Management of Multiple Myeloma: The Changing Paradigm

Frontline Therapy for Newly Diagnosed Patients

Saad Usmani, MD FACP
Levine Cancer Institute
Introduction:
Case Presentation

• 64-year-old woman with a 3-month history of progressive fatigue, generalized weakness, and the recent onset of progressively worsening right-sided rib and lower back pain, which keeps her up at night.

• Anemia and elevated total proteins on labs, referred to Hematologist. SPEP and immunofixation showed IgG kappa monoclonal protein. Serum free kappa light chains elevated 980 mg/L and kappa/lambda ratio 350. Beta-2 macroglobulin 3.9 mg/dL, normal serum albumin.

• Skeletal survey shows numerous lytic lesions.

• BM biopsy showed 70% plasma cells, normal cytogenetics and FISH results.

![Serum Protein Electrophoresis (SPEP)*](image)
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.

Ask your doctor if you are a candidate for a clinical 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></td>
<td>Thalomid (thalidomide)</td>
<td>T or Thal</td>
<td></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>
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<tr>
<td></td>
<td>Doxil (liposomal doxorubicin)</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkeran or Evomela (melphalan)</td>
<td>M or Mel</td>
<td></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>
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Current Treatment Approaches: Active Myeloma

Are you a candidate for an autologous stem cell transplant?

**YES**
- 4 cycles of therapy (induction)
  - Triples (Preferred): RVD, VTD, CyBorD, VCD
  - Doublets: Vel/dex, Rev/dex
  - Clinical trial
- High-dose chemotherapy (melphalan) and autologous transplant

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

Consolidation/maintenance?
- Supportive care

For t(4;14): combination including Velcade (V) is critical.
Treatment Sequence for Active Myeloma

NCCN Category 1* Recommendations

Frontline treatment
- Induction: Vel/Dex, Vel/Dex/Dox, Vel/Thal/Dex, Rev/Dex, RVD, Clinical trial
- Consolidation: SCT, Clinical trial

Maintenance
- Observation: Velcade
- Revlimid: Vel/Doxil
- Thalomid: Kyprolis/Rev/Dex

Relapsed
- Rescue: Clinical trial

*Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
<table>
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<tr>
<th>Key Steps to Take on Your Journey</th>
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<tbody>
<tr>
<td>1. Weighing your therapy options</td>
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<tr>
<td>2. What to expect on therapy</td>
</tr>
<tr>
<td>3. Assessing your response to therapy</td>
</tr>
<tr>
<td>4. Maintenance options</td>
</tr>
<tr>
<td>5. Consider clinical trials</td>
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</table>
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
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>
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<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.
Velcade in Frontline Therapy

How is Velcade administered?
- Options:
  - Injection under the skin (subcutaneous), once or twice weekly
  - Intravenous once or twice weekly

What are the possible side effects?
- 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
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)

*Do not take any supplements without consulting with your doctor.

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.
# 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>
<th>Freelite</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood</td>
<td>Urine</td>
<td>Immunofixation</td>
<td>PC</td>
</tr>
<tr>
<td>Complete response</td>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>sCR</td>
<td>0</td>
<td>0</td>
<td>Negative</td>
<td>&lt;5%</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>
<td>–</td>
</tr>
<tr>
<td>Partial response</td>
<td>PR</td>
<td>&gt;50%</td>
<td>&gt;90%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stable disease</td>
<td>SD</td>
<td></td>
<td></td>
<td>Does not meet criteria for response or progressive disease</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>PD</td>
<td></td>
<td></td>
<td>An increase of 25% in M-protein; an increase of 10% in bone marrow plasma cells</td>
<td></td>
</tr>
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Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

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

- Small amounts of myeloma cells despite CR (as measured by standard tests)
- Patients who are MRD negative may have better outcomes
- More-sensitive tests/newer technologies to detect and monitor MRD are now available
  - Flow cytometry
  - Molecular tests
    - Polymerase chain reaction (PCR)
    - Sequenta ClonoSIGHT*: novel, highly sensitive test

Talk to your doctor about types of tests available in your area.

*The Multiple Myeloma Research Foundation is using the Sequenta ClonoSIGHT test in the CoMMpass research study.
Including Minimal Residual Disease as Response Criteria in Clinical Trials

<table>
<thead>
<tr>
<th>IMWG MRD negativity criteria (Requires CR as defined below)</th>
<th>Response subcategory</th>
<th>Response criteria $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained MRD negative</td>
<td>MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart. $^2$ Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)</td>
<td></td>
</tr>
<tr>
<td>Flow MRD-negative</td>
<td>Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry $^4$ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells or higher</td>
<td></td>
</tr>
<tr>
<td>Sequencing MRD negative</td>
<td>Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells $^5$ or higher</td>
<td></td>
</tr>
<tr>
<td>Imaging MRD-negative</td>
<td>MRD negative as defined by Next-generation flow or Next-generation sequencing PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT $^3$</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.

Kumar S et al. Lancet Oncol 2016 (In press)
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
Velcade alone or in combination with other myeloma drugs:
Velcade + Thalomid
Velcade + prednisone

**REVLIMID**
Reduction in myeloma progression (3 large studies)
Improved survival (1 of 3 studies)
Small risk of second cancers when used after melphalan
# Ongoing Clinical Studies for Newly Diagnosed Patients

**SMM**

**Patients at High Risk of Disease Progression**
- Revlimid vs observation
- *Empliciti* + Revlimid ± Dex
- Darzalex* (3 doses)
- Siltuximab†
- Kyprolis* + Revlimid + Dex
- Pembrolizumab†
- Ninlaro* + Dex
- Kyprolis*
- Darzalex*

**Active MM (Phase 3)**

**Induction (Transplant Candidates)**
- Revlimid + Dex with Velcade or Kyprolis*
- Revlimid + Dex ± Ninlaro*
- Velcade + Thalomid + Dex ± Darzalex*

**Induction (Nontransplant Candidates)**
- Velcade + Mel + P ± Darzalex*
- Kyprolis* + Mel + P vs Velcade + Mel + P
- Revlimid + Dex ± Darzalex*
- Revlimid + Dex ± Pembrolizumab†
- Revlimid + Dex ± Empliciti*

**Maintenance**
- Ninlaro* (± following ASCT)
- Revlimid 25 mg vs 5 mg
- Revlimid + Dex ± Ninlaro*
- Kyprolis* + Revlimid + Dex vs Revlimid

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*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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**Ask your doctor if you are a candidate for clinical trials.**
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
Conclusion:
Case Presentation

- Diagnosed with ISS II, R-ISS II IgG kappa MM.

- Induction: RVd x 4 cycles achieving VGPR.
  - Developed grade 2 neuropathy after 2 cycles and receiving gabapentin along with dose reduction to Velcade

- High Dose Melphalan and Autologous Stem Cell Transplant achieving CR.

- Maintenance: Revlimid with good tolerance approaching 2-year mark post transplant.
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.
Thank you for your attention!