A Collaborative Practice Approach to Managing Patients With Multiple Myeloma: Minimizing Toxicity and Improving Outcomes

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Beth Faiman, PhDc, MSN, APN-BC, AOCN®

Objectives
1. Describe the key practice changes in the treatment of multiple myeloma, including the expanding role of the newer generation of immunomodulatory agents and proteasome inhibitors
2. Understand the unique side-effect profiles and toxicity management of targeted therapy agents within the role of the advanced practitioner
3. Identify means to improve collaboration among oncologists and advanced practitioners in oncology

MULTIPLE MYELOMA
DISEASE OVERVIEW
Myeloma Disease Overview: Meet Jane

- Jane is a very active 41-year-old mother of twin boys
- She wants to go back to school for RN degree
- On routine physical for school she has the following labs:

**CBC values**
- WBC count 3,300/µL
- Hemoglobin 9.3 g/dL
- Platelet count 158,000/µL

**Chemistry values**
- Creatinine 1.0 g/dL
- Calcium 10.2 mg/dL
- Albumin 3.2 g/dL
- Total protein 10.9 g/dL

Case Presentation: Jane

- MPA shows IgG 4,700 mg/dL and kappa 5,200 mg/dL
- M spike 4.2 g/dL
- 24-hr urine was normal < 0.16 g/24 hr
- β2-microglobulin normal 1.6 mg/L
- Bone marrow biopsy showed 20% plasma cells; normal cytogenetics, no IgH translocations. NORMAL IRON STAINS
- Bone survey showed osteopenia
- Diagnosis?

Multiple Myeloma: A Cancer of the Plasma Cells

- Healthy plasma cells produce immunoglobulins in response to foreign body invasion
- Myeloma cells produce abnormal immunoglobulin
  - 65% IgG; 20% IgA
  - 5% to 10% light chains (monoclonal kappa, lambda light chains, Bence-Jones proteins)
- Uncommon IgD, IgE, IgM, or nonsecretory disease

Epidemiology, Risk Factors, Survival

- Incidence
  > 50,000 currently are living with MM in the US

- Risk factors
  - Age
  - Gender
  - Race
  - Obesity
  - Genetics
  - Environment

- Clinical presentation
  - Back, bone pain
  - 20% asymptomatic


Myeloma Patient Median Survival by Diagnosis Year

OS = median overall survival

Patients now live more than twice as long with myeloma!

Diagnosis and Monitoring of MM

M-Protein – SPEP/UPEP
- Myeloma is a monoclonal disease (arises from a single cell)
- The abnormal immunoglobulin produced by myeloma cells is called M-protein

M-Protein and Electrophoresis- M SPIKE
- All proteins from serum or urine produce an abnormal spike

M-Protein and Free Light Chain
- The ratio of free kappa to free lambda light chain is a strong indicator of monoclonality

Heavy-Light Chain Assay
- Highly abnormal H/L ratios are correlated with shorter survival

Specific Diagnostic Tests

- Laboratory analysis
  - Complete blood count and complete metabolic panel
    - β2M, LDH
  - M proteins

- Radiologic imaging
  - Skeletal survey, MRI/CT, PET

- Bone marrow biopsy

- Specific tests to rule out other causes of anemia, renal insufficiency, hypercalcemia, etc.

MM is like a puzzle. You have to put all the pieces together before you see the big picture.
**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>MGUS (1-4 Monoclonal Gammopathy of Undetermined Significance)</th>
<th>Smoldering Multiple Myeloma (1-5)</th>
<th>Multiple Myeloma (6,7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active treatment</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M-protein (g/dl)</td>
<td>&lt; 3 g</td>
<td>≥ 3 g</td>
<td>≥ 3 g</td>
</tr>
<tr>
<td>Clonal plasma cells</td>
<td>&gt; 10%</td>
<td>≥ 10%</td>
<td>&gt; 10%</td>
</tr>
<tr>
<td>End-organ damage</td>
<td>None</td>
<td>None</td>
<td>3 or more CRAB criteria</td>
</tr>
<tr>
<td>Likelihood of progression</td>
<td>1% per year</td>
<td>Difficult to decide for first 5 yrs, &gt;1% per year thereafter</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Disease Progression in SMM and MGUS Patients**

- **MGUS**
- **Smoldering Multiple Myeloma**

10% risk of progression per year^* 1%

- First year: Screen every 6 to 12 months
- After first year: Screen at least every 1 to 3 years
- 5% of people over 50 years old
- 5% of people over 70 years old

- 1% risk of progression per year

**Which is NOT considered one of the CRAB criteria for diagnosis of myeloma?**

A. Calcium elevation  
B. Anemia  
C. Bone lesions  
D. Renal insufficiency or renal failure  
E. Elevated blood monoclonal proteins
CRAB Criteria: A Hallmark of Active MM

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcemia &gt;11.5 g/dL</td>
<td>13%</td>
</tr>
<tr>
<td>Renal failure (creatinine &gt; 2 mg/dL)</td>
<td>19%</td>
</tr>
<tr>
<td>Anemia (Hb &lt;10 g/dL or 2 g/dL &lt; normal)</td>
<td>72%</td>
</tr>
<tr>
<td>Bone disease/osteopenia</td>
<td>80%</td>
</tr>
<tr>
<td>Type of M protein: IgG</td>
<td>52%</td>
</tr>
<tr>
<td>IgA</td>
<td>21%</td>
</tr>
<tr>
<td>Light chain</td>
<td>16%</td>
</tr>
<tr>
<td>Bone marrow plasma cells &gt;10%</td>
<td>96%</td>
</tr>
</tbody>
</table>


Multiple Myeloma Disease Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Durie-Salmon System</th>
<th>International Staging System</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All of the following:</td>
<td>Serum beta-2 microglobulin &lt; 3.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin &gt; 10 mg/dL</td>
<td>and</td>
</tr>
<tr>
<td></td>
<td>• Serum Ca normal or 12 mg/dL</td>
<td>Serum albumin ≥ 3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>• By x-ray, normal bone or solitary bone plasmacytoma only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low M-component production rates:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG value &lt; 5 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA value &lt; 3 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bone-Jones protein &lt; 4 g/24 hr</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Fitting neither stage I nor III</td>
<td>Not stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>One or more of the following:</td>
<td>Serum beta-2 microglobulin ≥ 5.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin &lt; 8.5 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Serum Ca &gt; 12 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Advanced lytic bone lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low M-component production rates:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgG value &lt; 5 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IgA value &lt; 3 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bone-Jones protein &lt; 4 g/24 hr</td>
<td></td>
</tr>
</tbody>
</table>


Sergio Giralt

HISTORICAL AGENTS, STANDARDS OF CARE
First question: Does Jane need treatment?

- Jane is a very active 41-year-old mother of twin boys
- YES she is anemic
- She has SYMPTOMATIC MYELOMA and therefore needs treatment

**CBC values**
- WBC count 3,300/µL
- Hemoglobin 9.3 g/dL
- Platelet count 158,000/µL

**Chemistry values**
- Creatinine 1.0 g/dL
- Calcium 10.2 mg/dL
- Albumin 3.2 g/dL
- Total protein 10.9 g/dL
Goals of Therapy

For a young MM patient such as Jane, the goal of therapy should be long-term disease control.

How do we achieve this?

CR is an important surrogate for survival.

OS After 1 or 2 Transplants

IFM 99 trials courtesy of J. L. Harousseau.


Approach to Multiple Myeloma Treatment

in Transplant-Eligible Patients*

Bort/Dex (cat 1)
Bort/Cyclo/Dex (cat 1)
Bort/Dox/Dex (cat 1)
Bort/Thal/Dex (cat 1)
Len/Dex (cat 1)

MEL 200
ASCT

Observation
Thal (cat 1)
Len (cat 1)
Bort

*Lenalidomide is not FDA approved for treatment of newly diagnosed multiple myeloma (MM) patients.

Thalidomide is not FDA approved as maintenance therapy for MM patients.

Lenalidomide is not FDA approved as maintenance therapy for MM patients.

Bortezomib is not FDA approved as maintenance therapy for MM patients.

Bendamustine is not FDA approved for the treatment of multiple myeloma.

Etoposide is not FDA approved for the treatment of multiple myeloma.

Cisplatin is not FDA approved for the treatment of multiple myeloma.
Is there an optimal induction therapy for Jane?

Importance of collaborative practice in the optimal management of myeloma patients

Goals of Induction Therapy: The Potential Transplant Patient

- Rapid responses
- Depth of responses (high response rates)
- Durable responses
- Improve performance status
- Not limit PBSC mobilization
  - No use of melphalan in induction therapy
  - No over-treatment with lenalidomide
- Overall goal of MM therapy: Extend survival while maintaining quality of life
  - Treatment decisions made early in the course of the disease should not adversely compromise subsequent therapeutic options available to the patient

The Primary Myeloma Care Team

Dr. Perez: Prepares the treatment plan for Jane and supervises therapy; will be assessing toxicity and response and discussing referral to SCT program.

Brad, NP, or Dennis, PA: Delivers and assesses toxicity and treatment responses weekly, advises Dr. Perez of any unexpected side effects and issues that arise. Assesses and intervenes to prevent or treat treatment toxicities.

Ginna, RN: Administers treatment and assesses toxicities; advises the treatment team of any emerging side effects and issues that arise. Educates Jane on strategies to minimize toxicities and improve treatment tolerance and compliance.
### Common Myeloma Regimens

<table>
<thead>
<tr>
<th>Regimen Combination</th>
<th>Abbreviation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/dexamethasone</td>
<td>VD or Vd</td>
</tr>
<tr>
<td>Bortezomib/cyclophosphamide/dexamethasone</td>
<td>CyBorD</td>
</tr>
<tr>
<td>Bortezomib/doxorubicin/dexamethasone</td>
<td>Bortezomib/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>Bortezomib/thalidomide/dexamethasone</td>
<td>VTD or VTd</td>
</tr>
<tr>
<td>Lenalidomide/dexamethasone</td>
<td>Rd</td>
</tr>
<tr>
<td>Carfilzomib/lenalidomide/dexamethasone</td>
<td>DT-PACE; VTD-PACE</td>
</tr>
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</table>

### Transplant

#### Primary Induction

<table>
<thead>
<tr>
<th>Regimen Combination</th>
<th>Abbreviation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan/prednisone/bortezomib</td>
<td>VMP or MPB</td>
</tr>
<tr>
<td>Melphalan/prednisone/lenalidomide</td>
<td>MPR or MPL</td>
</tr>
<tr>
<td>Melphalan/prednisone/thalidomide</td>
<td>MPT</td>
</tr>
</tbody>
</table>

#### Salvage Regimens

There is no standard of care for the treatment of MM at diagnosis or relapse.

### Individualizing Induction Therapy

- Dr. Perez and Brad discuss Jane’s case. Brad advises Dr. Perez that Jane has had significant side effects to prior birth control pills, including a DVT 2 years ago that required 6 months of anticoagulation.
- Based on this, Dr. Perez and Brad discuss with Jane beginning induction therapy with cyclophosphamide, bortezomib, and dexamethasone (CyBORD). Jane is advised that she needs to take adequate birth control measures (barrier methods or abstinence during chemotherapy).

**What other measures does the care team need to make sure are in place for initiation of induction therapy?**
Which of the following is needed prior to beginning Jane’s induction therapy?

A. Acyclovir for herpes zoster prevention
B. Educate Jane on the signs and symptoms of neuropathy
C. Educate Jane on the toxicities of CYBORD, including need to restrict salt and sugar intake
D. Reinforce need for adequate contraception, even if she is not taking an IMiD
E. All of the above.

Monitoring Toxicities

During the 1st cycle of CYBORD, Jane emails Brad a picture of the bortezomib injection site. She is very worried. Brad advises her this is to be expected. He also reviews with Gina an excellent article he just read in the Journal of the Advanced Practitioner in Oncology.
Monitoring Toxicities

• During the 3rd cycle of CYBORD, Jane emails Brad and advises him that she is coming in for her last dose of bortezomib, and that she has more numbness and tingling in her feet with occasional “electric shock” pains. Dennis asks her to come in but NOT to get her shot. He advises Dr. Perez and Ginna too. He examines Jane, who has a normal neuro exam including reflexes, but does refer to significant feelings of “pins and needles” in the soles of her feet.

• Brad calls Dr. Perez in. They decide to cancel the last dose of bortezomib and see Jane in 2 weeks.

• When Jane returns in 2 weeks, her symptoms have significantly improved. Dr. Perez writes for a 4th cycle of CYBORD, but using weekly bortezomib at a reduced dose of 1 mg/m².

Stem Cell Collection

• After the fourth cycle of CYBORD she has achieved a VGPR, with her M peak now at 0.2 g/L and hemoglobin improved to 12 g/dL.

• She advises Dennis the PA that she really feels well and thinks that she does not need further treatment. She is very scared about the prospect of stem cell transplantation. Dennis sits down with her and discusses that further treatment would be beneficial. He arranges for Dr. Perez to see Jane later in the afternoon.

HDT-ASCT is a Well-Supported Option, Not a Requirement
What Are the Talking Points?

• Rationale
  - Why does it work?
  - Why do we do it?
• History
  - How did we come up with this idea?
• Review data and compare with other alternatives
• What can Jane expect from the treatment?

Explain that high dose chemotherapy works by eliminating myeloma cells that have been resistant to regular chemo. But to be able to give high dose therapy we have to collect stem cells to rescue the patients NORMAL marrow from that effect.

**RATIONALE FOR HIGH-DOSE THERAPY**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

Lethal bone marrow toxicity

Lethal toxicity to other organs

What can Jane expect from the treatment?
What data do we need to make an informed decision?
What data do we have?

Risk profile

Optimal induction regimen

COLLECT NO THERAPY + SCT

Maintenance

Harvest and Hold SCT upon Relapse

JADPRO LIVE

Treatment schedule

- 402 patients (younger than 65 years) randomized from 62 centers
- Patients: Symptomatic disease, organ damage, measurable disease

随机化（2x2设计）

Rd

MPR

四28天疗程

MEL 200

两疗程

R MAINTENANCE

28天疗程直到进展

NO MAINTENANCE

MPR

Six 28-day courses

R MAINTENANCE

28天疗程直到进展

NO MAINTENANCE

MPR

Six 28-day courses

MEL 200

Two courses

R MAINTENANCE

28天疗程直到进展

NO MAINTENANCE

MPR

Six 28-day courses

MEL 200

Two courses


MPR vs MEL200

Progression-free survival

Overall survival

HR 1.69, 95% CI 1.32-2.17, P < 0.001

HR 1.25, 95% CI 0.84-1.85, P = 0.27

Points to Be Made

- Achieving a CR is important for long-term disease control. Jane is not in CR. Four cycles is NOT enough to achieve long-term disease control.
- High-dose melphalan with auto-SCT is the therapy associated with the highest response rate.
- Although not easy, it is safe (less than 2% mortality) and effective.
- Currently with high-dose melphalan followed by lenalidomide maintenance, the average remission is almost 4 years. 4-year survival is more than 80%.
- Encourage Jane to participate in a clinical trial. We need more participation in clinical trials to answer important questions aimed at improving myeloma care.

Can Jane Delay Transplant?

- No prospective data yet from well-designed clinical trials using novel primary therapies
  - Trials to address this are ongoing…refer patients to clinical trial
- There are retrospective data
  - This type of data is not as strong, but thus far the data agrees and represents what we have to base an informed discussion upon today
Early versus delayed ASCT in patients receiving novel therapies for multiple myeloma

Retrospective analysis of outcome of MM patients receiving novel agent based induction treatment and received first ASCT within 12 months of diagnosis (early ASCT, N = 102), or at a later date (late ASCT, N = 65).

No statistical significance in PFS or OS between the two groups.

Stratification for Myeloma and Risk-adapted Therapy [mSMART] – off study

FISH

- Standard Risk
  - t(11;14)
  - del(17p)
  - Hyperdiploid
- Intermediate
- High Risk
  - del(17p)
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - GEP High Risk Signature

Transplant eligibility

- Autologous stem cell tx
- 4 cycles of Rd* or CyBorD
- Collect Stem Cells
- Continue Rd**

- Autologous stem cell tx
- 4 cycles of CyBorD
- Autologous stem cell tx
- Autologous stem cell tx

- Collect Stem Cell
- Continue Rd**
- Observation
- Bortezomib maintenance**

- Bortezomib based therapy
  - for minimum of 1 year
  - Observation if not in CR
  - VRD* for minimum of 1 year

Transplant ineligibility

- Transplant ineligible
- Standard Risk
- Cytogenetic deletion 13q
- Or hypodiploidy
- Or PCLI>3%

IFM/DFCI 2009 Study

Newly Diagnosed MM Pts (SCT candidates)

Randomize, stratification ISS & FISH

Induction

- VRD x 3
- CY (3 g/m²)

Consolidation

- Mephalan 200 mg/m²
- ASCT

Maintenance

- Lenalidomide 12 mo

http://www.clinicaltrials.gov/ct2/show/NCT01208662?term=nct01208662&rank=1
• Brad refers Jane to a social worker, who advises the myeloma care team of a difficult family situation.
• Her main hesitation is fear of something bad happening to her, and that she does not think she is in good enough shape to go through the procedure.
• After the myeloma care team explains the transplant procedure, she is concerned about what to do with her twins.
• Jane does agree to see the SCT team, proceed to collections, and visit with the SCT social worker.
• She collects 10 million CD34+ cells, and with social worker and family assistance, is able to undergo stem cell transplantation. She is seen 3 months post-SCT and is in a complete remission.
• The stem cell transplant team is recommending maintenance. Jane wants to wait before starting to talk to Dr. Perez and her team.

Role of Maintenance Therapy in Myeloma

Phase 3 IFM 2005-02: Lenalidomide as Consolidation/Maintenance Post-ASCT

Primary endpoints = PFS

N=614

First-line ASCT < 65 yr

≤ 6 months No PD

Lenalidomide: 25 mg/d Days 1–21/month 2 months

Lenalidomide: 10–15 mg/d until relapse

Lenalidomide: 25 mg/d Days 1–21/month 2 months

Placebo until relapse

**PFS According to Response Preconsolidation**

HR = 0.37, CI 95% (0.25–0.58)

HR = 0.54, CI 95% (0.37–0.78)

**CALGB 100104 Schema**

Registration

Restaging Days 90–100

Randomization

- Stage 1–3, < 70 years
- ≥ 2 cycles of induction
- Attained SD or better
- ≥ 1 yr from start of therapy
- ≥ 2 x 10⁷ CD34 cells/kg

**Stratification based on registration**

2M level and prior thalidomide and lenalidomide use during induction. Primary endpoint: powered to determine a prolongation of TTP from 24 to 33.6 months (9.6 months).

**CALGB 100104, NEJM 2012**

ITT Analysis with a median follow-up from transplant of 34 months. *P* < 0.001 Estimated HR = 0.48 (95% CI 0.36 to 0.63), Median TTP: 46 months versus 27 months.
Secondary Malignancies in MM


CALGB 100104, NEJM 2012 follow up to 10/31/2011

35 deaths in the lenalidomide arm and 53 deaths in the placebo arm, P = 0.028, HR 0.62 or a 40% reduction in death with the cross-over

Median follow-up of 34 months

R maintenance vs No maintenance

Progression-free survival
48% reduced risk of progression

Overall survival
38% reduced risk of death

Secondary Malignancies in MM

Behavioral factors

Environmental factors

Host genetic factors

Treatment of MM

MM related factors

Second Malignancy

HR 0.52, 95% CI 0.40-0.67, P < .0001

HR 0.62, 95% CI 0.62-0.93, P = .02
Death From SPM vs. Other Causes

- Overall cumulative incidence of any SPM was 7.4% at 5 yr and 15.9% at 10 yr
- Cumulative incidence of SPMs for patients > 55 yr approached 21.8% at 10 yr
- Cumulative incidence of MDS/AML was 1.8%
- Cumulative incidence of solid tumors was 13.0%*

Reviewing the Data for Maintenance Therapy in Myeloma

- Dr. Perez reviews with Brad, Dennis, and Gina the data for maintenance lenalidomide in myeloma and puts it into perspective for Jane.
- There is a strong progression-free survival benefit.
- There may be a survival benefit.
- Jane will need to take lenalidomide and have either an IUD placed or surgical sterilization while on lenalidomide (both will have potential repercussions for future fertility).
- Brad and Dennis remind Dr. Perez that with her prior history of DVT, Jane will need to be on full-dose coumadin or LMWH while on lenalidomide.

Would you recommend maintenance to Jane?

A. Yes
B. No
The New Challenge

Jane remains 4 years in complete remission and in Jan 2012 has a recurrence in her M spike with no other manifestations of disease. Bortezomib is added to lenalidomide but unfortunately she is now showing signs of disease progression.

What should you do?

Relapse Approaches

CONSIDER CLINICAL TRIAL WITH A NOVEL AGENT

EARLY

LENALIDOMIDE-BASED
- Initial therapy with len/tx Underlying PN

BORTEZOMIB-BASED
- Initial therapy len/tx Bort Long DOX with prior len/tx Renal dysfunction

TRANSPLANT
- No previous SCT Long remission post-SCT

AGGRESSIVE, RAPID, OR MULTIPLE RELAPSE

CT-BASED
- DCEP vs DT-pace Oral vs IV CT PS plays an important role

SCT-BASED
- Likely to be short-lived Reconstitute marrow

CT + NOVEL AGENT
- Combinations of len and Bort with other agents

Consider combination therapy. Don’t wait for symptomatic relapse.


Most patients will respond to treatment. But how do you decide?

- Proteasome inhibitor–based
  - Bortezomib, carfilzomib
- IMiD based
  - Lenalidomide, pomalidomide, thalidomide
- Combination therapy
  - One- vs. two- vs. three-drug induction
  - Four-drug induction therapies are rare
- Maintenance
- Response to treatment often depends on cytogenetic risk

Once Treatment Fails, Trouble Begins

Overall Survival From Start of Therapy by Regimen Number

Survival with Bz/Len Refractory Dx

RECENTLY APPROVED AGENTS: CARFILZOMIB AND POMALIDOMIDE, Side Effect Management

What is the recommended starting dose of carfilzomib for patients with relapsed MM?

A. 20 mg/m² IV days 1, 2, 8, 9, 15, and 16 of a 28-day cycle
B. 27 mg/m² IV days 1, 2, 8, 9, 15, and 16 of a 28-day cycle
C. 36 mg/m² IV days 1, 8, and 15 of a 28-day cycle
D. 20 mg/m² IV days 1, 8, and 15 of a 28-day cycle
Recently Approved Options for Relapsed Patients: Carfilzomib

- **Trade name**: KYPRLIS®
- **Class**: Proteasome inhibitor
- **Indication**: Patients with multiple myeloma who
  - Have received at least 2 prior therapies including bortezomib and an immunomodulatory agent AND demonstrated disease progression on or within 60 days of completion of last therapy
  - NCCN lists in front-line setting but not FDA-approved indication
- **FDA Approval**: July 20, 2012
- **Administration**: IV
- **Metabolism/Clearance**
  - Renal function status had no effect on clearance; cycle 1 start dose 15 mg/m²
  - CYP450 plays a minor role

Pre-medicate: 4 mg dexamethasone before carfilzomib in:
- All doses cycle 1
- 1st dose cycle 2
- Additional doses/cycles if infusion reactions develop or reappear

Hydrate: 250 to 500 mL IV saline before carfilzomib after (optional) for all doses cycle 1; additional if needed

Monitor for overhydration

Administer carfilzomib IV over 2 to 10 minutes (longer if needed)

Monitor: may require dose adjustment for toxicities

Neuropathy risk is relatively low (14% all grades)

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**Carfilzomib AEs**

<table>
<thead>
<tr>
<th>Carfilzomib Grade 3 or 4 AEs &gt; 10%</th>
<th>Adverse Event</th>
<th>GR3 %</th>
<th>GR4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>23</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>10</td>
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</tr>
<tr>
<td>Lymphopenia</td>
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</tr>
<tr>
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<tr>
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<td>10</td>
<td>&lt;1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Carfilzomib AEs (all grades) in &gt; 30%</th>
<th>Adverse Event</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

**Nursing Implications**

- HBV prophylaxis
- Monitor blood counts
- Monitor for infection
- Cardiac EKG for patients with cardiac history. ECHO baseline, intermittently
- Educate patient:
  - Shortness of breath (dyspnea)
  - Fatigue
  - Anemia/thrombocytopenia
  - Infection prevention
- Interventions:
  - Minimize fluid boluses, diuretics
  - Inhalers
  - Dose reduction, growth factors
Patients with myeloma who are receiving an immunomodulatory drug (IMiD) such as pomalidomide are at risk for blood clots.

Which of the following is NOT a risk factor for developing blood clots?

A. Drugs (erythropoietin [EPO])
B. History of thromboembolic event
C. Low BMI (< 25)
D. Concurrent cardiac or renal disease, diabetes, acute infection
E. Surgery

Recently Approved Options for Relapsed Patients: Pomalidomide

- Trade name: POMALYST®
- Class: IMiD
- Indication: Patients with multiple myeloma who have received at least 2 prior therapies including lenalidomide and bortezomib and demonstrated disease progression on or within 60 days of completion of the last therapy
- FDA Approval: February 8, 2013
- Administration: Oral
- Metabolism/Clearance: Liver via CYP1A2 and CYP3A4
- Can be given with or without low-dose dex
- REMS program similar to thalidomide, lenalidomide

Pomalidomide Nursing Implications: Administration

Discuss Administration With Patient
- 4 mg once daily on days 1-21 of 28-day cycle
- Available in strengths: 1, 2, 3 or 4 mg capsules
- Take without food
  - 2 hr before, after a meal
- Do not break, chew, or open the capsules
- Adherence: consistent schedule (AM or PM)
  - Take immediately if < 12 h since missed dose
  - Skip and take next regular dose if > 12 h

Nursing Implications
- Anti-thrombotic treatment required, risk stratify
  - Female of child-bearing age
    - Two negative pregnancy tests
    - Abstinence or 2 forms birth control
  - Male: Drug present in semen
    - Latex or synthetic condom with females of reproductive potential

Female of child-bearing age: Two negative pregnancy tests
Abstinence or 2 forms birth control
Male: Drug present in semen
Latex or synthetic condom with females of reproductive potential
Pomalidomide Nursing Implications: AEs and Patient Management

<table>
<thead>
<tr>
<th>AEs and Patient Management</th>
<th>Nursing Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT prophylaxis</td>
<td>Monitor blood counts</td>
</tr>
<tr>
<td>Monitor for neuropathy</td>
<td>(especially in patients with prior therapies)</td>
</tr>
</tbody>
</table>

Educate patients on

- DVT prophylaxis
- ASA, risk stratify
- Infection risk/blood counts
- Fatigue

<table>
<thead>
<tr>
<th>Grade 3/4 AEs in &gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia 47</td>
</tr>
<tr>
<td>Anemia 22</td>
</tr>
<tr>
<td>Thrombocytopenia 22</td>
</tr>
<tr>
<td>Neutropenia 20</td>
</tr>
<tr>
<td>Fatigue and anemia 11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3/4 AEs in &gt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue and anemia 55</td>
</tr>
<tr>
<td>Constipation 38</td>
</tr>
<tr>
<td>Nausea 36</td>
</tr>
<tr>
<td>Diarrhea 35</td>
</tr>
<tr>
<td>Cough 34</td>
</tr>
<tr>
<td>Upper resp. tract infec 32</td>
</tr>
<tr>
<td>Back pain 32</td>
</tr>
<tr>
<td>Fatigue (pom + dex) 30</td>
</tr>
</tbody>
</table>

Management of Additional Side Effects

- Renal
- Bone
- Infection, immunizations
- Peripheral neuropathy
  - Subcutaneous bortezomib, dose reductions, schedule changes
  - Duloxetine, gabapentin, pregabalin, amino acids
- Survivorship
  - Patients with MM are just as likely to develop cardiovascular disease and other cancers as counterparts of same age
  - Recommend blood pressure and cholesterol screening, regular physical examinations

Health Assessment and Management Care Plan

Ongoing and Individualized for Each Patient

<table>
<thead>
<tr>
<th>What is the risk of VTE?</th>
<th>Increased if prior VTE, receiving RWE, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone health</td>
<td>Are bisphosphonates indicated? Skeletal survey/imaging yearly</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>Is your patient at high risk for infection?</td>
</tr>
<tr>
<td>GI</td>
<td>Antiemetic prior to bortezomib, docetaxel, carfilzomib</td>
</tr>
<tr>
<td>Health Assessment and Management Care Plan</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Ongoing and Individualized for Each Patient</strong></td>
<td></td>
</tr>
<tr>
<td><strong>(TABLE CONTINUED FROM PREVIOUS SLIDE)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td>Review increased risk of PN with</td>
</tr>
<tr>
<td></td>
<td>bortezomib and thalidomide</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Avoid renal toxic agents, 24-hr urine albumin(bisphosphonates), dose reduction (lenalidomide, melphalan, opioids, acyclovir)</td>
</tr>
<tr>
<td><strong>Cardio/Respiratory</strong></td>
<td>Assess shortness of breath, cardiac</td>
</tr>
<tr>
<td><strong>Disease Monitoring</strong></td>
<td>CBD diff, CMP, SPEP, UPEP, 24-hr urine, sFLC</td>
</tr>
<tr>
<td><strong>Health Maintenance</strong></td>
<td>Immunizations, exercise, nutrition, lipids, cancer screening</td>
</tr>
</tbody>
</table>

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Sergio Giralt and Beth Faiman

**WORKING IN A COLLABORATIVE PRACTICE**

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**Cancer and the Collaborative Team**

- The diagnosis and management of MM require input from various specialties or advance specialty training
- Optimal management of patients with cancer often requires the expertise of specialists from different disciplines
- Patient-centered approach
Components of an Interprofessional, Collaborative Team

- Physical Therapist/Medical
- Primary Oncologist/Hematologist
- Palliative Medicine Team
- Triage Staff
- Social Work
- Pathology
- Other Subspecialty Clinicians (GI/Neuro, Gyn)
- Surgical Oncology
- Radiation Oncology
- Triage Staff
- Social Work
- Pathology
- Other Subspecialty Clinicians (GI/Neuro, Gyn)
- Surgical Oncology
- Radiation Oncology

Clinical Trials

- NCCN believes the best management of any cancer patient is in a clinical trial, and that participation in clinical trials is especially encouraged
- With a large number of trials actively recruiting
  - Consider patient inclusion/exclusion criteria
  - Consider trials for agents that are phase II/III
  - Consider trial center accessibility for your patient
  - Educate your patient

Conclusions

- Advances in MM over the past 10-15 years have led to increased overall survival, more treatment options
- New and emerging drugs show promise
- Advanced practitioners (APs) within a collaborative team should anticipate, prevent, and manage side effects
- APs should also recognize the importance of health maintenance and secondary cancer surveillance, as patients are living longer than ever.