Multiple Myeloma: Treatment when you’re first diagnosed

Caitlin Costello, MD
Associate Clinical Professor of Medicine
Division of Blood and Marrow Transplant
Moores Cancer Center
University of California, San Diego
A 60 year-old woman was seen by her primary care physician for new onset low back pain. She was found to be anemic with a high calcium level in her blood and worsening kidney function.

Her astute primary care physician checked an SPEP, which revealed a large M-spike.

A follow-up PET scan showed multiple bone lesions, and a bone marrow biopsy showed 60% plasma cells.
Introduction: Example Patient Case

- She is referred to see Dr. Myeloma in initial consultation.
  - What factors does Dr. Myeloma use to decide what to treat with her?

- How should Dr. Myeloma monitor her response to treatment?

- What other issues are important for Dr. Myeloma to consider?
No one treatment plan is right for everyone.

If you are comfortable with it, consider a clinical trial if available.

If you are not comfortable, consider a 2nd opinion.
Goals of Therapy

- Achieving good response (≥VGPR)
- High response rate; rapid response
- Improve performance status
- Minimal side effects
Natural History of Multiple Myeloma

- **MGUS or smoldering myeloma**
  - Asymptomatic
  - Symptomatic

- **ACTIVE MYELOMA**
  - M Protein (g/L): 20
  - 50
  - 100

- **First-line therapy**
  - Plateau remission

- **Second-line therapy**

- **RELAPSE**
  - 1.
  - 2.
  - Refractory relapse
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; ongoing studies are 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></td>
<td>Kyprolis (Carfilzomib)</td>
<td>K or Carf</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Cytoxan (cyclophosphamide)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxil (liposomal doxorubicin)</td>
<td>D</td>
<td>Oral or intravenous</td>
</tr>
<tr>
<td></td>
<td>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>
<td></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, KRD
  - Doublets: Vel/dex, Rev/dex
  - Clinical trial
- High-dose chemotherapy (melphalan) and autologous transplant
- Consolidation/maintenance?

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

For t(4;14): combination including Velcade (V) is critical.
Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Induction Regimens for Transplant-Eligible Patients: 3 is Better Than 2

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/lenalidomide/dexamethasone (RVD)</td>
<td>18-mo PFS: 75%</td>
</tr>
<tr>
<td></td>
<td>18-mo OS: 97%</td>
</tr>
<tr>
<td>Carfilzomib/lenalidomide/dexamethasone (KRd)</td>
<td>12-mo PFS: 97%</td>
</tr>
<tr>
<td></td>
<td>24-mo PFS: 92%</td>
</tr>
<tr>
<td></td>
<td>3-yr PFS: 79%</td>
</tr>
<tr>
<td></td>
<td>3-yr OS: 96%</td>
</tr>
<tr>
<td>Carfilzomib/thalidomide/dexamethasone (KTd)</td>
<td>3-yr PFS: 72%</td>
</tr>
<tr>
<td>Bortezomib/cyclophosphamide/dexamethasone (CyBorD)</td>
<td>5-yr PFS: 42%</td>
</tr>
<tr>
<td></td>
<td>5-yr OS: 70%</td>
</tr>
<tr>
<td>Ixazomib/lenalidomide/dexamethasone</td>
<td>12-mo PFS: 88%</td>
</tr>
<tr>
<td></td>
<td>12-mo OS: 94%</td>
</tr>
</tbody>
</table>

**VRd vs Rd: SWOG So777 Data**

3-Drug Regimen as Initial Induction

**Treatment-naive MM without intent for immediate ASCT**
(N = 525)

Stratifications: ISS; intent to transplant at progression

### VRd†: Bortezomib Lenalidomide Dexamethasone
(n = 264)

Eight 21-day cycles

### Rd: Lenalidomide Dexamethasone
(n = 261)

Six 28-day cycles

### Primary endpoint: PFS

<table>
<thead>
<tr>
<th>VRd</th>
<th>Rd</th>
<th>HR; P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mo</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>75</td>
<td>64</td>
</tr>
</tbody>
</table>

VRd showed better PFS in patients with high- or standard-risk vs Rd‡

- All patients received aspirin (325 mg/d).
- Patients received HSV prophylaxis.
- High-risk cytogenetics included: t(4;14), t(14;16), or del(17p); preliminary data from 316 patients.
### Key Steps to Take on Your Journey

1. **Weighing your therapy options**
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
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.
# Velcade in Frontline Therapy

## How is Velcade administered?
- Options:
  - Injection under the skin (subcutaneous), once or twice weekly
  - Intravenous once or twice weekly – NO MORE!

## 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
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

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

**Standard Tests to Measure Response**
- Blood and urine tests: M-protein, free-light chains
  - Electrophoresis: M-protein levels
  - Immunofixation: sensitive test that measures type of M-protein
  - Freelite™: free light chains
- Bone marrow: plasma cells (antibody producing cells)

**Frequency of Testing**
- Patients on active treatment
  - Blood/urine tests: monthly
  - Bone marrow: best response, relapse
- Not on active treatment:
  - blood/urine tests every 3-6 months
Measuring Response to Therapy

<table>
<thead>
<tr>
<th>Response Type</th>
<th>M Protein</th>
<th>Plasma Cells in Bone Marrow/</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete response (sCR)</td>
<td>None (blood/urine)</td>
<td>No abnormal plasma cells</td>
<td>No free light chains</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>None (blood/urine)</td>
<td>Less than 5%</td>
<td>Disappearance of soft tissue plasmacytomas*</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>Greater than 90% reduction (blood)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>Greater than 50% reduction in blood          + Greater than 90% reduction in urine</td>
<td>NA</td>
<td>Greater 50% reduction in the size of soft tissue plasmacytomas</td>
</tr>
<tr>
<td>Minimal response (MR):</td>
<td>25%-49% reduction in blood and reduction of 50%-89% in urine</td>
<td>NA</td>
<td>25%-49% reduction in the size of soft tissue plasmacytomas and no increase in size/ number of bone lesions</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Does not meet criteria for response or progressive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>Greater than 25% increase (blood or urine)</td>
<td>Greater than 10%</td>
<td>Other changes: bone lesions, soft tissue plasmacytomas, high calcium levels</td>
</tr>
</tbody>
</table>

*Soft tissue plasmacytomas: collection of plasma cells outside the bone
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
- New response types incorporating use of new technologies
  - Immunophenotypic CR
  - Molecular CR

*The Multiple Myeloma Research Foundation is using the Sequenta ClonoSIGHT test in the CoMMpass research study.

Talk to your doctor about types of tests available in your area.
Time to Progression for Patients in Conventional CR who are either MRD Positive or Negative by Deep Sequencing


©2014 by American Society of Hematology
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: Example Patient Case

- Dr. Myeloma determines that the patient is an excellent transplant candidate

- RVd is given for 5 cycles, and the patient achieves a CR. The patient has mild fatigue and calf cramps which are relieved by hydration and electrolyte repletion.

- The patient undergoes autologous stem cell transplant followed by low-dose Revlimid maintenance for 2 years.

- Three years later, the patient remains in a CR, with active surveillance of her myeloma labs every 3 months.
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)
  - Autologous stem cell transplant
  - 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.*
TRANSPLANT??
High dose chemotherapy: Melphalan 200 mg/m² → Autologous stem cell rescue → Maintenance therapy
High-Dose Chemotherapy and Stem Cell Transplantation

- Offers best chance for durable remission based on current data
  - Outcomes improving with the use of newer drugs prior to transplantation
  - New trials comparing novel drugs vs transplant
- Can be done as part of frontline therapy or at relapse (or both)
- More patients considered candidates than in the past
  - Based on overall health and age
  - Criteria varies by cancer center
  - Talk to your doctor to see if you qualify
High-Dose Chemotherapy and Stem Cell Transplantation

- NEJM 2017, IFM2009 study: Auto-SCT improves PFS (versus continued chemotherapy)\(^1\) - 50 months vs 36 months
  - Increased likelihood of MRD negativity with ASCT
  - No difference in how long you’ll live - TOO SOON?!

- 2014 Italian study: Auto-SCT improves PFS and OS\(^2\)

- American study is in progress

1. Attal, NEJM 2017
2. Palumbo et al, NEJM 2014
Types of Stem Cell Transplantation

Transplant Type
- Autologous*
  - Your own cells
- Allogeneic
  - A donor’s cells (requires a match)

Stem Cell Source
- Peripheral blood

Transplant Process
- Mini-allo
- Tandem
- Single autologous

*Most common
Overview: ASCT

- **Stem cell mobilization**
  - Neupogen
  - Neulasta
  - Leukine
  - Cytoxan
  - Mozobil

- **Collection of stem cells from the bloodstream**

- **Freezing of stem cells**

- **High-dose chemotherapy**
  - Evomela (melphalan)

- **Thawing and infusion of stem cells**
“Should I get a transplant?”
“Should I get a transplant?”
Questions To Ask Your Doctor

- Am I a candidate for high-dose chemotherapy and stem cell transplantation?
- What are the pros and cons of stem cell transplantation in my case?
- When is the best time for me to undergo transplantation?
- Does your center do stem cell transplants? How many transplants has your center performed in multiple myeloma in the last year? Is procedure performed as an inpatient or outpatient?
- How long will I be in the hospital?
- What is the recovery period?
- What kind of changes in my lifestyle will I need to make?
- When do I go back to you for follow-up?
Example transplant schedule

<table>
<thead>
<tr>
<th>SUNDAY</th>
<th>MONDAY</th>
<th>TUESDAY</th>
<th>WEDNESDAY</th>
<th>THURSDAY</th>
<th>FRIDAY</th>
<th>SATURDAY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5 GCSF</td>
<td>6 GCSF</td>
</tr>
<tr>
<td>7 GCSF</td>
<td>8 GCSF</td>
<td>9 collection</td>
<td>10 collection</td>
<td>11 collection</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>14</td>
<td>15</td>
<td>16 melphalan</td>
<td>17 melphalan</td>
<td>18</td>
<td>19 Stem cell infusion</td>
<td>20</td>
</tr>
<tr>
<td>21</td>
<td>22</td>
<td>23</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>28</td>
<td>29 egraftment</td>
<td>30</td>
<td>May 1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6 Discharge (if in patient)</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10 Release to clinic</td>
<td>11</td>
</tr>
</tbody>
</table>
OK but am I too old to get a transplant ??
“60 is the new 50!”

“70 is the new 60!”
Data for older patients

- CIBMTR Analysis of Trends in MM-SCT\(^1\)
  - More people are being referred to SCT
  - But still not same proportion of older patients as younger patients

- However, age alone does not appear to predict poor outcome from process of SCT
  - No difference in death, TRM, PFS and OS for patients < or > 60\(^2\)
  - Patients > 70 undergoing SCT have similar response and OS compared with younger patients\(^3\)
  - Patients even up to age 80 can undergo SCT safely\(^4\)

2. Reece et al, BMT 2003
Summary:
High-Dose Chemotherapy and Stem Cell Transplantation

- Offers best chance for long-term remission for eligible patients based on current data

- Research questions:
  - Given the availability of the novel agents, what is the role of high-dose chemotherapy and stem cell transplantation?
  - Which patients achieve the greatest benefit?
  - When is the best time to undergo transplantation?
  - What is the role of maintenance therapy? How long should patients remain on maintenance therapy?
Thank you!