Management of Multiple Myeloma: The Changing Paradigm

Frontline Therapy for Newly Diagnosed Patients

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Introduction: Patient Case

- John, a 55-year-old lawyer, presents to PCP with 2 months’ history of progressive fatigue and left chest pain; he also refers constipation
- PE exam remarkable for pale and dry mucosas and left chest 4cm painful mass
- Labs showed anemia (Hgb 8.5 gm/dL), hypercalcemia (Ca 14.6 gm/dL), renal insufficiency (Cr 3.5 mg/dL), and elevated total protein (12.2 gm/dL), albumin (3.2 gm/dL), β2 microglobulin 6.8 mg/dL
- SPEP: M spike of 4.3 gm/dL IgGk
- Bone marrow: 50% plasma cells, cytogenetics normal, FISH 13 q deletion
- Bone survey:-multiple lesions, CF at L2–3,lt rib lesion and mass
Patient Case
Important Questions

- Is this an emergency?
- What is first step in management of this patient?
- What is diagnosis?
- What is stage?
- What is the risk stratification?
- What is goal of therapy?

Initial treatment options:
1. RVd
2. CyBord
3. KRd
4. Clinical trial

Your Personal Treatment Plan:
Partnering With Your Health Care Team

Your Overall Health and Characteristics of Your Myeloma
- Age and general health
- Other conditions
- Test results
- Symptoms

Your Preferences and Personal Goals
- Eliminate vs control disease
- Willingness to tolerate side effects
- Symptom relief
- Personal lifestyle/situation

No one treatment plan is right for everyone.
Goals of Therapy

- Achieving good response (≥VGPR)
- High response rate; rapid response
- Improve performance status
- Minimal side effects

Current Treatment Approaches: Smoldering Myeloma

Smoldering Myeloma

- No active treatment*

- Close monitoring: every 3–4 months (physical exam, possible blood/urine tests)
- Bisphosphonates for bone loss or damage (pamidronate or Zometa given intravenously)

*Promising but limited studies to date.

One phase 3 study of Revlimid + dex followed by Revlimid maintenance in patients with high-risk SMM suggests a benefit; confirmatory study is under way.

Additional studies include: Empliciti* + Revlimid ± dex; Darzalex* (three doses); Siltuximab; Kyprolis + Revlimid + dex; Pembrolizumab; Ninlaro + dex; Kyprolis

Ask your doctor if you are a candidate for a clinical trial.

Bold = MMRC trial
Frontline Therapy:
Standard Drug Overview

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Name</th>
<th>Abbreviation</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMiD (immunomodulatory drug)</td>
<td>Revlimid (lenalidomide)</td>
<td>R or Rev</td>
<td>Oral</td>
</tr>
<tr>
<td>Proteasome inhibitor</td>
<td>Velcade (bortezomib)</td>
<td>V or Vel or B</td>
<td>Intravenous or subcutaneous injection (under the skin)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Cytoxan (cyclophosphamide)</td>
<td>C</td>
<td>Oral or intravenous</td>
</tr>
<tr>
<td></td>
<td>Evomela (melphalan)</td>
<td>M or Mel</td>
<td>Oral or intravenous</td>
</tr>
<tr>
<td>Steroids</td>
<td>Decadron (dexamethasone)</td>
<td>Dex or D or d</td>
<td>Oral or intravenous</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>P</td>
<td>Oral or intravenous</td>
</tr>
</tbody>
</table>

Current Treatment Approaches: Active Myeloma

Are you a candidate for an autologous stem cell transplant?

- **YES**
  - 3–4 cycles of therapy (induction)
    - Triplets (generally preferred): RVD, VTD, CyBorD, VCD
    - Doublets: Vel/dex, Rev/dex
    - Clinical trial
  - High-dose chemotherapy (melphalan) and autologous transplant
  - Consolidation/maintenance?
  - Supportive care

For t(4;14): combination including Velcade (V) or Kyprolis is critical.

- **NO**
  - Any of the regimens listed for transplant candidates
  - Doublets option, particularly for patients with health/side effect concerns
  - Clinical trial
**Treatment Sequence for Active Myeloma**

**NCCN Category 1* Recommendations**

<table>
<thead>
<tr>
<th>Frontline treatment</th>
<th>Maintenance</th>
<th>Relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td><strong>Consolidation</strong></td>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td>Vel/dex</td>
<td>SCT</td>
<td>Velcade</td>
</tr>
<tr>
<td>Vel/dex/dox</td>
<td></td>
<td>Vel/Doxil</td>
</tr>
<tr>
<td>Vel/thal/dex</td>
<td></td>
<td>Kyprolis/Rev/dex</td>
</tr>
<tr>
<td>Rev/dex</td>
<td></td>
<td>Empliciti/Rev/dex</td>
</tr>
<tr>
<td>RVD</td>
<td></td>
<td>Ninlaro/Rev/dex</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Observation</td>
<td>Velcade</td>
</tr>
<tr>
<td></td>
<td>Revlimid</td>
<td>Vel/Doxil</td>
</tr>
<tr>
<td></td>
<td>Clinical trial</td>
<td>Kyprolis/Rev/dex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Empliciti/Rev/dex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ninlaro/Rev/dex</td>
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<tr>
<td></td>
<td></td>
<td>Rev/dex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Farydak/Vel/dex</td>
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<tr>
<td></td>
<td></td>
<td>Pom/dex</td>
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<tr>
<td></td>
<td></td>
<td>Darzalex/Vel/dex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Darzalex/Rev/dex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

*Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.


**Key Considerations for Optimal Disease Management**

1. **Know the standard of care**
2. **What to expect on therapy**
3. **Assessing your response to therapy**
4. **Maintenance options**
5. **Consider clinical trials**
### Revlimid in Frontline Therapy

**How is Revlimid administered?**
- Capsule; usually taken once daily for 21 days out of a 28-day cycle (3 weeks on, 1 week off)
- Blood thinners (for example, aspirin or low-molecular-weight heparin [LMWH]) are given along with Revlimid to reduce the risk of blood clots

**What are the possible side effects?**
- Potential for blood clots
  - Reduced blood counts
    - Low white blood cells (neutropenia): infections
    - Low red blood cells: anemia
    - Low platelets (thrombocytopenia): blood clotting problems
- Rash
- Fatigue
- Muscle pain (myalgia)
- Diarrhea
- Small chance of second new cancers when given with melphalan

**What combinations are being studied?**
- Revlimid + dex with Velcade or Kyprolis
- Revlimid + dex ± Ninlaro
- Revlimid + dex ± Darzalex
- Revlimid + dex ± Empliciti
- Revlimid + dex ± pembrolizumab

### Patients Taking Revlimid: Some Patients Are More Susceptible to Blood Clots

**Key Risk Factors for Blood Clots**
- Newly diagnosed active myeloma
- Taking other medications:
  - Chemotherapy (melphalan, cyclophosphamide, Doxil)
  - Dexamethasone
  - Red blood cell growth factors for anemia (erythropoietin)
- History of previous blood clots

**Other Risk Factors**
- High level of myeloma cells
- Older age
- Other medical conditions such as infections or disease of the lung or kidney
- Obesity
- Family history
- Thrombophilia, a condition where clots form easily
- Orthopedic procedures, such as hip or knee replacement
- Being immobilized (for example, confined to bed, long airplane trips)
- Presence of central venous catheter (a special catheter often used to administer cancer drugs)
What Can You Do To Prevent Blood Clots?

<table>
<thead>
<tr>
<th>Risk of Blood Clots*</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Aspirin</td>
</tr>
<tr>
<td>High risk†</td>
<td>LMWH (for example, Lovenox)</td>
</tr>
</tbody>
</table>

*Also applies to other IMiDs (ie, Thalomid, Pomalyst).
†Patients with many risk factors may receive other drugs, including Coumadin, Xarelto, Pradaxa, or Eliquis (ongoing phase 3 clinical trial evaluating the use of Eliquis in the prevention of thromboembolic disease in patients with myeloma treated with IMiDs).

Talk to your doctor to see what treatments are best for YOU.

What are the possible side effects?

- Options:
  - Injection under the skin (subcutaneous), once or twice weekly
  - Intravenous once or twice weekly

- Peripheral neuropathy (numbness, tingling, burning sensations and/or pain due to nerve damage)
- Occurs less often when subcutaneous or once weekly dosing is used
- Low platelets (thrombocytopenia): blood clotting problems
- Gastrointestinal problems: nausea, diarrhea, vomiting, loss of appetite
- Fatigue
- Rash

What combinations are being studied?

- Velcade + Mel + P ± Darzalex
- Revlimid + dex with Velcade or Kyprolis
- Thalomid + Revlimid + Velcade + Zolinza

Velcade in Frontline Therapy
Understanding Peripheral Neuropathy

- Peripheral neuropathy is nerve damage that causes pain, tingling, burning sensations, and numbness in the hands and feet
  - Typically improves or resolves after treatment dose is reduced or treatment is stopped
- Risk of peripheral neuropathy varies
  - Greater risk if you have pre-existing neuropathy
  - Velcade dose and type of administration

Be sure to discuss the benefits and risks of taking Velcade with your doctor if you have severe pre-existing neuropathy.

Managing Peripheral Neuropathy

- Managed by reducing the Velcade dose (with no impact on effectiveness)
- Other possible ways to prevent or reduce symptoms (less proven):
  - Vitamins and other supplements*
  - Certain medications such as gabapentin (Neurontin)
  - Acupuncture

Your health care team will check for peripheral neuropathy before treatment and prior to each dose of Velcade.

Be sure to tell your health care team about any symptoms you experience.

*Do not take any supplements without consulting with your doctor.
### Measuring Response to Therapy

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Abbreviation</th>
<th>M-Protein Reduction</th>
<th>Tests</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood</td>
<td>Urine</td>
<td>Immunofixation</td>
</tr>
<tr>
<td>Complete response</td>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>sCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunophenotypic complete response</td>
<td>iCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Molecular complete response</td>
<td>mCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>VGPR</td>
<td>&gt;90%</td>
<td>&lt;100 mg/24 hrs</td>
<td>—</td>
</tr>
<tr>
<td>Partial response</td>
<td>PR</td>
<td>&gt;50%</td>
<td>&gt;90%</td>
<td>—</td>
</tr>
<tr>
<td>Stable disease</td>
<td>SD</td>
<td>Does not meet criteria for response or progressive disease</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>PD</td>
<td>An increase of 25% in M protein; an increase of 10% in bone marrow plasma cells</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

*By multiparametric flow cytometry; †Allele-specific oligonucleotide PCR

### Testing for Minimal Residual Disease (MRD): An Emerging Approach

1 \times 10^{12}

At diagnosis

1 \times 10^{11}

Partial response – 50% reduction in M protein

1 \times 10^{10}

Near complete remission – immunofixation positive only

1 \times 10^{9}

Complete remission – immunofixation negative

1 \times 10^{8}

Nonquantitative ASO-PCR

1 \times 10^{7}

Quantitative ASO-PCR flow cytometry

MRD

Number of Myeloma Cells

Talk to your doctor about types of tests available in your area.
Should Patients Receive Maintenance Therapy as an Option?

- What are the benefits vs risks?
- Who should get maintenance therapy?
- How long should patients get maintenance therapy?

**NINLARO**  
Oral proteasome inhibitor

**VELCADE-BASED TREATMENT**  
Supported by several smaller studies

**REVLIMID**  
Reduction in myeloma progression (3 large studies)  
Improved survival (1 of 3 studies)  
Small risk of second cancers when used after melphalan

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Additional Drugs for Newly Diagnosed Disease

- A number of new agents—though they are not yet approved in the front-line setting by the FDA—are showing promise in clinical trials
  - Kyprolis and Ninlaro have been studied as components of induction regimens such as KRD\(^1-3\) or IRD\(^4\), demonstrating highly encouraging response rates
- Early-stage trials are investigating the use of monoclonal antibodies Darzalex and Empliciti as part of four-drug induction combinations
  - Although the addition of a fourth agent has not conferred an added survival benefit in previous trials, the use of both Darzalex and Empliciti as fourth agents has now shown enough promise to advance into phase 3 testing in the induction setting

## Ongoing Clinical Studies for Newly Diagnosed Patients

<table>
<thead>
<tr>
<th>SMM</th>
<th>Induction (Transplant Candidates)</th>
<th>Induction (Nontransplant Candidates)</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients at High Risk of Disease Progression</strong></td>
<td><strong>Revlimid vs observation</strong></td>
<td><strong>Velcade + Mel + P ± Darzalex</strong></td>
<td><em><em>Ninlaro</em> (± following ASCT)</em>*</td>
</tr>
<tr>
<td></td>
<td>• Empliciti* + Revlimid ± dex</td>
<td>• Kyprolis* + Mel + P vs Velcade + Mel + P</td>
<td>• Revlimid 25 mg vs 5 mg</td>
</tr>
<tr>
<td></td>
<td>• Darzalex* (3 doses)</td>
<td>• Velcade + Mel + P ± Darzalex*</td>
<td>• Revlimid + dex ± Ninlaro*</td>
</tr>
<tr>
<td></td>
<td>• Siltuximab†</td>
<td>• Kyprolis* + Mel + P vs Velcade + Mel + P</td>
<td>• Kyprolis* + Revlimid + dex vs Revlimid</td>
</tr>
<tr>
<td></td>
<td>• Kyprolis* + Revlimid + dex</td>
<td>• Revlimid + dex ± Empliciti*</td>
<td>• Velcade 25 mg vs 5 mg</td>
</tr>
<tr>
<td></td>
<td>• Pembrolizumab†</td>
<td>• Thalomid + Revlimid + Velcade + Zolinza‡</td>
<td>• Empliciti* + Revlimid + Velcade + dex</td>
</tr>
<tr>
<td></td>
<td>• Ninlaro* + dex</td>
<td>• Darzalex*</td>
<td>• Thalomid + Revlimid + Velcade + Zolinza‡</td>
</tr>
<tr>
<td></td>
<td>• Kyprolis*</td>
<td></td>
<td>• Pembrolizumab†</td>
</tr>
</tbody>
</table>

Ask your doctor if you are a candidate for clinical trials.

*FDA-approved for RR disease; †Experimental therapy not yet FDA approved; ‡FDA approved for a non-MM indication

**Bold = MMRC trial**

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## When Considering a Treatment Regimen, Find Out From Your Doctor...

- What treatment options should I consider?
- What lab values and test results are important to track for a response or to monitor for side effects?
- Is there a clinical trial that might be better suited for my type of myeloma or prognosis?
- Can I bank my bone marrow?*

*Tissue banking may not be an option at some oncology offices
In general, the best treatment we can offer a newly diagnosed myeloma patient as first line therapy, is induction therapy with a 3-drug combination, followed by autologous transplant, followed by maintenance therapy.

A. True  
B. False
Question

Patients with smoldering myeloma are asymptomatic and should be observed or consider participation in clinical trial.
A. True
B. False

Question

The goal of therapy in a patient with newly diagnosed symptomatic myeloma is:
A. Complete response or remission
B. Partial response
C. Restore or improve quality of life
D. A and C are correct
## Summary: Treating Newly Diagnosed Patients

- **Smoldering multiple myeloma (SMM)**
  - Close monitoring plus bisphosphonates for bone loss
  - Potential for treatment for high-risk patients; clinical trials ongoing
- **Symptomatic (active) myeloma:**
  - Combination therapies including Revlimid and/or Velcade, along with other drugs (triplets or doublets)
  - ASCT
  - Maintenance
- **Side effects of therapy can be managed**
- **Research to improve up-front outcomes is ongoing**

*Partner with your health care team to select the treatment plan that is right for you.*