Welcome and Introductions

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Multiple Myeloma (MM)

- Prevalence
  - 20,180 estimated new cases in the U.S. in 2010
  - Median age at diagnosis: 70 years
  - Median survival
    - 3 years conventional therapy
    - 4–5 years high-dose therapy
  - >10,000 patients with MM die each year in the U.S.
- Population subgroups
  - Incidence is twice as high in African Americans
  - More frequent in men than in women
  - Long-term disease control is possible in a fraction of patients

Multiple Myeloma – Description

- Characterized by a plasma cell dyscrasia producing a monoclonal immunoglobulin
- Proliferation often results in extensive skeletal destruction (e.g., osteolytic lesions, hypercalcemia, anemia)
- Excess production of M protein can result in renal failure, hyperviscosity syndrome, recurrent bacterial infections, and hematopoietic and immune dysfunction

Myeloma Cells
The Immunoglobulin Molecule

- B-cell final product is immunoglobulin (Ig)
- Ig is key piece of immune function
- B cells are stimulated by T cells as well as APCs
M Protein Analysis

Criteria for Diagnosis of Myeloma

**MGUS**
- <3 g M spike
- <10% plasma cells

**SMM**
- ≥3 g M spike
- ≥10% plasma cells

**Active MM**
- ≥10% plasma cells
- M spike +

AND

No anemia, bone lesions, normal calcium, or kidney function

AND

Anemia, bone lesions, high calcium, or abnormal kidney function

MGUS, monoclonal gammopathy of unknown significance; SMM, smoldering multiple myeloma.

Smoldering Multiple Myeloma (SMM)

- 27% will convert in 15 years
  - Roughly 2% per year
- 40% will convert in 4 years
  - Roughly 10% per year

Free Light Is Useful for Risk Assessment in SMM

Table 3. Multivariate analysis of prognostic factors for progression of SMM to myeloma and related disorders

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow plasma cells more than 10%</td>
<td>3.1 (1.8-6.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Abnormal FLC ratio less than 0.126 or more than 8</td>
<td>1.9 (1.3-2.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Serum M protein size, more than 30 g/L</td>
<td>1.9 (1.4-2.6)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
Updated IMWG Criteria for Diagnosis of Multiple Myeloma

**MGUS**
- M protein <3 g/dL
- Clonal plasma cells in BM <10%
- No myeloma defining events

**SMM**
- M protein ≥3 g/dL (serum) or ≥500 mg/24 hours (urine)
- Clonal plasma cells in BM ≥10%–60%
- No myeloma defining events

**Multiple Myeloma**
- Underlying plasma cell proliferative disorder
- AND 1 or more myeloma defining events
- ≥1 CRAB* feature
- Clonal plasma cells in BM ≥60%
- Serum free light chain ratio ≥100
- >1 MRI focal lesion

*C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than upper limit of normal)
*R: Renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
*A: Anemia (hemoglobin <10 g/dL or 2 g/dL < normal)
*B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

BM, bone marrow; CT, computed tomography; IMWG, International Myeloma Working Group; PET, positron emission tomography.

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**Improving Survival in MM**

- The use of high-dose therapy (HDT) or melphalan-based novel agent induction therapy has doubled median survival for nearly all patients

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Goals of Induction Therapy

- Achieving maximal response
  - \( \geq \) Very good partial response (VGPR) vs complete response (CR) vs minimal residual disease (MRD)
- High response rate; rapid response
- Improve performance status
- Minimize negative effects on quality of life
- Not limit PBSC mobilization (for younger patients)
  - Do goals depend on cytogenetics and/or prognostic factors?
  - Is CR the main endpoint?

**PBSC, peripheral blood hematopoietic stem cell.**

**Benefit Associated With CR**

**IFX- CR in young patients**
- N=635
- EFS
- IFX- CR in elderly patients
- N=1175
- PFS
- OS

**MRD- CR in young patients**
- N=147
- EFS
- OS

EFS, event-free survival; IFX-, immunofixation negative; MRD-, minimal residual disease negative; OS, overall survival; PFS, progression-free survival.


MRD negative
- Median : 71 mo
- P = 0.009
- 59%
- 87%

MRD positive
- Median : 37 mo
- P < 0.001
- 30%
- 62%
3 Drugs Are Better Than 2

Factors That Influence Improved Outcomes

- Better induction
- Increasing role of maintenance
- Longer duration of therapy
- Increased use of HDT

Better Drugs

Better Depth of Response
Transplant in Era of Novel Agents: Survival Benefit Continues


Getting to MRD: New Definitions for CR

S.S. Patient

Disease burden

Newly diagnosed $1 \times 10^{12}$

CR $1 \times 10^8$

Stringent CR

Molecular/Flow CR $1 \times 10^4$

?-Cure? $0.0$

Bortezomib Lenalidomide Antibodies
What Happens When the Best Are Combined?

RVD Induction ➔ HDT ➔ RVD Consolidation ➔ Lenalidomide Maintenance

Current Considerations for Initial Treatment of MM

➢ Induction for younger patients
  - 3-drug induction followed by autologous transplant and consolidation in first response¹
  - Maintenance therapy post-autologous transplant²
  - Maximize duration of first response³,⁴
  - Assessing depth of response and understanding implications for patient outcomes⁵

Recommendations for Salvage Therapy in Multiple Myeloma

**Preferred Regimens**

- **NCCN Category 1**
  - Bortezomib
  - Bortezomib + PLD
  - Lenalidomide + dexamethasone (RD)

- **NCCN Category 2A**
  - Repeat induction if relapse >6 months
  - Bortezomib + dexamethasone (VD)
  - Lenalidomide + bortezomib + dexamethasone (RVD)
  - Carfilzomib
  - Cyclophosphamide + VD, or RD
  - HD cyclophosphamide
  - DCEP
  - DT-PACE ± bortezomib
  - Pomalidomide/dexamethasone
  - Thalidomide + dexamethasone (TD) ± bortezomib

**Other Regimens**

- **NCCN Category 2A**
  - Bendamustine
  - Bortezomib + vorinostat
  - Lenalidomide + bendamustine + dexamethasone

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DCEP, dexamethasone/cyclophosphamide/etoposide/cisplatin; DT-PACE, dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide; NCCN, National Comprehensive Cancer Network; PLD, pegylated liposomal doxorubicin.


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**Questions in the Relapsed Setting**

- Is 3 better than 2 in early relapse?
- Is 2 more than enough in late relapse?
- How do we choose among salvage treatments in early relapse (proteasome inhibitor vs immunomodulatory drug based)?
Selecting Salvage Therapy: General Principles\textsuperscript{1,2}

- Patients with indolent disease, first relapse:
  - Bortezomib or lenalidomide, depending on response to and composition of initial treatment, presence of renal dysfunction, or underlying peripheral neuropathy
  - Watch and wait for low-level M protein (0.2/0.3)

- Patients with aggressive disease, rapid progression, multi-relapse:
  - Combination therapy preferred; do not wait for symptomatic relapse
  - Combinations of novel agents with chemotherapy/dexamethasone an option

- Patients who relapse from non-SCT treatment or Patients with long duration of benefit from first SCT or Patients in whom response likely to be short lived:
  - Transplant-based salvage therapy a potential option in eligible patients
  - New additions: carfilzomib, pomalidomide
  - Emerging agents: elotuzumab, ixazomib, panobinostat

**Drugs in Relapse**

- Proteasome inhibitors
  - Bortezomib, carfilzomib, MLN 9708, oprozomib

- Immunomodulatory drugs (IMiDs)
  - Lenalidomide, pomalidomide

- Histone deacetylase (HDAC) inhibitors
  - Panobinostat, Acy-2115

- Antibodies
  - Elotuzumab, daratumumab

- Other
  - KSP, CDK, KPT

Tao of Myeloma Therapy: Mutations Are Not Everything

Tamoxifen
Androgen Ablation

“Normal” Cell Biology

Proteasome Inhibitors
IMiDs?

“Tumor” Cell Biology

Melphanal
Doxil

IMiDs?
Anti-DKK1?

FGFR3 Inhibitors

BRAF inhibitors?

Need to Define Targeting Plasma Cell Biology and Targeting Proliferation

 Targets for Monoclonal Antibodies

Figure 1

CD229
CD200
CD23
CD13

CD138

IL-6
Siloximab

BAP
Tabalumab

APRD

MM cell


In clinical development
Preclinical activity
Potential targets
Daratumumab Response

Lokhorst et al. ASCO. 2013.

Elotuzumab Background

Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein. CS1 is highly expressed on >95% of MM cells - Lower expression on NK cells - Little to no expression on normal tissues

Elotuzumab is believed to work primarily through NK cell-mediated ADCC against myeloma cells

In a MM xenograft mouse model, the combination of elotuzumab + lenalidomide significantly reduced tumor volume compared with either agent alone

ADCC, antibody-dependent cellular cytotoxicity; mAb, monoclonal antibody; NK, natural killer.

Progression-Free Survival (PFS) From the Phase II Cohort

- In the 10-mg/kg cohort, median PFS was 33 months
- In the 20-mg/kg cohort, the median PFS was 18 months

Safety Summary: IMiDs in 2014

**Thalidomide**
- Neuropathy
- DVT
- Myelosuppression
- Rash

**Lenalidomide**
- DVT
- Myelosuppression
- Rash

**Pomalidomide**
- Neutropenia at ↑ doses
- DVT

DVT, deep vein thrombosis.
Managing Myelosuppression With IMiDs

- Myelosuppression associated with IMiDs requires early recognition and management to avoid infections and treatment interruption

<table>
<thead>
<tr>
<th>Neutropenia Management in Myeloma Patients Receiving Pomalidomide¹</th>
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<tbody>
<tr>
<td><strong>When Neutrophils Fall to &lt;500/mcL or FN (fever ≥38.5°C and ANC &lt;1,000/mcL)</strong></td>
</tr>
<tr>
<td>Recommendation</td>
</tr>
<tr>
<td>ANC return to ≥500 per mcL</td>
</tr>
<tr>
<td>For each subsequent drop to &lt;500/mcL</td>
</tr>
<tr>
<td>Return to ≥500/mcL</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; CBC, complete blood count; FN, febrile neutropenia.


Thrombosis in Myeloma: Risk Factors and Prevention¹

<table>
<thead>
<tr>
<th>Individual Risk Factors</th>
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<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>History of VTE</td>
</tr>
<tr>
<td>Central venous catheter</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Cardiac disease</td>
</tr>
<tr>
<td>Immobilization</td>
</tr>
<tr>
<td>Surgery</td>
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<tr>
<td>Inherited thrombophilia</td>
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<table>
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<tr>
<th>Myeloma-Related Risk Factors</th>
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</thead>
<tbody>
<tr>
<td>Diagnosis</td>
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<tr>
<td>Hyperviscosity</td>
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0 or 1 individual risk factor present: once-daily aspirin

≥2 individual or myeloma-related risk factors: LMWH (once-daily enoxaparin) or full-dose warfarin

LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Thrombosis in Myeloma: Risk Factors and Prevention (Cont’d)

Therapy-Related Risk Factors

- High-dose dexamethasone
- Doxorubicin
- Chemotherapy with thalidomide or lenalidomide (likely with all IMiDs)

- LMWH or full-dose warfarin regardless of additional risk factors

- In low-risk patients receiving lenalidomide, aspirin appears to be effective thromboprophylaxis


Other Important Safety/Adjunctive Issues

<table>
<thead>
<tr>
<th>When Neutrophils</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone protective therapy¹</td>
<td>Bisphosphonates recommended for all patients with myeloma receiving primary therapy</td>
</tr>
<tr>
<td>Hydration</td>
<td>Assess patient for dehydration, counsel on fluid intake, and intervene aggressively to correct</td>
</tr>
<tr>
<td>GI/Nutritional issues associated with steroids</td>
<td>Caution: overzealous hydration may lead to hyponatremia</td>
</tr>
<tr>
<td></td>
<td>Counsel patients on maintaining weight</td>
</tr>
<tr>
<td></td>
<td>Fruit/vegetable-rich diet</td>
</tr>
<tr>
<td></td>
<td>Protein intake, avoid concentrated sweets and carbohydrates</td>
</tr>
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</table>

GI, gastrointestinal.

Discussion: Speaking With the Patient About Adverse Events

In collaboration with nurse professional...

• Discuss the potential for toxicity such as peripheral neuropathy or myelosuppression when combining proteasome inhibitors with IMiDs

• Discuss options for thromboprophylaxis with IMiDs

• Antibiotic prophylaxis with proteasome inhibitors
  – Possibly for all patients with myeloma

• Recommend/educate the patient on nonpharmacologic strategies for adverse events/symptoms

PETHEMA Cure With Old Drugs: What About All the Clones?

![Figure 2](image)

Functional cure?

Conclusions

- Defining symptomatic MM is in evolution
- Aggressive therapy continues to require aggressive induction (3 drugs) and consolidation with transplant and maintenance
- Options in relapse are increasing and, for now, are not used based on a biomarker
- Immune therapy is on the way!

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IMS

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IMS
Question-&-Answer Session

The speaker’s slides are available for download at [www.LLS.org/programs](http://www.LLS.org/programs)

The Leukemia & Lymphoma Society (LLS) offers:

- Live, weekly Online Chats are moderated by an oncology social worker and provide a friendly forum to share experiences.
  - WEBSITE: [www.LLS.org/chat](http://www.LLS.org/chat)

- Co-Pay Assistance Program offers financial assistance to qualified cancer patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.
  - WEBSITE: [www.LLS.org/copay](http://www.LLS.org/copay)
  - TOLL-FREE PHONE: (877) LLS-COPAY

- For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.
  - TOLL-FREE PHONE: (800) 955-4572
  - EMAIL: infocenter@LLS.org