Hot Topics in Multiple Myeloma Treatment

Webinar 2, October 4, 2017
Pros and Cons of Maintenance Therapy

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Multiple Myeloma Research Foundation

**Moderator:**
- **Mary DeRome**
  Multiple Myeloma Research Foundation
  Norwalk, Connecticut

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**Speakers**

**Jonathan L. Kaufman, MD**
Winship Cancer Institute of Emory University
Atlanta, Georgia

**Charise Gleason, MSN, NP-BC, AOCNP**
Winship Cancer Institute of Emory University
Atlanta, Georgia

**Billy Levine**
Patient Advocate
Atlanta, Georgia
Topics for Discussion

- Importance of maintenance therapy
- Duration of maintenance therapy
- Risks and benefits
- Patient perspective

Treatment of Multiple Myeloma

- Initial therapy
- Consolidation
- Maintenance
- Treatment of relapsed disease
- Consolidation/maintenance/continued therapy
- Supportive care

Transplant-eligible patients

Transplant-ineligible patients
Why Maintenance Therapy?

Can maintenance therapy...

- Prevent or delay disease progression?
- Convert partial responses to complete responses?
- Improve overall survival?

Overview of Phase 3 Maintenance Studies

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Existing Evidence on Drugs Used as Maintenance Therapy

### Revlimid
- Reduction in myeloma progression (3 large studies)
- Improved survival (1 of 3 studies)
  - Small risk of second cancers when used after melphalan
- Now approved for use as maintenance treatment after ASCT

### Velcade-based treatment
- Supported by several smaller studies

### Ninlaro
- Oral proteasome inhibitor

### Additional agent under investigation: Kyprolis

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**Revlimid Maintenance: Overall Survival**

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival.

<table>
<thead>
<tr>
<th>N = 1,209</th>
<th>LENALIDOMIDE</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI), mos</td>
<td>NE (NE–NE)</td>
<td>86.0 (79.8–96.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.74 (0.62–0.89)</td>
<td>0.001</td>
</tr>
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</table>

HR, hazard ratio; NE, not estimable; OS, overall survival.
Maintenance Therapy in Myeloma

**What we know**

- Progression-free survival advantage
- Overall survival improvements?
- Toxicities of treatment
  - Myelosuppression
  - Second primary malignancies
- Quality of life
- Cost

**What we don’t know**

- Whether all patients benefit from maintenance
- Which agent to use and duration of therapy
- Response to higher doses of Revlimid at relapse
- Evolution of resistant clones

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### Current Studies on Duration of Maintenance

<table>
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<tr>
<th>Trials</th>
<th>Duration</th>
<th>After ASCT</th>
<th>After Induction</th>
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<tr>
<td></td>
<td></td>
<td>PFS</td>
<td>OS</td>
</tr>
<tr>
<td>LEN vs control</td>
<td>Until progression</td>
<td>42–50 vs 22–24 mos(^1,(^2)</td>
<td>NYR vs 73 mos(^2)</td>
</tr>
<tr>
<td>BZ vs THAL(^6)</td>
<td>2 years after ASCT</td>
<td>35 vs 28 mos</td>
<td>61% vs 55% (5-yr)</td>
</tr>
<tr>
<td>BZ + THAL (VT) vs THAL vs aIFN(^7)</td>
<td>3 years after ASCT</td>
<td>43 vs 36 vs 28 mos</td>
<td>–</td>
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<tr>
<td>VT vs none(^8)</td>
<td>2 years</td>
<td>–</td>
<td>–</td>
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PFS, progression-free survival; OS, overall survival; NYR, not yet reached.

Continuous Therapy vs Fixed-Duration Therapy in Newly Diagnosed Myeloma

<table>
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<tr>
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<th>CT</th>
<th>FDT</th>
<th>HR</th>
<th>P Value</th>
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<tr>
<td>Median PFS1, mos</td>
<td>32</td>
<td>16</td>
<td>0.47</td>
<td>&lt;0.001</td>
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<tr>
<td>Median PFS2, mos</td>
<td>55</td>
<td>40</td>
<td>0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4-year OS, %</td>
<td>69</td>
<td>60</td>
<td>0.69</td>
<td>0.003</td>
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</table>

- Continuous therapy reduced the risk of first disease progression or death by 53% and extended the median PFS1 by 16 months compared with fixed-duration therapy.
- Similarly, continuous therapy reduced the risk of second disease progression or death by 39% and prolonged the median PFS2 by 15 months.
- Continuous therapy reduced the risk of death by 31% and improved the 4-yr OS rate by 9% compared with FDT (69% vs 60%, respectively).

CT, continuous therapy; FDT, fixed duration of therapy; HR, hazard ratio.

Ongoing Studies on Duration of Maintenance

**IFM/DFCI 2009 Trial**
- **US:** 1-year maintenance
- **EU:** until PD
- Initial therapy: RVD: 3 cycles
- Stem cell collection
- Cytoxan
- HD Chemo-therapy + ASCT
- Consolidation: RVD: 2 cycles
- Maintenance: Revlimid 18 months
- Early ASCT

**STAMINA Trial (BMT-CTN0702)**
- **3-year maintenance**
- ASCT MEL 200 mg/m²
- ASCT at relapse
- RVD × 4
- LEN × 3 yrs
- No consolidation
- LEN × 3 yrs
- MEL 200 mg/m²
- LEN × 3 yrs
- ASCT at relapse
- RVD × 4
- LEN × 3 yrs
- No consolidation
- LEN × 3 yrs
- MEL 200 mg/m²
- ASCT at relapse
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- No consolidation
- LEN × 3 yrs
- MEL 200 mg/m²
The anti-myeloma benefits of continuous therapy must be balanced with the toxicities of prolonged treatment.

A major concern with the use of maintenance therapy is the development of toxicity that limits long-term use and potentially compromises the ability to receive optimal treatment in the future.

Continuous Therapy Concerns

- Effects on immune system
- Effects on blood production/bone marrow
- Potential effects on drug resistance
- Toxicity
  - Early → fatigue, GI toxicity, reduction in blood cell production, peripheral neuropathy, blood clots, diarrhea, others
  - Late → secondary primary cancer, decreased marrow reserve

GI, gastrointestinal
**Revlimid Maintenance: Cumulative Incidence of Second Primary Malignancies**

- Hematologic
  - **Lenalidomide** vs **Control**
  - HR (95% CI): 2.03\(^a\) (1.14–3.61)
  - \(P=0.015\)\(^b\)

- Solid Tumor
  - **Lenalidomide** vs **Control**
  - HR (95% CI): 1.71\(^a\) (1.04–2.79)
  - \(P=0.032\)\(^b\)

\(^{a}\)HR based on Cox proportional hazards model.
\(^{b}\) \(P\) value is based on log-rank test.


**Management of Common Toxicities With Revlimid Maintenance**

- **Fatigue**
  - Dosing: every night at bedtime (?)
  - Dose reduction

- **Diarrhea**
  - Antidiarrheal agents
  - Bile salt binders/low-fat diet (for example, colesvelem, cholestyramine)*

- **Rash**
  - Topical steroids/oral antihistamines
  - Hold/reduce dose

- **Thrombosis**
  - Prophylaxis with aspirin

- **Muscle spasms**
  - Quinine sulfate 300 mg every night at bedtime
  - Clonazepam in severe cases

Minimizing Toxicity of Velcade

### Peripheral neuropathy
- Weekly dosing
- Subcutaneous administration

### Gastrointestinal
- Ondansetron premedication
- Antidiarrheal agents
- Subcutaneous administration

### Infection
- Antizoster prophylaxis with acyclovir or related antiviral agent

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Summary

The body of evidence from phase 3 trials indicates that maintenance (or “continuous”) therapy improves progression-free, and likely overall, survival.

The optimal duration is uncertain; however, data to date suggest that it should be given until progression.

- Trials are evaluating various durations of therapy (1 year, 3 years, or until progression; StAMINA, IFM/DFCI 2009 trials, respectively)

Given the heterogeneity of myeloma, some patients likely do not need maintenance, whereas others may do well with truncated courses.

- However, we currently do not have the ability to determine these patients prospectively or during therapy.

Minimizing toxicity and maximizing quality of life are essential to the success of maintenance therapy.

- Choice of agents/regimens
- Dose adjustments
- Symptom management
- Monitoring incidence/risk factors for late toxicity important
My Presentation and Initial Diagnosis

• Diagnosed August 2011
• Presented with
  – Severe kidney issues
  – Anemia
  – Some bone issues
• I have what?
  – Myeloma diagnosis was confirmed with blood work and bone marrow biopsy
  – Considered high risk
• Started induction therapy at Winship Cancer Institute (a Center of Excellence)

My Treatment Plan: Induction Therapy and Preparing for ASCT

Have a plan!

Multiple myeloma is a very individualized disease.

January 2012, ASCT: successful!

Took practically 1 year after ASCT to fully recover.

Throughout 2013, I got my immunizations; strength fully returned.

ASCT, autologous stem cell transplantation
Hot Topics in Multiple Myeloma Treatment
Webinar 2: Pros and Cons of Maintenance Therapy

My Maintenance Therapy

• In April 2012 I started maintenance therapy with Revlimid, Velcade, and dexamethasone
  – Revlimid pill 21 days in a row and then had 7 days off
  – Velcade injection every week at the cancer center
• 3 years would be my time to be on this maintenance therapy

My Side Effects

• Had pretty much all the side effects
  – Muscle cramps
  – Gastrointestinal (GI) issues (all stop or all go!)
  – Insomnia
  – Neuropathy
  – Fatigue
• Velcade
  – Splotchy looking bruise every time – tender at site
  – GI issues (all stop)
• Revlimid
  – No specific issues.
  – GI issues (all go)
• Other medications needed
  – Aspirin
  – Acyclovir
  – Omeprazole
  – Cholesterol drug
My Current Phase of Treatment

At the end of 3 years, I had maintained remission.

Research has been tremendous for myeloma since my diagnosis: new drugs, new delivery methods.

With all these advances—my docs say—we have a number of bullets to put in the gun if we need to.

I don’t feel like maintenance therapy has been too much of an imposition; if we had needed to adjust, we would have.

My Definitions of Treatment Stages

- **Induction**
  - Defense against the disease

- **Autologous stem cell transplantation**
  - Change the paradigm

- **Maintenance**
  - Offense against the disease
Questions & Answers

Closing
Hot Topics in Multiple Myeloma Treatment
Webinar 2: Pros and Cons of Maintenance Therapy

Resources for You!

**MMRF Patient Support Center**

Have questions about the trials or information you heard today?

Call our MMRF Nurse Patient Navigators.

Our MMRF Nurse Patient Navigators can guide you through your multiple myeloma journey every step of the way.

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<tr>
<td>Hot Topics</td>
<td>Precision Medicine</td>
<td>November 1, 2017</td>
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## MMRF Multiple Myeloma Summits

**Fall 2017**

**Saturday, October 14, 2017**
Charlotte, North Carolina
- Manisha Bhutani, MD—Co-Chair
- Saad Z. Usmani, MD—Chair
- Peter M. Voorhees, MD—Co-Chair
  Levine Cancer Institute

**Friday, November 3, 2017**
New York City, New York
- Ajai Chari, MD—Chair
  Mount Sinai Health System

**Saturday, November 18, 2017**
Los Angeles, California
- James Berenson, MD—Co-Chair
  Institute for Myeloma and Bone Cancer Research
- Amrita Y. Krishnan, MD—Co-Chair
  Judy and Bernard Briskin Center for Multiple Myeloma Research
  City of Hope Medical Center

To register, please visit: theMMRF.org/Patient