’t dividing rapidly. And then with the development of FISH, fluorescent in situ hybridization with antibodies that are fluorescent, you can identify mutations, extra chromosomes in the plasma cells that we didn’t see with routine cytogenetics, and that’s really changed the landscape of how we manage multiple myeloma now.

Here’s the usual kind of picture of routine metaphase cytogenetics, and this is a normal pattern. What we rarely see is an abnormal pattern with
metaphase cytogenetics. And one thing to remember is that when you do see an
abnormal metaphase cytogenetics patient in a patient with multiple myeloma,
that’s usually a high-risk feature. Those patients don’t tend to do well. This is a
picture of a FISH, and this particular translocation is 11;14 translocation which is
a fairly well described mutation, and again just showing you how these will light
up, and you can see the mutation of 11 and 14 together.

The importance of the FISH studies is shown on this slide, and this was
published by my colleague, Dr. Rafael Fonseca over ten years ago now showing
that the different mutations we find with FISH are prognostic. And with the top
green curve, you can see the 11;14 translocation and other things like
hyperdiploid or extra chromosomes as being a relatively good prognostic profile.
We used to actually call that good risk, and now we refer to it more as standard
risk. The changes of the translocation is 4;14, 14;16, 14;20, and deletion of
chromosome 17 are high-risk features and portend a poor prognosis.

And this is an example just showing what happens when you treat even
with modern three-drug regimens; this is a group of patients treated with
Cytoxan, bortezomib, and dexamethasone. If you look at the higher risk 4;14
translocation and deletion 17, their progression-free survival is markedly different
from patients that don’t have those high-risk cytogenetics. We also know that
stem cell transplant, which is a very common treatment modality for patients with
myeloma, doesn’t change the poor prognostic factors. And you can see here the
patients, that even with transplant, those that have a 4;14 translocation have a
shorter survival after transplant.
So the genetic classification is really two different groups of patients. There is the hyperdiploid. Those patients have extra copies of chromosomes and it’s usually the odd numbered chromosome. So it could be chromosome 5, 9, 11, 19 frequently, 15 frequently, and that’s a good prognostic profile. The nonhyperdiploid myelomas tend to do worse, and this includes some of those high-risk translocations or hypodiploid where there are fewer than the number of chromosomes in the particularly bad FISH translocations I’ve listed there, the 4;14, 14;16, and then of course deletion 17. So in the non-hyperdiploid group, there is the 11;14 translocation which is in that group, but this is actually one of the better prognostic markers. Now, conversely, that is sometimes the most common one seen in patients that have plasma cell leukemia. So the FISH profile by itself doesn’t tell you what the patient is necessarily going to do. It’s also associated with IgM myeloma which is a rare form of myeloma, and patients that have CD20-positive plasma cells will usually see the 11;14 translocation.

Translocation 4;14 again is a poor prognostic marker. I’m going to talk a little bit more about that in a minute. The 14;16 translocation is another poor prognostic marker, not as common. 14;20, another bad prognostic marker but relatively uncommon. And probably the worst thing that we can find in FISH is deletion of 17p, and that usually involves deletion of p53. I’ll just mention the deletion of chromosome 13 which is a very common mutation in myeloma. When you find it only by FISH, it doesn’t have any real prognostic significance. It’s highly associated with other mutations that are of poor prognosis. But if that’s the only mutation you find on FISH, it really is not a bad prognostic marker.
So myeloma prognosis—a lot of things are involved. We worry about the genetics of the disease, but also the age, performance status, the stage of the disease—as Angela mentioned, stage I, II, and III—and then whether or not patients have a response to therapy. And it’s important to know what the prognosis is when you’re talking to a patient. So we want to be able to find what is a high-risk patient and treat them appropriately, and we’ve talked about the FISH, also the metaphase cytogenetics abnormality is a high-risk feature. If you do a test to look at the proliferative index, we commonly do a plasma cell labeling index, when that’s high that’s a poor prognostic factor. Plasma cell leukemia: of course patients have a relatively poor outcome. High LDH is a very strong prognostic marker. Beta-2 microglobulin and albumin of course because they’re a part of the International Staging System criteria. And also failure to respond to one of the novel agents. So if you have a patient that’s on Revlimid and dexamethasone or bortezomib and dexamethasone for induction therapy and fails to have a response, those patients do quite poorly.

And this is actually from Dr. Gertz, presented a couple years ago, showing that even with transplantation the difference in patients that have a plateau or response to their novel agent before they go to transplant versus those that are refractory. There’s a very different outcome as far as survival. Gene expression profiling is one of the newest tools we have to look at the genetic makeup of the plasma cell, and this was first done at University of Arkansas and a French group did shortly after that, and showed that at certain signature, they can predict what the prognosis was. And the problem was in the first two studies that were done
looking at the gene expression profile, there wasn’t much overlap between the two different signatures. And I think there are other people doing signature profiling now and hopefully over time we’ll see that we’re going to have the best profile to tell us what’s going to happen. This is from the Arkansas group, and you can see there are two distinct signatures that are predicted for outcome in myeloma.

So I’m going to talk a little bit about mSMART now. This is the Mayo Stratification for Myeloma and Risk-Adapted Therapy, and this is a consensus from all the people at Mayo involved with myeloma care, and it’s based on the genetics and also other prognostic factors that we just mentioned. And this is something that we actually put on the internet. There’s mSMART.org. You can go to that site and this site is updated every year or two. There’ll be a new update after ASH in December. Probably in January we’ll have a new update. I’m not going to go through the fine print here, but just mention that this is a risk stratification to individualize treatment for the patient. It also takes in not just the cytogenetic risks, but stage of the disease, LDH, and other factors.

This is the classification looking mainly at the genetic makeup. The high-risk patients are over on the left, again showing the mutations by FISH. We also put in there the high-risk GEP signatures. We think that’s high risk. Intermediate: I mentioned earlier the 4;14 translocation we used to consider a high-risk mutation. We put it in the intermediate group and I’ll explain that in just a minute. Deletion 13. Then there’s standard risk. Patients have the extra chromosomes, the hyperdiploid patients, 11;14 and the 6;14. So if you look at the 4;14 patients,
we now realize that that is not really always a high-risk feature. If you combine that with the ISS stage, and this study was published a couple years ago on leukemia, patients that have the 4;14, if they have a low staging system, they don’t do as bad. But the 4;14 translocation will lower each stage prognosis. You can see the blue curve at the top is absence of 4;14, and then the red curve below that is the presence. But that’s still doing much better than the patients that don’t have the 4;14 translocation who are at advanced stage disease. So we now think this is more of an intermediate risk factor.

So these are guidelines for management of patients based on their risk. There’s standard risk, intermediate, and high risk. And again, patients that have hyperdiploid, the trisomies or the 11;14 translocation, patients can be managed with Revlimid and dexamethasone. They could be treated with Cytoxan, Velcade dexamethasone, the CyBorD regimen, which we commonly will use. We’ll offer those patients transplant after their induction therapy, and then you can continue on therapy afterwards if they don’t have a good response. Patients that have intermediate risk will feel very strongly that they need to have a bortezomib-based therapy or another proteasome inhibitor-based therapy. We offer them transplant as well, but they need to have some maintenance therapy or consolidation afterwards with a proteasome inhibitor.

The high-risk patients, 17p especially, patients need to have all drugs up front. We need a proteasome inhibitor, an IMiD, dexamethasone with that for the best outcome. It’s important to get those patients rapidly into as deep a response as possible and then take them to transplant and then continue therapy
afterwards because transplant, as I showed you earlier for the 17 deleted and the 14;16 patients, if you just transplant and don’t put them on any kind of maintenance therapy, they’ll all relapse within about six months. The same scheme holds true if you’re not going to do transplant but you obviously need to continue therapy longer than the standard risk patients. The Rd patients, we keep those continually on Revlimid and dexamethasone. There’s no need to take them off. CyBorD, if you’re not going to go to transplant, they’re not eligible, then continue therapy for a year and then you can observe. Same for the high-risk patients. You need to continue them on primarily triplet therapy or at least have a proteasome inhibitor long term to try and maintain their remission.

So high-risk myeloma: we need to get a complete response for long-term control. You need to have very aggressive therapy, usually a triplet regimen, VRD, KRD. We’re waiting for the results of the endurance trial which is comparing carfilzomib to bortezomib kind of head to head for newly-diagnosed patients, and hopefully we’ll have that information in the next couple of months. The intermediate risk patients, the CyBorD or VCD regimen is an adequate therapy. And then for standard risk patients, we know the survival is the same. Whether or not you put them in a complete remission or a very good partial remission, they’re still going to have a good outcome so you can do more of a sequential therapy rather than giving all the drugs up front.

This shows the results of what we’re doing with moderate therapy. This is of the group of CyBorD patients looking at long term survival with triplet therapy. For all patients overall survival now is over 70 percent at five years. If you break
it down by their FISH, the high risk versus standard risk patients, it’s still clear that the standard risk patients are going to do very well. And at six years, over 80 percent of patients are still alive. So the usual treatment paradigm, Angela talked about induction therapy then transplant. Continuing therapy versus going to transplant is maybe an option for some patients, so I’m going to attend to just a couple more things about stem cell transplant.

Most of the transplant studies done have shown improvement in progression free survival compared to standard therapy without transplantation. A couple of them show overall survival benefit as well. The next point is that it’s a very low risk procedure. The mortality is about one percent, so even in elderly patients in their 70s, if they have minimal other comorbidities, they ought to be considered for transplant. We know that transplant deepens the response, so patients typically after induction therapy hopefully will have a partial, a very good partial response, even maybe a near complete response; they’re going to benefit by going through transplant. Second transplant after patients have had a relapse is still considered. It doesn’t seem to do much good if patients have a very short remission after their first transplant, but if someone’s had a remission of a year and a half or two years, we will usually do a second transplant, at least offer it.

I’m going to skip this slide for time’s sake and mention just some points about the induction therapy of patients going to transplant. Thalidomide probably doesn’t have any effect or detrimental effect on our ability to harvest stem cells, but lenalidomide can. If patients have more than four, five, or six months of therapy with lenalidomide, it’s harder to collect stem cells. Until we have the drug
AMD3100 or Mozobil, those patients could be tough to get stem cells from. Bortezomib doesn’t have any impact on the ability to collect stem cells, and the other chemotherapy drugs like the alkylating agents we showed with the CyBorD regimen showed that Cytoxan is not a problem; however, melphalan is. Melphalan is very toxic to stem cells. So if a patient has had induction therapy with a melphalan-based regimen, it can be impossible to collect stem cells. And I’m going to skip that one also.

Maintenance therapy: Thalidomide was studied in several different clinical trials to look and see if this would improve survival. And most of the studies showed benefit not just in progression-free survival, but some showed overall survival benefit. The problem with thalidomide was the toxicity. A very high percent of the patients actually came off the studies because of profound fatigue, constipation, and neuropathy. Lenalidomide is studied now in two different trials looking at the benefits. Both trials show benefits in progression-free survival. One of them shows some overall survival benefit.

The concern with lenalidomide maintenance has been secondary-cancer risk which appears to be a real phenomenon. The risk is not terribly high. And many proponents of lenalidomide maintenance say that the benefit of being in remission longer with your myeloma outweighs the risk of a second cancer. There is some early data with bortezomib maintenance. It does appear to be active. We don’t know what the right schedule is. I think a lot of people are using this at every two-week kind of schedules. Sometimes Cytoxan, bortezomib, dexamethasone every two weeks for the intermediate or high risk patients.
We have an mSMART classification for relapsed patients as well. I'm not going to go through all these slides. They're available on the internet so I'm going to skip ahead for time sake here. So for patients that have had a very aggressive relapse, that relapsed with new mutations, or may have acquired a 17p deletion or might have extramedullary disease or plasma cell leukemia, one of the regimens that can be effective is infusional therapy with DT-PACE or VDT-PACE. This is infusional therapy typically done in the hospital. It’s very active, very effective. It’s profoundly myelosuppressive, but it can get you results. It can get you a patient back in a remission. But unfortunately, those patients won’t stay in remission. You need to have a final plan. So if you take somebody to give them VD-PACE, you have to get them to another transplant or you have to get them on a clinical trial because this won’t produce any real long-term responses. It’s kind of a bridge to some other therapy.

Future therapies: so these are some of the newer drugs Angela mentioned, we now have oral proteasome inhibitors, ixazomib or MLN9708, oprozomib which is more akin to carfilzomib is studied. Monoclonal antibodies are some of the most exciting new drugs that are coming along in myeloma. KSP inhibitors, histone deacetylase inhibitors like panobinostat which was of course recently approved, Akt inhibitors, Bcl-2 inhibitors. We have an ongoing trial right now with an oral drug, ABT-199 that’s showing some pretty impressive results in subtypes of multiple myeloma. So that’s very exciting. Dinaciclib is a trial that we have at Mayo right now. The nuclear transport selinexor is a trial we have
ongoing right now at Mayo. I'm going to just skip ahead and mention the 38 antibodies.

So CD38 is present on nearly all plasma cells and there are two drugs now that are being looked at in clinical trials. One, daratumumab, and the other one is still abbreviated SAR from Sanofi. Both of these have gone through phase I and now in phase II and even for daratumumab phase III trials, and we're hoping that this is going to be like a Rituximab for myeloma. This is one of the early studies looking at responses, patients that had the full dose 16 mg/kg dose, 35 percent response rate, and this is in heavily-pretreated patients that have refractor myeloma. And that’s really a pretty impressive result. So I think what we’re going to see now is that drug combined with other active agents and see the drug moved up front to induction therapy like we saw with rituximab.

So to summarize, baseline genetic information should be obtained in all cases of multiple myeloma. The minimal testing needed is FISH panel, LDH, beta-2 microglobulin, and albumin. So the ISS staging, FISH, and LDH. GEP signatures I think ideally we’ll get more information and know where to use those and I think eventually they’re going to be more powerful than doing FISH. Again, there are multiple tools. You have to risk stratify your patient, and then risk determination is going to be important for you to guide your patient to have the best outcome. This is a group of our myeloma consultants in Rochester, Arizona, and Florida. And I think we’ll stop. We’ve got a couple minutes for questions.

WENDY SMITH, RN, MSN, ACNP, AOCN I’m going to ask you all to just quickly do the post-test questions and then we’ll open it up for Q and A for Dr.
Reeder and Angela here. So if we can get those back up. Number one: During initial diagnosis and workup for patients with multiple myeloma, FISH analysis showed hyperdiploidy, translocation 11;14, and translocation 6;14. What would you classify this as? High risk, intermediate risk, or standard risk? And then second question: You are seeing a patient who is on pomalidomide after receiving prior therapy with lenalidomide and bortezomib. She presents with cough, dyspnea, and pleuritic chest pain. Which of the following would be the top of your list for differential diagnosis? So just take a moment there. All right. And then we will open it up for questions if you have them. Questions? There’s one back here.

ATTENDEE Thanks, Wendy. Hi, thank you. Excuse me. Thank you very much. Julie Ponto from Rochester. I’m just wondering if any of the genetic alterations are more or less common by race or ethnicity. So is there a prevalence of any of the particular generic alterations in African Americans or Caucasians, or has that been looked at?

DR. REEDER I’m not sure that’s been looked at. I can’t answer that. I’m not sure that’s been looked at.

Ms. ANGELA MAYO I saw something that was—I don’t know that it was conclusive, but it was in—I was doing some research about African Americans and multiple myeloma that actually more of them seem to have hyperdiploid or less aggressive disease, but sometimes their outcomes still were less favorable, and so that was one other thing that we were looking at is how to treat those people more effectively.