Applying a Congruent Oncology Pharmacy Strategy – From Guidelines to Specialty Pharmacy: Steps for Success with Multiple Myeloma

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Optimizing Therapeutic Decision-Making for Multiple Myeloma: A Clinical Overview
Part 1

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Disclosures

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Outline

• Multiple Myeloma (MM): Definition and Description
• Principles of MM Management
  – NCCN guidelines
  – Indicators of Treatment Outcomes
  – Risk Stratification and Staging
• Treatment of MM
  – Initiating treatment
  – When to transplant
  – Post-transplant therapy
  – How to treat relapse
• Summary
Definition and Description
Prevalence and Burden of Multiple Myeloma

- 22,350 new cases and 10,710 deaths from MM are projected for the United States in 2013
  - Accounts for 1% of all malignancies and about 10% of hematological cancers
  - Accounts for 2% of deaths from all cancers and 20% of deaths from hematological cancers
- Slightly more common in men than women
- Incidence in African Americans is about twice that of whites
- Median age at diagnosis is 69 years for men and 71 years for women
  - Age <50 years: 10%
  - Age <40 years: 2%

Features of Multiple Myeloma

- B-cell malignancy derived from antibody-producing plasma cells in the bone marrow
- Proliferation of myeloma cells leads to
  - Excessive production of a monoclonal antibody (M-protein)
  - Adverse events on various organ systems

Reproduced with permission from the Multiple Myeloma Research Foundation Web site. Available at: http://www.multiplemyeloma.org/about_myeloma/index.html

Serum Protein Electrophoresis

Normal

Monoclonal Protein in Myeloma

Principles of Multiple Myeloma Management
MM Follows a Course of Response and Remission


MGUS=monoclonal gammopathy of unknown significance.
Progression to Symptomatic MM

- **MGUS**: Up to 3% of persons 50 years of age or older and ~ 6% of those older than 70 years
- For asymptomatic myeloma, maximum risk in the first 5 years

![Graph showing progression of MGUS and Smoldering MM](image)

**MGUS**=monoclonal gammopathy of unknown significance.

NCCN Clinical Practice Guidelines Provide Evidence-Based Direction to MM Care

- Includes standards for diagnosis, prognosis, treatment, and follow-up
- Comprehensive guidance across the natural history of the disease
- Identifies primary treatment modalities
- Includes supporting references, background information, and discussion of ongoing controversies
- Integrates clinical data and expert judgment

NCCN=National Comprehensive Cancer Network.
National Comprehensive Cancer Network. Available at: NCCN.org.
MM Survival is Improving

Median 7.3 years

5 Year Survival by Age

<table>
<thead>
<tr>
<th>Time Period</th>
<th>≤ 65 years</th>
<th>&gt; 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2010</td>
<td>73%</td>
<td>56%</td>
</tr>
<tr>
<td>2001-2005</td>
<td>63%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Trial Endpoints Beginning to Influence MM Reimbursement Decisions

- Payers are increasingly insisting that agents and regimens demonstrate improvement in outcomes before their cost will be fully reimbursed.
- Overall Survival (OS) has historically been the gold standard endpoint for a new oncology drug approval.
- Recently, approval has been based on surrogate endpoints, including objective response rate (ORR), progression-free survival (PFS), disease-free survival (DFS), and time to progression (TTP).
  - However, surrogate endpoints do not always translate into a survival benefit as long-term data mature.
- Use of different endpoints makes the practice of comparing therapies difficult.

### Multiple Myeloma Response Criteria

<table>
<thead>
<tr>
<th>Response category</th>
<th>Response criteria</th>
</tr>
</thead>
</table>
| **Stringent complete response (sCR)** | • CR as defined below plus:  
• Normal free light chain ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence |
| **Complete response (CR)** | • Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow |
| **Very good partial response (VGPR)** | • Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 hr |
| **Partial response (PR)** | • ≥50% reduction of serum M-protein and reduction in 24 hr urinary M-protein by ≥90% or to <200mg per 24 hr |
| **Minimal response (MR)** | • ≥25% but ≤49% reduction of serum M-protein and reduction in 24 hr urine M-protein by 50%-89% |

Which Disease Response Criteria is Best?

Depth of Response is related to TTP

TTP=time to progression; MR=minimal response; PR=partial response; VGPR=very good partial response; nCR=near complete response; CR=complete response; sCR=stringent complete response; iCR=initial complete response.

# Staging of MM: Key Components

<table>
<thead>
<tr>
<th>ISS Stage</th>
<th>Criteria</th>
<th>Median Overall Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum β2-microglobin &lt;3.5 mg/dL AND Serum albumin ≥3.5 g/dL</td>
<td>62</td>
</tr>
<tr>
<td>II*</td>
<td>Neither Stage I nor Stage III</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2-microglobin ≥5.5 mg/dL</td>
<td>29</td>
</tr>
</tbody>
</table>

*There are 2 categories for Stage II: serum b2-microglobin <3.5 mg/dL, but serum albumin <3.5 g/dL, or serum b2-microglobin <3.5 to <5.5 mg/dL, irrespective of the serum albumin level.

ISS=International Staging System.

## Risk-Stratification Based on Tumor Biology

<table>
<thead>
<tr>
<th>High Risk*</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
</table>
| • 17p deletion  
• t(14;16) (C-MAF)  
• t(14;20) (MAF-B)  
• GEP | • t(4;14) (FGFR3/MMSET) | All others including:  
• Hyperdiploidy  
• t(11;14) (CCND1)  
• t(6;14) (CCND3) |

- Complete Response appears critical
- Bortezomib critical
- Excellent outcome

*Presence of trisomies ameliorates high risk.

C-MAF=cellular musculoaponeurotic fibrosarcoma oncogene homolog; MAF-B=musculoaponeurotic fibrosarcoma oncogene homolog B; GEP=gene expression programming; FGFR3=fibroblast growth factor receptor 3; MMSET=multiple myeloma set domain; CCND1= cyclin D1; CCND3= cyclin D3.

Complete Response (CR) is Critical in Patients With High-Risk Myeloma

Low-Risk MM (87%)

High-Risk MM (13%)

CR=complete response; NR=no response.

Multiple Myeloma Treatment Strategies
Approach to Newly Diagnosed MM

**High Risk**
- VRD x 4 cycles
- Transplant Eligible
- ASCT; 2nd ACST if not in CR or VGPR
- Bortezomib-based maintenance

**Intermediate Risk**
- VCD x 4 cycles
- Transplant Eligible
- ASCT; 2nd ACST if not in CR or VGPR
- Bortezomib maintenance for 2 years

**Standard Risk**
- Rd (or VCD) x 4 cycles
- Transplant Eligible
- Early ASCT (preferred) or Delayed ASCT*†
- Lenalidomide maintenance if not in CR or VGPR following ASCT

†Dexamethasone usually discontinued after 12 months; continued long-term lenalidomide is an option for patients who tolerate treatment well.

VRD=bortezomib + lenalidomide + dexamethasone; VCD=bortezomib + cyclophosphamide + dexamethasone; Rd=lenalidomide + low dose dexamethasone; ASCT=autologous stem cell transplant; CR=complete response; VGPR=very good progressive response.

VTD vs TD After Double ASCT in Newly Diagnosed MM

**VTD**
- **n=480**
- **RANDOMIZE**
  - ≤ 65 years
  - 3 x 21-day cycles
  - PBSC collection
  - CTX
- **CONSOLIDATION**
- **Bortezomib 1.3 mg/m² days 1, 4, 8, 11**
- **Thalidomide 100 → 200 mg/days 1-63**
- **Dexamethasone 320 mg/cycle**

**TD**
- **Thalidomide 200 mg/day, days 1-63**
- **Dexamethasone 320 mg/cycle**

**Primary endpoint:**
- CR/near CR after 3 cycles of induction

VTD=bortezomib + thalidomide + dexamethasone; TD=thalidomide + dexamethasone; PBSC=peripheral blood stem cell; CTX=cyclophosphamide; MEL200=melphalan 200 Mg/m2; CR=complete response.

VRD Phase Combination Therapy in Newly Diagnosed MM: Phase I/II Trial

- MTD based on phase I: lenalidomide 25 mg/day; bortezomib 1.3 mg/m2; dexamethasone 20 mg/day, cycles 1–4, 10 mg/day, cycles 5–8
- Antithrombotic therapy: Aspirin 81–325 mg daily; Acyclovir or equivalent for HZV prophylaxis
- With a median follow up of 27.3 months TTP, PFS, and OS have not been reached
  - 18-month PFS: 75%
  - 24-month OS: 97%

VRD=bortezomib (Bz) + lenalidomide + dexamethasone (Dex); MTD=maximum tolerable dose; HZV=herpes zoster virus; TTP=time to progression; PFS=progression-free survival; OS=overall survival.

## Best Response to VRD

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (n=66)</th>
<th>Phase II (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>CR</td>
<td>19 (29)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>nCR</td>
<td>7 (11)</td>
<td>7 (20)</td>
</tr>
<tr>
<td>VGPR</td>
<td>18 (27)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>PR</td>
<td>22 (33)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>CR + nCR</td>
<td>26 (39)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(29, 50)</td>
<td>(42, 71)</td>
</tr>
<tr>
<td>CR + nCR + VGPR</td>
<td>44 (67)</td>
<td>26 (74)</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(56, 76)</td>
<td>(59, 86)</td>
</tr>
<tr>
<td>At least PR</td>
<td>66 (100)</td>
<td>35 (100)</td>
</tr>
<tr>
<td>(90% CI)</td>
<td>(96, 100)</td>
<td>(92, 100)</td>
</tr>
</tbody>
</table>

- Response improvement seen in 42/56 patients (75%) from Cycle 4–8 and 20/38 patients (53%) beyond Cycle 8
- Median (range time) to best overall response was 2.1 (0.6, 20) months

VRD=bortezomib + lenalidomide + dexamethasone; CR=complete response; nCR=near complete response; VGPR=very good partial response; PR=partial response; CI=confidence interval.

Evaluation of the 3 Drug Combination VRD in Newly Diagnosed MM

**SWOG/ECOG S0777: Phase III Newly Diagnosed MM**

- **Primary Objective:** Compare progression-free survival of patients with newly diagnosed MM treated with lenalidomide and low-dose dexamethasone with or without bortezomib.
- **n=440**

VRD=bortezomib + lenalidomide + dexamethasone; SWOG=Southwest Oncology Group; ECOG=Eastern Cooperative Oncology Group; RD= lenalidomide + dexamethasone; CR=complete response; PR=partial response.

### Bortezomib Induction with CyBorD in Newly Diagnosed MM

<table>
<thead>
<tr>
<th></th>
<th>CyBorD</th>
<th>Modified CyBorD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response ITT</strong></td>
<td>n=33</td>
<td>n=30</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>88%</td>
<td>93%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td>CR/nCR</td>
<td>39%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 AE</td>
<td>48%</td>
<td>37%</td>
</tr>
<tr>
<td>Grade 4 AE</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>PN Grades 1/2</td>
<td>58%</td>
<td>57%</td>
</tr>
<tr>
<td>PN Grade 3</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- CyBorD: cyclophosphamide 300mg/m2 orally on days 1, 8, 15 and 22, bortezomib 1.3mg/m2 IV on days 1, 4, 8 and 11, and dexamethasone 40 mg orally on days 1–4, 9–12 and 17–20 on a 28-day cycle for 4 cycles
- Modified CyBorD: cyclophosphamide, weekly bortezomib, and reduced-dose dexamethasone

ITT=intention to treat; ORR=objective response rate; PR=partial response; VGPR=very good partial response; CR=complete response; nCR=near complete response.

**EVOLUTION Trial: VRD vs VCD vs VDCR in Previously Untreated MM**

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>VDCR (n=48)</th>
<th>VRD (n=42)</th>
<th>VCD (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>25%</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>58%</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>88%</td>
<td>85%</td>
<td>82%</td>
</tr>
</tbody>
</table>

VRD=bortezomib + lenalidomide + dexamethasone; VCD=bortezomib + cyclophosphamide + dexamethasone; VDCR=bortezomib + dexamethasone + cyclophosphamide + lenalidomide; CR=complete response; VGPR=very good partial response; ORR=objective response rate; PR=partial response.

CRd in Newly Diagnosed MM

Initial Treatment: 28-day cycles

Untreated Patients

CRd x 4

> PR

CRd x 4

Untreated

Lenalidomide

CRd Maintenance

(Identical to initial CRd except no Cfz on days 8, 9)

SCC

ASCT deferred

Dex, 40 mg/day days 1, 8, 15, and 22; 20 mg, cycles 5–8, and maintenance

CRd=carfilzomib (Cfz) + lenalidomide (Len) + dexamethasone (dex); PR=partial response; ASCT=autologous stem cell transplant; SCC=stem cell collection.

Response to CRd by Cycle

<table>
<thead>
<tr>
<th>Response, %</th>
<th>2 cycles (n=25)</th>
<th>4 cycles (n=22)</th>
<th>8 cycles (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR/CR/nCR</td>
<td>24</td>
<td>36</td>
<td>67</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>40</td>
<td>59</td>
<td>83</td>
</tr>
<tr>
<td>≥ PR</td>
<td>96</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

CRd=carfilzomib (Cfz) + lenalidomide (Len) + dexamethasone (dex); sCR=stringent complete response; CR=complete response; nCR=near complete response; PR=partial response; VGPR=very good partial response.

Combinations of Newer Agents in the Upfront Treatment of MM Results in Near 100% ORR

ORR=objective response rate; VGPR=very good partial response; CR=complete response; nCR=near complete response; VAD=vincristine + adriamycin + dexamethasone; TD=thalidomide + dexamethasone; RD= lenalidomide + dexamethasone; PAD=bortezomib + doxorubicin + dexamethasone; VTD=bortezomib + thalidomide + dexamethasone; CVD= cyclophosphamide + bortezomib + dexamethasone; RVD=lenalidomide + bortezomib + dexamethasone; CRD= carfilzomib + lenalidomide + dexamethasone.

Transplant

- When do I take patients to transplant?
- How do I manage poor risk cytogenetics?
- What about maintenance therapy?
IFM DFCI 2009: Lenalidomide, Bortezomib, Dexamethasone vs High-Dose Treatment With SCT

- Randomized, international, phase III trial in previously untreated MM patients who are candidates for HDT-ASCT
- Patients: Symptomatic MM with measurable disease
  - <65 yrs and transplant-eligible; ECOG <2 (KPS ≥60%)

**Arms**

**Arm A**
- RVD Cycles 2-3
- HD Cytoxan and SC collection
- RVD Cycles 4-8
- Maintenance lenalidomide for 12 months (HD melphalan + SCT at relapse)

**Arm B**
- RVD Cycles 2-3
- HD Cytoxan and SC collection
- HD melphalan + ASCT
- RVD for additional 2 cycles
- Maintenance lenalidomide for 12 months

- Primary Endpoint: PFS
- Secondary Endpoints: RR, TTP, OS, toxicity, quality of life, pharmacoeconomics

*SRandomization within 1st cycle*S

SCT=stem cell transplant; HDT=high-dose therapy; ASCT=autologous stem cell transplantation; ECOG=Eastern Cooperative Oncology Group; RVD=lenalidomide + bortezomib + dexamethasone; HD=high-dose; PFS=progression-free survival; RR=; TTP=time to progression; OS=overall survival.

Maintenance

- Which patient receives maintenance therapy?
- Which drug should be used?
- How long should maintenance be continued?
Usual Maintenance Scenario

**Disease**

**Maintenance treatment**

**Clinical detection limit**

**MRD**

**Clonal selection or secondary resistance and relapse**
(ex: Imatimib and CML)

MRD=minimal residual disease; CML=chronic myelogenous leukemia.

Adapted from Gareth Morgan.
Ideal Maintenance Treatment

Disease

Clinical detection limit

Maintenance treatment

MRD

Clonal extinction and cure

Ex: Chemotherapy of ALL

MRD=minimal residual disease; ALL=acute lymphoblastic leukemia.

Adapted from Gareth Morgan.
Overview: Thalidomide Maintenance Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Maintenance</th>
<th>EFS or PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 99-02[1]</td>
<td>597</td>
<td>Thal + pamidronate vs no maintenance</td>
<td>3-yr EFS: 52% vs 37%; P&lt;.009</td>
<td>4-yr OS: 87% vs 74%; P&lt;.04</td>
</tr>
<tr>
<td>Spencer, 2009[2]</td>
<td>243</td>
<td>Thal (12 mos) + prednisone vs prednisone</td>
<td>3-yr PFS: 42% vs 23%; P&lt;.001</td>
<td>3-yr OS: 86% vs 75%; P=.004</td>
</tr>
<tr>
<td>Total Therapy 2[3]</td>
<td>668</td>
<td>Thal vs no maintenance, until progression</td>
<td>5-yr EFS: 56% vs 45%; P=.0005</td>
<td>5-yr OS: 67% vs 65%, 8-yr OS: 57% vs 44%; P=.09</td>
</tr>
<tr>
<td>Lokhorst, 2010[4]</td>
<td>556</td>
<td>Thal vs IFN, until progression</td>
<td>Median PFS: 34 vs 25 mos; P&lt;.001</td>
<td>Median: 73 vs 60 mos; P=NS</td>
</tr>
<tr>
<td>Ludwig, 2010[5]</td>
<td>289</td>
<td>Thal + IFN vs IFN, until progression</td>
<td>Median PFS: 27.7 vs 13.2 mos; P&lt;.0068</td>
<td>Median: 52.6 vs 51.4 mos; P=NS</td>
</tr>
<tr>
<td>MRC Myeloma IX[6]</td>
<td>820</td>
<td>Thal vs no maintenance, until progression</td>
<td>Median PFS: 23 vs 15 mos; P&lt;.0003</td>
<td>Median: 60 vs 58 mos; P=NS</td>
</tr>
</tbody>
</table>

EFS=event-free survival; PFS=progression-free survival; OS=overall survival; Thal=thalidomide; IFM=Intergroupe Francophone du Myélome; IFN=interferon; NS=not significant; MRC=Medical Research Council.

CALGB 100104: Lenalidomide Maintenance vs Placebo

- Randomized, double-blind, placebo-controlled phase III trial

**Restage Days**

90-100

MM patients with Durie-Salmon stage I-III disease, SD following induction, and adequate stem cells

(N=568)

Stratified by baseline β₂-M, thalidomide or lenalidomide therapy during induction

Primary endpoint: TTP following ASCT
Secondary endpoints: CR after ASCT, PFS, OS, feasibility of long-term lenalidomide

SD=stable disease; ASCT=autologous stem cell transplantation; CR=complete response; PR=partial response; PD=progressive disease; TTP=time to progression; PFS=progression-free survival; OS=overall survival.


Phase III IFM 2005-02: Lenalidomide as Consolidation/Maintenance Post-ASCT

N=614

1\textsuperscript{st} line ASCT < 65 years

Consolidation

Lenalidomide 25 mg/d days 1-21/month 2 months

≤ 6 months No PD

Lenalidomide 25 mg/d days 1-21/month 2 months

Maintenance

Lenalidomide 10-15 mg/d until relapse

Placebo until relapse

Primary endpoint: Progression-free survival

ASCT=autologous stem cell transplantation; PD=progressive disease.

## Maintenance with Lenalidomide

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>n</th>
<th>At Randomization</th>
<th>Lenalidomide vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median PFS after Randomization</td>
</tr>
<tr>
<td>Attal et al(^1)</td>
<td>SCT</td>
<td>614</td>
<td>3 m post SCT</td>
</tr>
<tr>
<td>McCarthy et al(^2)</td>
<td>SCT</td>
<td>460</td>
<td>SCT</td>
</tr>
<tr>
<td>Palumbo et al(^3)</td>
<td>MPR</td>
<td>305</td>
<td>Diagnosis</td>
</tr>
</tbody>
</table>

*\(^*\)P<0.001; †P=0.03.

PFS=progression-free survival; OS=overall survival; SCT=stem cell transplantation; MPR=melphalan + prednisone + lenalidomide.

Bortezomib Before and After ASCT Improves Outcomes in MM Patients with Deletion 17p

<table>
<thead>
<tr>
<th>Arm A</th>
<th>N</th>
<th>Randomization of 399 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomized</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>no FISH data</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Off protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not eligible</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomization of 399 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>182 patients included in analysis</td>
</tr>
<tr>
<td>VAD</td>
</tr>
<tr>
<td>n=182 (100%)</td>
</tr>
<tr>
<td>0 cycles n= 3</td>
</tr>
<tr>
<td>1-2 cycles n= 15</td>
</tr>
<tr>
<td>3 cycles n= 162</td>
</tr>
<tr>
<td>4 cycles n= 2</td>
</tr>
</tbody>
</table>

| CAD + G-CSF                   | CAD + G-CSF                   |
| n=158 (87%)                   | n=152 (88%)                   |

| HDM                           | HDM                           |
| N=156 (86%)                   | N=1496 (87%)                  |
| 1 HDM n= 38                   | 1 HDM n= 23                   |
| 2 HDM n= 118                  | 2 HDM n= 126                  |

| Thalidomide maintenance       | Bortezomib maintenance        |
| n=128 (70%)                   | n=120 (70%)                   |

Bortezomib Induction and Maintenance in Patients with Newly Diagnosed MM

Adverse Events in the HOVON-65/GMMG-HD4 Trial

<table>
<thead>
<tr>
<th>WHO CTC grade</th>
<th>VAD arm thalidomide</th>
<th>PAD arm bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>3-4</td>
<td>1-2</td>
</tr>
<tr>
<td>3-4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DVT %</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNP %</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HZV %</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VAD=vincristine + adriamycin + dexamethasone; PAD=bortezomib + adriamycin + dexamethasone; WHO=World Health Organization; CTC=common toxicity criteria; DVT=deep vein thrombosis; PNP=peripheral neuropathy; HZV=herpes zoster virus.

Bortezomib Improved Median PFS and 3-year OS Rates in MM Patients with Deletion 17p

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

How I Treat Relapse
# Treatment Approaches to Relapse

<table>
<thead>
<tr>
<th>Salvage Therapy</th>
<th>Factors to Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early relapse</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Lenalidomide-based</strong></td>
<td>• Prior treatment with bortezomib</td>
</tr>
<tr>
<td></td>
<td>• Long duration of response (&gt;1 year) with initial lenalidomide therapy, eg,</td>
</tr>
<tr>
<td></td>
<td>maintenance intensification</td>
</tr>
<tr>
<td></td>
<td>• Pre-existing neuropathy</td>
</tr>
<tr>
<td></td>
<td>• Patient wants an oral regimen</td>
</tr>
<tr>
<td><strong>Bortezimib-based</strong></td>
<td>• Prior treatment with lenalidomide or thalidomide</td>
</tr>
<tr>
<td></td>
<td>• Long duration of response (&gt;1 year) with bortezomib therapy</td>
</tr>
<tr>
<td></td>
<td>• Existing renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Prior thrombosis</td>
</tr>
<tr>
<td><strong>Autologous Stem Cell Transplant</strong></td>
<td>• No previous autologous stem cell transplant</td>
</tr>
<tr>
<td></td>
<td>• Long remission post-ASCT (&gt;2 year)</td>
</tr>
<tr>
<td><strong>Aggressive Relapse</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chemotherapy plus novel agents</td>
</tr>
<tr>
<td></td>
<td>• DT PACE; EDAP</td>
</tr>
<tr>
<td></td>
<td>• Salvage transplant; second autologous or allo-stem cell transplant</td>
</tr>
</tbody>
</table>

DTPACE = dexamethasone + thalidomide + cisplatin + doxorubicin + cyclophosphamide + etoposide;  
EDAP = etoposide + dexamethasone + cytarabine + cisplatin  
Lenalidomide + Dexamethasone for Relapsed MM: MM-009/010 Trial Response Rates

- Overall and CR rates were significantly higher in the LEN + DEX arm of each trial compared with placebo + DEX ($P<0.001$)

CR=complete response; LEN=lenalidomide; DEX=dexamethasone; nCR=near complete response; PR=partial response; ORR=overall response rate; PBO=placebo.

APEX Trial: Bortezomib in Relapsed MM

- N=669 pts with 1-3 prior therapies (not DEX refractory)
- Primary endpoint: time to progression
- Secondary endpoints: OS, 1-yr OS, ORR, DOR

*n=336

- **dexamethasone 40 mg***
  - days 1–4, 9–12, 17–20 of four 5-week cycles
  - followed by days 1–4 of five 4-week cycles
- **bortezomib 1.3 mg/m² IV**
  - days 1, 4, 8, 11 of eight 3-week cycles
  - followed by days 1, 8, 15, 22 of three 5-week cycles

*n=333

Treatment for 280 days
Treatment for 273 days

*Patients on DEX who had disease progression were eligible to cross over to BORT in a companion study.

APEX=Assessment of Proteasome Inhibition for Extending Remissions; DEX=dexamethasone; OS=overall survival; ORR=overall response rate; DOR=duration of response; IV=intravenous; BORT=bortezomib.

Survival for Dual Refractory Disease

Median EFS of 5 months and Median OS of 9 Months for Patients Refractory to Both BTZ* and THAL/LEN**

*BTZ refractory defined as no response, progression on therapy, or progression within 60 days of stopping therapy.

**Pts were relapsed and/or refractory, intolerant, or ineligible to receive therapy with LEN or THAL.

EFS = event-free survival; OS = overall survival; BTZ = bortezomib; THAL = thalidomide; LEN = lenalidomide.

MM-003 Trial: Pomalidomide + LoDEX vs Single-Agent HiDEX in Relapsed/Refractory MM

• Patients with relapsed/refractory myeloma have few therapeutic options, except high-dose dexamethasone as a salvage therapy

- Patients stratified by number of previous therapies, refractory and relapsed/refractory disease
  - Refractory to both lenalidomide and bortezomib: 73% in POM + LoDEX and 71% in HiDEX arms

DEX=dexamethasone; POM=pomalidomide; PD=progressive disease; AE=adverse event; OS=overall survival; SPM=secondary primary malignancy.

<table>
<thead>
<tr>
<th>Survival Outcomes by Patient Group, Months</th>
<th>POM + LoDEX (n=302)</th>
<th>HiDEX (n=153)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent to treat population</td>
<td>3.6</td>
<td>1.8</td>
<td>0.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Refractory to bortezomib</td>
<td>3.6</td>
<td>1.8</td>
<td>0.47</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Refractory to lenalidomide</td>
<td>3.7</td>
<td>1.8</td>
<td>0.38</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Refractory to bortezomib and lenalidomide</td>
<td>3.2</td>
<td>1.7</td>
<td>0.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT population</td>
<td>NR</td>
<td>7.8</td>
<td>0.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Refractory to bortezomib</td>
<td>NR</td>
<td>8.1</td>
<td>0.56</td>
<td>.037</td>
</tr>
<tr>
<td>Refractory to lenalidomide</td>
<td>NR</td>
<td>8.6</td>
<td>0.39</td>
<td>.003</td>
</tr>
<tr>
<td>Refractory to bortezomib and lenalidomide</td>
<td>NR</td>
<td>7.4</td>
<td>0.56</td>
<td>.003</td>
</tr>
</tbody>
</table>

- In patients with poor renal function, POM + LoDEX provided longer PFS and OS as compared with HiDEX

OS=overall survival; POM=pomalidomide; DEX=dexamethasone; PFS=progression-free survival; NR=no response.

Phase 3 ASPIRE Trial: Carfilzomib + Lenalidomide + Dexamethasone in Relapsed MM

**Phase 3**
N=780 (targeted)

Relapsed pts treated with 1-3 prior therapies

Stratification by B2M (< vs ≥2.5 mg/L), prior BTZ, and prior R

---

**Randomization**

**RCd**
R: 25 mg
C: 20 mg/m² cycles 1-2, then 27mg/m² thereafter
Dex: 40 mg/week

**Rd**
R: 25 mg/d
Dex: 40 mg/week

---

**1º Objective**
- PFS

**2º Objectives**
- OS
- ORR
- DOR
- Disease control rate
- Safety
- TTP
- Time to next tx

---

aR: days 1-21 of each 28-day cycle.
C: days 1, 2, 8, 9, 15, 16 (cycles 1-12); days 1, 8, 15 (cycles 13-18); cycles 19+ no CFZ will be given.
Dex: weekly

ASPIRE= Carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone for the treatment of Patients with Relapsed multiple myeloma; RRMM=relapsed/refractory multiple myeloma; B2M= β2 microglobulin levels; BTZ=bortezomib; RCd=lenalidomide + carfilzomib+low dose dexamethasone; R=lenalidomide; C=carfilzomib; R=lenalidomide; Dex=dexamethasone; PFS=progression-free survival; OS=overall survival; ORR=overall response rate; DOR=duration of response; TTP=time to progression.

Carfilzomib in Relapsed/Refractory MM: Results in Response-Evaluable Patients (n=257)

Results in Response-Evaluable Patients (n=257)

- **DOR (≥PR) and (≥MR)=8.3 mo**
  - DCR=69%
  - CBR=37%
  - ORR=24%

*response-evaluable population

DOR=duration of response; MR=minimal response; DCR=disease control rate; CBR=clinical benefit rate; ORR=overall response rate; CR=complete response; VGPR=very good partial response; PR=partial response; SD=stable disease; PD=progressive disease.

Elotuzumab: An Anti-CS1 Monoclonal Antibody for the Treatment of MM

- CS1 is highly and uniformly expressed on MM cells
- Elotuzumab is a humanized monoclonal IgG1 antibody targeting CS1
- Clinical trial of elotuzumab in MM achieved SD
- Anti-MM activity of elotuzumab enhanced by lenalidomide in preclinical models
- Phase I/II trials: 80% to 90% response to lenalidomide/DEX/elotuzumab in relapsed MM
- Phase III trial of lenalidomide/DEX/elotuzumab vs lenalidomide/DEX in relapsed MM for new drug approval

CS1=cell surface glycoprotein; IgG1=immunoglobulin G; SD=stable disease; DEX=dexamethasone.

Elotuzumab (+ LEN + DEX): Efficacy

- Response rates were high with combination therapy
- Median PFS was not reached with a median follow-up of 14.1 months

![Graph showing response rates](image)

**PR** | **VGPR** | **CR/sCR**
--- | --- | ---
≥PR:82% | 12 | 36 |
≥PR:92% | 14 | 39 |
≥PR:73% | 11 | 32 |

LEN=lenalidomide; DEX=dexamethasone; PFS=progression-free survival; PR=partial response; VGPR=very good partial response; CR=complete response; sCR=stringent complete response; ELO=elotuzumab.

Oral Proteasome Inhibitor MLN9708 for Front Line MM Treatment: Preliminary Phase 2 Results

- Patients received 4.0 mg/kg MLN9708 on days 1, 8, and 15 (plus lenalidomide and dexamethasone on the same schedule)
- 53 patients received a median of 7 cycles of therapy (range, 1-19 cycles)
- At data cutoff, 52/53 patients were evaluable for response; 26 remained on therapy
- Efficacy
  - ORR: 90%
  - 58% of patients achieved ≥VGPR
  - 3 patients completed 12 cycles; 2 achieved a CR; 1 achieved a VGPR
  - Minimal residual disease was assessed in 8 patients who had a complete response and found negative in 88%
  - At data cutoff, 50/52 responders remained in response, with responses durable for up to 13.2+ months
  - Median time to first response was 0.92 months (range 0.89–6.44)

ORR=overall response rate; VGPR=very good partial response; CR=complete response.

• Safety
  – Treatment-emergent peripheral neuropathy reported in 21 patients (32%); 13 patients, grade 1; six patients, grade 2; and two patients, grade 3
  – There was one on-study death
  – Most common grade 3/4 adverse events: rash (18%); neutropenia (9%); vomiting (8%); back pain (7%); thrombocytopenia, anemia, fatigue, diarrhea, and hyponatremia (all 6%); and nausea, dehydration, hypokalemia, and hypophosphatemia (all 5%)

Summary

- Myeloma is not one size fits all disease
- Toxicity
- Efficacy
- Quality of life
- Survival
Applying a Congruent Oncology Pharmacy Strategy – From Guidelines to Specialty Pharmacy: Steps for Success with Multiple Myeloma

This activity is supported by educational grants from Celgene Corporation, Millennium: The Takeda Oncology Company, and Onyx Pharmaceuticals.
Optimizing Therapeutic Decision-Making for Multiple Myeloma: A Clinical Overview Part 2

Sandra Kurtin, RN, MS, AOCN®, ANP-C
Hematology/Oncology Nurse Practitioner
The University of Arizona Cancer Center
Clinical Assistant Professor of Nursing
University of Arizona
Disclosures

• The **faculty** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

  Sandra Kurtin, RN, MS, AOCN®, ANP-C

  – *Consulting Fees*: Onyx Pharmaceuticals, Celgene Corporation, and Millennium: The Takeda Oncology Company

  – *Fees for Non-CME/CE Services*: Onyx Pharmaceuticals, Celgene Corporation, and Millennium: The Takeda Oncology Company
Outline

• Pathobiology of multiple myeloma
  – Common signs and symptoms
• Review of treatment options
  – Relationship of treatment to supportive care requirements
Pathobiology

- Clonal (lymphoid) plasma cell malignancy
- Complex interaction
  - Malignant progenitor cells
  - Bone marrow stroma
    - Stromal dysregulation
  - Bone marrow microenvironment
    - Cytokine abnormalities
    - Oncogene dysregulation
- These attributes are key to the presenting signs and symptoms and current approach to treatment

Genetic and Molecular Defects Lead to Overproduction of Abnormal Plasma Cells and Associated Serum Proteins (Immunoglobulins)

- Cytopenias
- Renal impairment
- Genetic and Molecular Defects
- MM Bone Marrow
- Invasion of bone
- Abnormal Plasma Cells
- Lytic Lesions
- Hypercalcemia
- Immunodeficiency
- Neurological Disease

Common Presenting Signs and Symptoms

- Most common complaint at presentation is bone pain and fatigue
- Signs and symptoms result from an overproduction of immunoglobulins with secondary processes

<table>
<thead>
<tr>
<th>Disease Process</th>
<th>Symptoms</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cell invasion of the bone</td>
<td>Bone pain (58%)</td>
<td>Lytic lesions (66%)</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td>Compression fractures or other skeletal fractures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercalcemia (13%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Osteoporosis, Osteopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cord compression</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>Fatigue (32%)</td>
<td>Anemia (73%)</td>
</tr>
<tr>
<td></td>
<td>Infections</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>Bleeding</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Process</th>
<th>Symptoms</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal injury</td>
<td>• Fatigue</td>
<td>• Elevated creatinine (19%)</td>
</tr>
<tr>
<td></td>
<td>• Oliguria (late finding)</td>
<td>• Acute renal failure (ARF)</td>
</tr>
<tr>
<td></td>
<td>• Hematuria</td>
<td>• Chronic renal insufficiency (CRI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Chronic renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hyperviscosity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urate nephropathy</td>
</tr>
<tr>
<td>Abnormal immunoglobulin function</td>
<td>• Fever</td>
<td>• Hypogammaglobulinemia</td>
</tr>
<tr>
<td></td>
<td>• Infections</td>
<td>• Infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Neurological disease</td>
</tr>
<tr>
<td>Hyperviscosity</td>
<td>• Pain</td>
<td>• Peripheral neuropathy (5%)</td>
</tr>
<tr>
<td></td>
<td>• Paresthesia</td>
<td>• Strokes</td>
</tr>
<tr>
<td></td>
<td>• Immobility</td>
<td></td>
</tr>
</tbody>
</table>

Disease Trajectory

Nonmalignant Accumulation

Disease Trajectory

Nonmalignant Accumulation

Malignant Transformation

Aggressive and Stromal Independent

MGUS

< 3 g M protein
< 10% clonal BMPC
No MM-related end-organ damage

Smoldering Myeloma

≥ 3g M protein
< 10% clonal BMPC
No MM-related end-organ damage

Multiple Myeloma

≥ 10% clonal BMPC
M protein in serum and/or urine
≥ 1 CRAB features of disease related organ damage

C: Calcium elevation > 11.5 mg/L or ULN

R: Renal dysfunction serum creatinine > 2 mg/dL

A: Anemia Hb < 10 g/dL or 2 g < normal

B: Bone disease lytic lesions or osteoporosis

BMPC=bone marrow plasma cells; Hb=hemoglobin; MGUS=monoclonal gammopathy of unknown significance; M protein=myeloma protein; IL6=interleukin-6; ULN=upper limit of normal

Adapted with permission from Kurtin SE. JAdPrO, 2010;1:19-29.
Disease Trajectory (2)

Nonmalignant Accumulation

Malignant Transformation

Aggressive and Stromal Independent

Plasma Cell Leukemia

ASYMPTOMATIC

SYMPTOMATIC

MGUS or SMOLDERING MYELOMA

ACTIVE MYELOMA

RELABSE

PLATEAU REMISSION

Therapy

Time

Beyond the CRAB Criteria: Myeloma Defining Event

**Calcium (either):**
- > 11mg/dl OR
- > 1mg/dL above ULN

**Renal:**
- creatinine >2mg/dL OR (at least one):
  - eGFR ≤ 50
  - eGFR ↓ ≥35% in 1y

**Biopsy confirmation**

**Anemia:**
- HgB <10g/dL OR
- 2g/dL below LLN

**Bone - lytic lesions on bone survey**
- Or, if x-rays negative -either:
  - > 3 hyperintense MRI foci
  - > 1 “large” MRI lesion
  - > 1 lytic lesion > 1cm PET/CT
  - > 3 small lytic PET/CT

---


Treatment Options Have Greatly Increased in the Past Decade

MM Therapies Introduction

1950
1960
1970
1980
1990
2000
2010

1958 Melphalan

1962 Prednisone

1969 Melphalan + Prednisone

1983 Autologous Transplantation

1986 High-Dose Dexamethasone (Dex)

2003 Bortezomib 3rd line

2005 Bortezomib 2nd line

2006 Lenalidomide + Dex 2nd line

2006 Thalidomide + Dex 1st line

2007 Doxorubicin + Bortezomib 2nd line

2012 Carfilzomib 3rd line

2012 Bortezomib SQ

2013 Pomalidomide 3rd line

2008 Bortezomib Frontline

FDA-Approved in MM
Novel Drugs Are Key for Improved Survival

Exposed to novel drugs

Not exposed to novel drugs

Proportion Surviving

Time From After ASCT Relapse (months)

P < 0.001

Novel therapy | Approval
---|---
Bortezomib | 2003
Thalidomide | 2006
Lenalidomide | 2006
Carfilzomib | 2012
Pomalidomide | 2013

ASCT=autologous stem cell transplant

### Drugs Used to Treat Multiple Myeloma

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Drug Class</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>VELCADE®</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Proteasome inhibitor</td>
<td>KYPHROLIS®</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Immunomodulatory agent</td>
<td>REVLIMID®</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Immunomodulatory agent</td>
<td>THALOMID®</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Immunomodulatory agent</td>
<td>POMALYST®</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Alkylating agent</td>
<td>ALKERAN®, ALPHALAN®</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent</td>
<td>CYTOXAN®</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Corticosteroid</td>
<td>DELTASONE®</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Corticosteroid</td>
<td>DECADRON®</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Bisphosphonate</td>
<td>AREDI®</td>
</tr>
<tr>
<td>Zoledronic Acid</td>
<td>Bisphosphonate</td>
<td>ZOMETA®</td>
</tr>
</tbody>
</table>

- In addition to new therapeutic options, combination and supportive care has also improved including use of bisphosphonates, antibiotics, and reduced doses of steroids.
- Improving quality of life and survival has become an important goal of treatment.
# Common Dosing Regimens for Novel Therapies

<table>
<thead>
<tr>
<th>Agent/Class</th>
<th>Dosing and Route of Administration</th>
</tr>
</thead>
</table>
| **Bortezomib**¹ **Proteasome inhibitor** | • 1.3 mg/m² IV or SC days 1,4,8,11, every 21 days x 2 cycles, then weekly dosing 3 weeks on/1 week off  
  • Variable dosing in combination regimens  
  • Dose modification for neuropathy, cytopenias |
| **Carfilzomib**² **Proteasome inhibitor** | • 20 mg/m² IV (cycle 1), 27 mg/m² (cycle #2-12) days 1,2,8,9,15,16, every 28 days  
  • Dose modifications for cytopenias, cardiopulmonary symptoms |
| **Lenalidomide**³ **Immunomodulatory agent** | • 25 mg/d by mouth for induction  
  • Variable dosing in combination regimens  
  • Dose modification based on renal function, cytopenias |
| **Pomalidomide**⁴ **Immunomodulatory agent** | • 4 mg/d days 1-21 using a 28 day cycle  
  • Dose modifications for cytopenias |
| **Thalidomide**⁵ **Immunomodulatory agent** | • 200 mg/d by mouth at bedtime  
  • Variable dosing in combination regimens  
  • Dose modification for neuropathy, cytopenias |

Common Adverse Events for Proteasome Inhibitors Used to Treat MM

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Proteasome Inhibitor Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bortezomib</td>
</tr>
<tr>
<td>All grades</td>
<td></td>
</tr>
<tr>
<td>Grade 3 /4</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia and Neutropenia</td>
<td>Thrombocytopenia (cyclic): 36% (29%) Neutropenia: 17%; (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>Two weekly IV: 53% (16%) Weekly IV: 41% (16%) Weekly SC: 24% (6%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Overall: 64% (16%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea: Overall: 52% (8%) Nausea: 57% (8%)</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>Dyspnea: 11%, Hypotension: 13% Congestive Heart Failure (CHF): 5%</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Varicella Zoster: 13-20%</td>
</tr>
<tr>
<td>Renal dose modification</td>
<td>No renal dose adjustment required</td>
</tr>
<tr>
<td>Thromboembolic Events</td>
<td>Not reported*</td>
</tr>
<tr>
<td>Rash</td>
<td>Not reported*</td>
</tr>
</tbody>
</table>

Based on clinical trials to date with incidence >5-10%; prescribing information for each agent (Palumbo A, Anderson K. *N Engl J Med*. 2011;364:1046-1060). *Data not available or incidence was below threshold for reporting. Kurtin SE, Bilotti E. *JAdPrO*. 2103 (accepted for publication).
**Common Adverse Events for Immunomodulatory Agents Used to Treat MM**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Immunomodulatory Agents</th>
<th>Immunomodulatory Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All grades</strong></td>
<td><strong>Lenalidomide (with dexamethasone)</strong></td>
<td><strong>Thalidomide (with dexamethasone)</strong></td>
</tr>
<tr>
<td><strong>Thrombocytopenia and Neutropenia</strong></td>
<td>Thrombocytopenia: 21% (12%) Neutropenia: 42% (33%)</td>
<td>Thrombocytopenia: 23% Neutropenia: 31%</td>
</tr>
<tr>
<td><strong>Peripheral Neuropathy</strong></td>
<td>Not significant</td>
<td>All Grades: 54% (3-5%) ↑ with higher doses and prolonged therapy</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>Overall: 43% (6%)</td>
<td>Overall: 81% (17%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Constipation: 40% (3%) Diarrhea: 38.5% (2%) Nausea: 26% (1%)</td>
<td>Constipation: 56% (8%) Nausea: 29% (5%)</td>
</tr>
<tr>
<td><strong>Cardiopulmonary</strong></td>
<td>Dyspnea: 23% (not reported) Hypotension: 7% (not reported)</td>
<td>Dyspnea: 41% (13%) Peripheral edema: 57% (6%) Bradycardia reported</td>
</tr>
<tr>
<td><strong>Infectious complications</strong></td>
<td>Pneumonia: 14%</td>
<td>Pneumonia: 35%</td>
</tr>
<tr>
<td><strong>Renal dose modification</strong></td>
<td>Requires renal dose adjustment</td>
<td>No dose modification required</td>
</tr>
<tr>
<td><strong>Thromboembolic Events</strong></td>
<td>Overall: 9.3%</td>
<td>Overall: 23%</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>Overall: 21%</td>
<td>Overall: 30%</td>
</tr>
</tbody>
</table>

Based on clinical trials to date with incidence >5-10%; prescribing information for each agent. (Palumbo A, Anderson K. *N Engl J Med*. 2011;364:1046-1060). *Data not available or incidence was below threshold for reporting.
Kurtin SE, Bilotti E. *JAdPrO*. 2103 (accepted for publication).
Factors Associated with High Risk for Chemotherapy-Induced Myelotoxicity

<table>
<thead>
<tr>
<th>Host related Factors</th>
<th>Disease and Treatment Related Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65</td>
<td>High tumor burden/extensive disease</td>
</tr>
<tr>
<td>Female gender</td>
<td>Previous history of chemotherapy or radiation</td>
</tr>
<tr>
<td>ECOG PS &gt;1</td>
<td>Pre-existing cytopenias</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Bone marrow involvement with tumor</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Type of chemotherapy</td>
</tr>
<tr>
<td>Comorbidities: COPD, diabetes, renal impairment, liver disease</td>
<td>Dose intensity of chemotherapy</td>
</tr>
<tr>
<td>Open wounds or recent surgery</td>
<td>Elevated lactate dehydrogenase (LDH)</td>
</tr>
<tr>
<td>Active infection or pre-existing fungal infections</td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Drug-drug Interactions</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Hematological malignancy</td>
</tr>
<tr>
<td></td>
<td>Hospitalization</td>
</tr>
</tbody>
</table>

ECOG PS=Eastern Cooperative Oncology Group performance status

Summary

• Although currently not curable, median overall survival has improved dramatically over the last decade
  – Understanding of the pathobiology of the disease will improve the rationale of supportive care requirements
  – Identification of new therapeutic targets
• Improved long-term survival if the goal
  – Early depth of response → sustained response with an acceptable level of toxicity
• Many new agents are on the way, most will be oral