Management of Multiple Myeloma

Survey of 100 Practicing Medical Oncologists and 28 Clinical Investigators on 9 Cases Presented by Contributing Faculty Members

Faculty
Rafael Fonseca, MD
Irene M Ghobrial, MD
Sagar Lonial, MD

Editor
Neil Love, MD

Faculty Interviews and PowerPoint Slides Included on Enclosed CD

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OVERVIEW OF ACTIVITY
It is important for medical oncologists, hematologists and fellows to be aware of similarities and differences between their patterns of cancer care and those of other community practitioners and multiple myeloma (MM) clinical investigators. Additionally, the recognition that heterogeneity exists within the treating oncology community underscores the existence of clinical situations for which the research evidence to support a single definitive approach may be suboptimal.

This program focuses on the self-described treatment approaches used by randomly selected community medical oncologists and hematologists in a variety of key clinical scenarios in MM. Also included are the parallel treatment approaches used by clinical investigators in academic practices, commentary from myeloma experts and references addressing these topics. This CME program will provide medical oncologists, hematologists and hematology-oncology fellows with information on national cancer patterns of care to assist with the development of best-practice clinical management strategies for MM.

LEARNING OBJECTIVES
• Compare treatment strategies used by community oncologists/hematologists and cancer clinical investigators, and apply this knowledge to the routine management of plasma cell disorders.
• Evaluate clinical issues for which relative agreement and heterogeneity exist in patterns of MM care, and make treatment decisions considering this information.
• Use clinical and molecular factors to risk stratify and select optimal treatment for patients with plasma cell disorders.
• Recognize practice-changing clinical research, and incorporate it into decision-making where applicable.
• Communicate the benefits and risks of evidence-based induction regimens to patients with MM who may or may not be eligible for transplant.
• Optimize the management of MM through rational integration of emerging data in the maintenance setting.
• Counsel appropriately selected patients about the availability of ongoing clinical trial participation.

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COMMERCIAL SUPPORT
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The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: Dr Fonseca — Advisory Committee: Bristol-Myers Squibb Company; Consulting Agreements: Amgen Inc, Celgene Corporation, Genzyme Corporation. Dr Ghobrial — Advisory Committee: Celgene Corporation, Novartis Pharmaceuticals Corporation; Speakers Bureau: Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation. Dr Lonial — Advisory Committee, Consulting Agreements and Paid Research: Bristol-Myers Squibb Company, Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation.

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ABOUT THIS SURVEY
This survey was completed in April 2010 by 100 community-based medical oncologists and 28 clinical investigators (see list on page 3) who treat multiple myeloma in the United States. The community-based oncologists were selected from a proprietary mail list used by Research To Practice for distribution of its CME programs, and the specialists included physicians who have participated in education programs with Research To Practice and others referred for this project.
Clinical Investigators Completing the Survey*

<table>
<thead>
<tr>
<th>CONTRIBUTING EDITORS</th>
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<tbody>
<tr>
<td>Rafael Fonseca, MD</td>
<td>Consultant, Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Deputy Director</td>
<td>Mayo Clinic Cancer Center</td>
<td>Scottsdale, Arizona</td>
</tr>
<tr>
<td>Irene M Ghobrial, MD</td>
<td>Assistant Professor in Medicine</td>
<td>Dana-Farber Cancer Institute</td>
</tr>
<tr>
<td>Scottsdale, Arizona</td>
<td>Harvard Medical School</td>
<td>Boston, Massachusetts</td>
</tr>
<tr>
<td>Sagar Lonial, MD</td>
<td>Associate Professor</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Associate Professor in Medicine</td>
<td>Mayo Clinic Cancer Center</td>
<td>Scottsdale, Arizona</td>
</tr>
<tr>
<td>Hematology and Medical Oncology</td>
<td>Director of Translational Research</td>
<td>Winship Cancer Institute</td>
</tr>
<tr>
<td>B-Cell Malignancy Program</td>
<td>Medical Oncology</td>
<td>Emory University School of Medicine</td>
</tr>
<tr>
<td>Morton Coleman, MD</td>
<td>Head, Multiple Myeloma BMT Program</td>
<td>Atlanta, Georgia</td>
</tr>
<tr>
<td>Director, Center for Lymphoma and Myeloma</td>
<td>Johns Hopkins University</td>
<td>Baltimore, Maryland</td>
</tr>
<tr>
<td>NewYork-Presbyterian Hospital/Weill Cornell Medical Center</td>
<td>Johns Hopkins University</td>
<td>Baltimore, Maryland</td>
</tr>
<tr>
<td>Clinical Professor of Medicine</td>
<td>Section of Hematology/Rush University</td>
<td>Chicago, Illinois</td>
</tr>
<tr>
<td>Weill Cornell Medical College</td>
<td>Professor of Medicine</td>
<td>Winship Cancer Institute</td>
</tr>
<tr>
<td>New York, New York</td>
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<td>Columbus, Ohio</td>
</tr>
<tr>
<td>Morie A Gertz, MD</td>
<td>Assistant Professor of Medicine</td>
<td>The Ohio State University</td>
</tr>
<tr>
<td>Kenneth C Anderson, MD</td>
<td>Assistant Professor of Oncology and Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Professor and Chair of Medicine</td>
<td>Chief, Myeloma Service</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Scottsdale, Arizona</td>
<td>Assistant Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
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<tr>
<td>Igin A Gregory, MD</td>
<td>Assistant Professor, Hematology and Medical Oncology</td>
<td>Winship Cancer Institute</td>
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<tr>
<td>Dana-Farber Cancer Institute</td>
<td>Director, Emory University School of Medicine</td>
<td>Atlanta, Georgia</td>
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<td>Chicago, Illinois</td>
<td>Assistant Professor of Medicine</td>
<td>Atlanta, Georgia</td>
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<tr>
<td>Craig Hofmeister, MD</td>
<td>Assistant Professor of Medicine</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>James R Berenson, MD</td>
<td>Assistant Professor of Oncology and Medicine</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>Medical and Scientific Director</td>
<td>Medical Director</td>
<td>Rocky Mountain Hospital</td>
</tr>
<tr>
<td>Institute for Myeloma Therapeutics</td>
<td>Blood and Marrow Transplant Program</td>
<td>Rocky Mountain Cancer Center</td>
</tr>
<tr>
<td>Boston, Massachusetts</td>
<td>Institute for Myeloma Therapeutics</td>
<td>Denver, Colorado</td>
</tr>
<tr>
<td>Kenneth C Anderson, MD</td>
<td>Professor of Medicine</td>
<td>University of Southern California</td>
</tr>
<tr>
<td>Kraft Family Professor of Medicine</td>
<td>Division of Hematologic Neoplasia</td>
<td>Los Angeles, California</td>
</tr>
<tr>
<td>Harvard Medical School</td>
<td>Director, Jerome Lipper Multiple Myeloma Center</td>
<td>NewYork-Presbyterian Hospital</td>
</tr>
<tr>
<td>Division of Hematologic Neoplasia</td>
<td>Director LeBow Institute for Myeloma Therapeutics</td>
<td>Chief, Myeloma Service</td>
</tr>
<tr>
<td>Director, Jerome Lipper Multiple Myeloma Center</td>
<td>Director, LeBow Institute for Myeloma Therapeutics</td>
<td>New York, New York</td>
</tr>
<tr>
<td>P Leif Bergsagel, MD</td>
<td>Director</td>
<td>Rocky Mountain Cancer Center</td>
</tr>
<tr>
<td>Consultant, Mayo Clinic</td>
<td>Associate Professor of Myeloma</td>
<td>Denver, Colorado</td>
</tr>
<tr>
<td>Scottsdale, Arizona</td>
<td>Associate Professor of Clinical Medicine</td>
<td>University of California</td>
</tr>
<tr>
<td>Ivan Borrello, MD</td>
<td>University of Southern California</td>
<td>Los Angeles, California</td>
</tr>
<tr>
<td>Associate Professor in Oncology</td>
<td>New York-Presbyterian Hospital</td>
<td>Los Angeles, California</td>
</tr>
<tr>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
<td>Associate Professor of Medicine</td>
<td>New York-Presbyterian Hospital</td>
</tr>
<tr>
<td>Baltimore, Maryland</td>
<td>Director, Department of Lymphoma and Myeloma; Associate Professor</td>
<td>Department of Experimental Therapeutics, Division of Cancer Medicine, The University of Texas</td>
</tr>
<tr>
<td>Paul G Richardson, MD</td>
<td>Associate Professor of Medicine</td>
<td>Dana-Farber Cancer Institute</td>
</tr>
<tr>
<td>Harvard Medical School</td>
<td>Clinical Director of the Jerome Lipper Center for Multiple Myeloma</td>
<td>Boston, Massachusetts</td>
</tr>
<tr>
<td>G David Roodman, MD</td>
<td>Professor of Medicine; Vice Chair for Research, Department of Medicine</td>
<td>University of Pittsburgh School of Medicine; Director of the Bone Biology Center, UPMC; Director of the Myeloma Program, UPCI</td>
</tr>
<tr>
<td>Mitchell R Smith, MD</td>
<td>Director</td>
<td>Fox Chase Cancer Center</td>
</tr>
<tr>
<td>Rhode Island Medical School</td>
<td>Associate Professor</td>
<td>Philadelphia, Pennsylvania</td>
</tr>
<tr>
<td>Keith Stewart, MBCchB</td>
<td>Associate Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Vasek and Anna Maria Polak</td>
<td>Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Michigan State University</td>
<td>Division of Hematology-Oncology</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Andrew M Mohrbacher, MD</td>
<td>Cancer Research</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>James R Berenson, MD</td>
<td>Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
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<td>Division of Hematology-Oncology</td>
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<td>Associate Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
<td>Associate Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Miami, Florida</td>
<td>Associate Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
</tr>
<tr>
<td>Baltimore, Maryland</td>
<td>Associate Professor of Medicine</td>
<td>Mayo Clinic Arizona</td>
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* One participant chose to remain anonymous.
Editor’s Note: What’s wrong with this picture?

The most striking difference in this survey relates to the lack of access to new agents on clinical trials in community-based medical oncology. This is not just about research but also patient care. My best example is a patient I’m currently looking after, who has had 4;14-positive myeloma for over 10 years. He received bortezomib early on in the APEX trial, then got lenalidomide/dexamethasone on the MM-009 study, then was on the HSP-90 trial, then a study of the FGFR3 antibody, and is now about to go on a trial of the new IMiD, pomalidomide. My best guess is that the only reason he survived this long is access to new agents.

Sagar Lonial, MD

Patterns of Care Multiple Myeloma 2010;2(1).

FIGURE 1

Over the past 2-3 years, have you changed your preferred induction regimen for patients **eligible** for transplant?

- Yes, for the majority of patients: 48%
- Yes, for a minority of patients: 28%
- No: 24%

Over the past 2 years, have you changed your preferred induction regimen for patients **not eligible** for transplant?

- Yes, for the majority of patients: 34%
- Yes, for a minority of patients: 27%
- No: 39%

Did any of your patients receive an experimental agent this year only available on a clinical trial?

- Yes: 98%
- No: 2%
Although there are a number of reasons why patients don’t end up on trials — most notably a national healthcare system that has been described as approaching a “state of crisis” — the truth for many patients with incurable diseases is that access to clinical trials can be a huge factor in quality of life and survival.

In addition to these more treatment-oriented findings, the study also shed some light on how myeloma fits into the professional lives of oncologists. Breast, lung and colorectal cancer dominate current medical oncology practice, but based on these results it is quite clear that patients with hematologic neoplasms like myeloma are regularly walking through oncologists’ doors (Figure 3).

Another relevant finding, and one that has been quite common in our other POC projects, is the significant heterogeneity in treatment approaches. For example, a number of preferred induction regimens exist for pretransplant and nontransplant situations (Figure 4), and although we have made similar observations in other tumor types with rapidly evolving research databases, such as breast cancer, the practice patterns in myeloma seem even more diverse. This is understandable when one considers the many different regimens that have been studied in well-designed and well-conducted clinical trials.

Which brings us back to the key finding from this survey and makes me wonder where we might be if half or even three quarters of the patients treated by our community-based respondents were entered onto trials. Would we see such diversity in treatment approach? Would other promising agents already be in the mix? As I reflect on this issue and Dr Lonial’s remarkable case I am reminded of an important fact: Participation in clinical research not only helps move the field forward, it also offers the hope of early access to often times effective new treatments.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
June 5, 2010

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Which of the following is generally your preferred induction regimen for patients **eligible** for transplant?

**Standard risk**

- **Rd**: 36%
- **RVD**: 21%
- **VD**: 14%
- **RD**: 0%
- **VTD**: 0%
- **TD**: 0%
- **VdoxD**: 0%
- **CyBorD**: 0%
- **Other**: 22%

**High risk**

- **Rd**: 50%
- **RVD**: 46%
- **VD**: 17%
- **RD**: 6%
- **VTD**: 14%
- **TD**: 1%
- **VdoxD**: 6%
- **CyBorD**: 14%
- **Other**: 20%

Which of the following is generally your preferred induction regimen for patients **not eligible** for transplant?

**Standard risk**

- **Rd**: 26%
- **MPT**: 21%
- **MPV**: 18%
- **RVD**: 7%
- **RD**: 0%
- **VD**: 5%
- **VTD**: 4%
- **TD**: 7%
- **Other**: 14%

**High risk**

- **Rd**: 8%
- **MPT**: 8%
- **MPV**: 18%
- **RVD**: 11%
- **RD**: 6%
- **VD**: 11%
- **VTD**: 4%
- **TD**: 11%
- **Other**: 13%
Case 1: A 55-year-old man is diagnosed with cytogenetic high-risk myeloma with anemia, renal dysfunction and bone lesions.

**Case 1 continued:** The patient’s bone marrow is tested by FISH for del 17p, t(4;14) and t(14;16), and results are negative for all 3. The final metaphase cytogenetic evaluation shows hypodiploidy and no chromosome 13 deletion.

Would this cytogenic information influence your induction treatment choice?

---

**RVD for high-risk multiple myeloma**

**DR LONIAL:** For a patient like this, we would offer RVD regardless of the results, so we don't necessarily wait for the FISH and the cytogenetics to come back. The results of the FISH analysis showed he didn't have deletion 17p, translocation 4;14 or 14;16. The final cytogenetics, however, revealed hypodiploid with no chromosome 13 deletion. A hypodiploid myeloma is certainly a karyotype of concern. I find hypodiploid to be one of the most challenging subsets of aggressive myeloma that we have. It's up there with 17p deletion.

A hypodiploid puts this patient at high risk — I believe that's clear. These patients simply do not fare well. It would not change my choice of induction therapy, however, because we had already chosen an aggressive regimen.

**Management of bortezomib-associated peripheral neuropathy**

The patient did develop some Grade II peripheral neuropathy after four cycles of therapy. It was mostly some numbness and a burning, as though his foot was asleep. He was an avid walker and an active person, which made it a little more challenging. We encourage patients to take a fistful of B vitamins and other simple things that we can do, in the absence of data. While I can make all sorts of recommendations, we don't have randomized data to support their use.

For patients who develop early neuropathy, we prefer pregabalin to gabapentin as our first choice, simply because we see less hypotension and it’s a better-tolerated agent. We also try using some antidepressants, such as duloxetine, in combination with pregabalin. We tell patients to keep their feet warm because the neuropathy tends to be worse in the winter months and if their feet get cold, it can be a greater problem.

As for bortezomib, it's interesting that in light of some of the data on weekly administration — rather than...
twice weekly, for the older patient — the use of the weekly schedule has started to come into play. This replaces dose reduction, which is the standard SUMMIT and APEX recommendation for bortezomib.

In this case, we reduced the dose from 1.3 to 1 mg/m² and kept him on the twice-weekly schedule because that’s what we did in the original trial. But in general, I believe this concept of the weekly schedule, especially with a triplet, is beginning to get more of a foothold. A couple of investigators were considering evaluating induction RVD with weekly bortezomib for older patients, so I believe we will have some clarity around this weekly schedule.

The patient’s neuropathy improved, and after a couple more cycles he decided he was done with ongoing therapy and wanted to go on to have a transplant. He underwent transplant, achieved a complete response and we then had to decide whether to use maintenance therapy.

Post-transplant maintenance therapy

I believe that before the CALGB-100104 data were reported, it was probably less likely that patients would receive maintenance therapy. Given the specifics of this case, a patient with hypodiploid disease is one for whom we would administer maintenance therapy and probably triplet therapy because of the high-risk nature of hypodiploid disease.

In the absence of data, today I would use weekly bortezomib three weeks on, one week off, with lenalidomide administered on days one through 21 and also a small amount of steroids weekly. Back when we cared for this patient, we were not doing that for all these cases.

He’s now a little less than a year out from his transplant and he’s faring well. He has not relapsed yet. His neuropathy now is not an issue and I believe that’s because we made an aggressive and early dose modification in his treatment.

### SELECT PUBLICATIONS

Case 1 continued: The patient receives RVD and a VGPR is achieved. Stem cells are collected after 4 cycles of treatment. The patient develops Grade II neuropathy without pain, predominantly on the soles of the feet.

Which of the following would be your most likely approach to further treatment for this patient?

<table>
<thead>
<tr>
<th>Option</th>
<th>CI (%)</th>
<th>PO (%)</th>
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<tbody>
<tr>
<td>Transplant at this time</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>Change to weekly bortezomib in the RVD regimen</td>
<td>29</td>
<td>19</td>
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<tr>
<td>Reduce bortezomib doses in the RVD regimen by 25%</td>
<td>18</td>
<td>26</td>
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<tr>
<td>Switch RVD to RD or Rd</td>
<td>3</td>
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Which schedule of bortezomib are you currently using, either alone or as part of a doublet combination, in patients with myeloma without neuropathy?

<table>
<thead>
<tr>
<th>Schedule</th>
<th>CI (%)</th>
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<tr>
<td>Standard twice-weekly schedule</td>
<td>36</td>
<td>66</td>
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<tr>
<td>Once-weekly schedule</td>
<td>18</td>
<td>6</td>
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<tr>
<td>Both</td>
<td>46</td>
<td>28</td>
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Case 1 continued: The patient undergoes autologous stem-cell transplant with high-dose melphalan and a CR is achieved.

Would you recommend maintenance therapy, other than bisphosphonates, for this patient?

Which of the following regimens would be your most likely choice for maintenance therapy for this patient?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CI (%)</th>
<th>PO (%)</th>
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<tr>
<td>Lenalidomide +/- steroid</td>
<td>78</td>
<td>74</td>
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<tr>
<td>Thalidomide +/- steroid</td>
<td>5</td>
<td>12</td>
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<tr>
<td>Bortezomib + lenalidomide</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Bortezomib +/- steroid</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>6</td>
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</table>
Case 2: A 92-year-old woman presents with a pathological fracture and is diagnosed with myeloma after hip replacement

**FIGURE 9**

**CASE 2:** A 92-year-old nursing home resident with a history of hypertension and in fair health for her age sustains a pathological hip fracture and undergoes a total hip replacement. Histopathology shows evidence of myeloma. Lab results show mild anemia (Hb 10.5 g/dL), normal calcium, normal kidney function and a monoclonal IgG spike of 3.8 g/dL. Skeletal survey shows a few other lytic lesions. The primary team has discussed hospice as an option and has called a hematologist to review further options with the patient.

— Rafael Fonseca, MD

Would you order a bone marrow evaluation for this patient?

<table>
<thead>
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<th>% answering yes</th>
<th>CI n = 27; PO n = 100</th>
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<tr>
<td>48%</td>
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Would you recommend systemic therapy to this patient?

<table>
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<tr>
<th>% answering yes</th>
<th>CI n = 27; PO n = 100</th>
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<tr>
<td>93%</td>
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**FIGURE 10**

*Lenalidomide and high-dose dexamethasone (RD) versus low-dose dexamethasone (Rd) as initial therapy for newly diagnosed multiple myeloma*

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<th>RD</th>
<th>Rd</th>
<th>p-value</th>
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<tr>
<td>1-year overall survival (n = 223, 221)</td>
<td>87%</td>
<td>96%</td>
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<td>≥ Grade III adverse events, first 4 months (n = 117, 76)</td>
<td>52%</td>
<td>35%</td>
<td>0.0001</td>
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<tr>
<td>Mortality, first 4 months (n = 222, 220)</td>
<td>5.4%</td>
<td>0.45%</td>
<td>0.003</td>
</tr>
</tbody>
</table>


**DR FONSECA:** Part of the thought process here was that this patient was going to receive maybe one line of treatment and it has to be something without major toxicity. Even though the results of the bone marrow probably would have little bearing on what one does over the long term, I was surprised that half of the people would say, “Skip the bone marrow evaluation,” which I believe could be defended as a reasonable alternative. The patient went through a hip replacement surgery, which is much more invasive than a bone marrow biopsy. At the same time, one could probably plan appropriate personalized therapy.

**Pragmatic considerations in myeloma treatment for the elderly**

We spent quite a bit of time talking to the patient and her family members. Her thought process was she had a good support system in place and would like to prolong her ability to keep her disease under control and maintain her level of activity. Thus, she stated, "If you have something to offer that is well tolerated, I am willing to try it.”

I believe it’s important to emphasize that for the elderly, the choice of therapy often is guided by pragmatic considerations, such as distance to the treatment center, comorbid conditions and the like, so the whole concept of risk stratification has been harder to implement in that patient population for that reason alone.

Many specific toxicities and nuances exist on how one manages the elderly. For instance, special attention needs to be paid to myelosuppression, the increased toxicity that the elderly may face with the corticosteroids and the appropriateness of some of the simpler regimens.

The elderly, in general, tend to have more indolent variants of myeloma.

**Front-line treatment with Rd or MP for the very elderly**

The overriding consensus here was therapy with either lenalidomide/low-dose dexamethasone (Rd) or MP. In this particular case I treated the patient with
MP. I did not want to administer triplet therapy and opted to go with the simplest of all interventions. This approach allowed the patient a reasonable opportunity of receiving benefit while also minimizing side effects. I would say Rd would be an equally reasonable choice for her.

We did not treat this patient with bisphosphonates because of logistic issues with having her come to our institution for the infusions. So we elected to treat her with MP without bisphosphonates after an extensive discussion with the family regarding a potential loss of the benefit with this approach, but it was going to be hard to administer the bone-targeted agents. As such, we elected to omit the bisphosphonates.

We discussed the specifics of what to expect in the future in terms of survival with and without treatment. Part of the reason these discussions became so interesting was because of the patient’s intellectual acuity and that of her family.

We discussed treatment as a way to prevent further complications and have her feel better as opposed to the thought process of, “We can make you live longer.” She felt she had lived a complete life, but she was still enjoying what she was doing and she thought, “If this could prevent complications and make me not develop further fractures and other complications, I’d be willing to try something like that.”

The patient completed a year’s worth of treatment and she fared well, though about a year after completing therapy she passed away from unrelated causes. I followed her for the duration of her treatment and then periodically afterward, and she had no further evidence of fractures and completed her life probably as she was destined to do.

SELECT PUBLICATION


---

**FIGURE 11**

**Which of the following would be your preferred treatment regimen?**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CI</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd</td>
<td>20%</td>
<td>44%</td>
</tr>
<tr>
<td>MP</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>RD</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>MPV</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>MPT</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>VD</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>TD</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>21%</td>
</tr>
</tbody>
</table>

CI n = 25; PO n = 75

**Would you recommend IV bisphosphonates for this patient?**

<table>
<thead>
<tr>
<th>Answer</th>
<th>CI</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>78%</td>
<td>52%</td>
</tr>
<tr>
<td>No</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Maybe</td>
<td>15%</td>
<td>36%</td>
</tr>
</tbody>
</table>

CI n = 27; PO n = 100
Case 3: A 58-year-old woman presents with renal dysfunction and anemia

DR GHOBRIAL: The kidney biopsy confirmed light chain nephropathy, and we treated the patient with bortezomib and dexamethasone.

Lenalidomide could be used in a patient with a creatinine of 2.4 as long as we’re careful. Because lenalidomide is excreted in the kidneys, the levels would be high in someone who doesn’t have normal kidney function, so we have to be careful with that dosing.

We should monitor these patients with serum free light chain assays. The assay is nice to follow, especially in someone who has a normal serum protein electrophoresis. The patient may have a light chain myeloma and, with this assay, one can see that the patient has Bence Jones protein.

The 24-hour urine protein electrophoresis also will help you identify Bence Jones proteins and quantify them, but most of our patients have a difficult time collecting a 24-hour urine sample. They spill it, they don’t bring it or they put it in the wrong bottle.

The serum free light chain assay will help follow these patients carefully. There may be occasional discrepancies, but it’s usually a good marker to use in patients with light chain myeloma.

As for a renal biopsy, that basically helps us differentiate whether or not this is myeloma kidney disease. The downside is that we have to be careful because the pathologist may read it incorrectly.

Light chains may be circulating already and some of them may stick near the glomeruli or the vascular areas of those tubules.

One has to be careful when staining for those kappa and lambda light chains to determine whether they are truly positive in the glomeruli or in the tubules. Is this myeloma kidney disease, or is this simply a bystander circulating kappa and lambda light chain that is not affecting the kidneys?

As long as we feel certain that the pathologist knows how to read them correctly — and not overread them — then I believe a kidney biopsy is fine, but we have to be careful.

Renal insufficiency in patients presenting with multiple myeloma

This is a situation we see a lot in practice — that is, patients presenting with some renal insufficiency, like this case with a creatinine of 2.4, and mild anemia that could be from the renal insufficiency or from something else. Then their nephrologist orders a serum protein electrophoresis (SPEP), light chain or a urine protein electrophoresis and finds some protein. They then refer the patients to us, saying, “Okay, this is now multiple myeloma.”

We then try to determine whether this is renal insufficiency from hypertension and the patient has anemia related to that, or whether this patient has active myeloma because the patient has two of the CRAB criteria: renal insufficiency and anemia. It’s hard to differentiate those, especially if the calcium is normal and no lytic lesions are present.

The proportion of patients who present with myeloma and baseline renal insufficiency varies in practices, depending on referrals and the types of patients physicians see in their clinics.

We don’t have too many clinical trials of patients with myeloma and renal insufficiency, and that’s an area that we should study more. Only one retrospective review has been done about the use of bortezomib in patients with renal insufficiency, and some retrospective reviews of lenalidomide have been published. However, no clinical trials or active follow-up of patients with renal

Use of serum free light chain assays

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Insufficiency have been conducted. In this patient, the renal function did not normalize after being treated. This is light chain myeloma and the light chains are the ones causing the nephrotoxic effects. If we treat those patients fast enough and aggressively enough, we usually see normalization and a return to normal renal function. It all depends on how much damage has already been done to the kidneys and how long this has gone on.

We’ve reverted patients who were on dialysis, as long as they were treated aggressively and fast enough, and they’ve returned to normal renal function.

However, if the damage continued for a long time, let’s say they stayed like this with high light chains for a month or so, it’s hard to get back to a normal renal function. We may reverse some of the function, but they may not completely recover normal function.

This patient had an excellent response to induction therapy. We went to very low-dose lenalidomide maintenance, only because at that time no data existed with bortezomib maintenance. Also, the patient had some mild neuropathy, so we didn’t want to continue the bortezomib.

She had a good response, but the renal function kept getting worse and worse and after two years she had to receive dialysis. No relapse was seen in the myeloma and no plasma cells were seen in the last bone marrow biopsy.

**Choice of bisphosphonate for patients with renal insufficiency**

Although more than half of the practicing oncologists selected to use reduced-dose zoledronic acid and then increase it later on with improved renal function, the majority of the investigators preferred pamidronate instead and used a lower dose — that is, infusions longer than 90 minutes and maybe less frequently. Most of us prefer pamidronate to zoledronic acid in a case like this because of the renal effects.

I believe denosumab could be a useful drug in cases like this. It’s not renally excreted, so it can be used in patients with renal insufficiency, and from the data I’ve seen presented, patients on this agent had the same rates of osteonecrosis of the jaw.

It is the policy of our center, which may be a little bit more conservative, not to perform transplants in patients with myeloma and renal insufficiency.
yet across the street in another center they do, so we refer our patients there. It’s center-specific. As long as physicians are careful with the melphalan and the post-transplant complications, I believe that’s fine.

The use of a lenalidomide-based induction therapy for patients with renal insufficiency is an issue, but I believe a lot of physicians now know how to use lenalidomide in patients with renal insufficiency. We can still use lenalidomide — it’s simply that dose reductions are important.

Use of triplet induction therapy

I believe physicians are more comfortable now with the idea of RVD compared to at least a year ago. It’s true that physicians used to prefer sequencing bortezomib/dexamethasone or lenalidomide/dexamethasone up front and then adding the third drug later rather than “shooting all their big guns up front.”

However, I believe we’re starting to see more and more physicians use RVD. It’s a well-tolerated three-drug regimen. It has such a high response rate and such a good complete remission or near-complete remission rate, and that depth of response is important. And we see that usually translates into a longer progression-free survival.

Part of the reason that we’re comfortable with using the three-drug combination is that we know when to dose-reduce. It’s important to dose-reduce when you see side effects, to manage it early on, before the patients develop a lot of neuropathy.

I would advise most of the doctors to consider using weekly bortezomib instead of the twice a week. It gives you a longer time to use it and less neuropathy in some of the patients. We’re starting to conduct a lot of those studies now with weekly bortezomib instead of twice a week.
Double-Blind, Randomized Study of Denosumab versus Zoledronic Acid (ZA) for the Treatment of Bone Metastases in Advanced Cancer or Multiple Myeloma

"Denosumab delayed the time to first on-study SRE (pathologic fracture, radiation therapy or surgery to bone, or spinal cord compression) and was noninferior to ZA (hazard ratio [HR]: 0.84; 95% CI: 0.71–0.98; P = 0.0007). The median time to first on-study SRE was 20.6 months for denosumab and 16.3 months for ZA...

Time to first-and-subsequent SRE was also numerically greater but not statistically superior for denosumab compared with ZA (HR: 0.90; 95% CI: 0.77–1.04; P = 0.14). Adverse events (96% denosumab, 96% ZA) and serious AEs (63% denosumab, 66% ZA) were consistent with what has previously been reported for these two agents. Overall survival was balanced between the groups (HR: 0.95; 95% CI: 0.83–1.08; P = 0.43). Osteonecrosis of the jaw was seen in 10 patients (1.1%) on denosumab and 11 patients (1.3%) on ZA (P = 1.0). In conclusion, denosumab was noninferior to ZA in delaying the time to first on-study SRE in patients with advanced solid tumors and MM."

SRE = skeletal-related event; CI = confidence interval

Henry D et al. Proc ECCO-ESMO 2009; Abstract 20LBA.

SELECT PUBLICATIONS


Case 4: A 59-year-old man undergoes a resection of a thoracic mass and is diagnosed with plasma cell dyscrasia

**Management of plasmacytoma**

**DR LONIAL:** In a case with no other sites of disease, radiation therapy alone is the standard approach.

If you’re concerned about irradiating an area close to the lung, systemic therapy will not necessarily completely eliminate the risk of bone-based residual plasmacytoma, so I believe radiation therapy is the first choice, presuming this patient can tolerate some form of radiation therapy.

I have a similar patient who did have marrow involvement and is on systemic therapy, specifically lenalidomide and low-dose dexamethasone (Rd). The difference between these two cases is solitary plasmacytoma versus systemic disease. This patient was also receiving oxygen and the cytogenetics and FISH were normal. When a patient clearly has significant marrow involvement, we’re going to end up using systemic therapy at some point anyway, so we may as well try while he’s at least a little bit stronger rather than waiting for him to physically weaken.

**Rd in patients with PS 2**

In the management of the patient with marrow involvement triplet therapy was not a viable option despite his young age, as his pulmonary reserve was simply too poor to tolerate any significant infections and his performance status (PS) was close to 2. We felt that he would not survive high-dose therapy. When it came down to selecting an easy, gentle regimen, we thought Rd was the best option for him. After some minor problems in the first few months — some cytopenias and toxicities during the first couple of cycles — he is now a year out from his initial surgery and is experiencing a very good partial response (VGPR) on lenalidomide with only 10 mg of weekly dexamethasone.

Sometimes we simply look at a patient and know that he or she will not fare well with a certain type of therapy. All things being equal, I believe that differences exist between a PS 1, a PS 2 and a PS 3. With this patient, it’s like excluding patients with lung cancer and PS 3 from induction therapy — you know that they will not fare as well. This patient had some problems with lenalidomide and low-dose dexamethasone. I believe that had we tried to administer a triplet, it would not have gone well. We administered aspirin prophylaxis, and he has fared well and had no thromboembolic phenomenon. We were worried about hemorrhage so close to surgery, so we didn’t want to put him on low-molecular-weight heparin.

**Maintenance therapy**

As for further management with a VGPR, for most lenalidomide-based approaches, we treat to progression. A trial conducted by Antonio Palumbo...
and presented at ASH 2009 compared melphalan/prednisone/lenalidomide (MPR) with no maintenance therapy versus MPR with maintenance therapy.

The group who received maintenance therapy clearly fared better. In that case, you could argue that it was ongoing therapy rather than maintenance therapy, but they received intense therapy for nine months and then switched over to a less intense therapy. So my approach is to continue patients on lenalidomide for as long as they can tolerate it.

NCCN Practice Guidelines in Oncology, Multiple Myeloma — v3.2010: Plasmacytoma

“For those patients with osseous plasmacytoma, primary radiation therapy (45 Gy or more) to the involved field is the initial treatment and is potentially curative. Extraosseous plasmacytomas are treated initially with radiation therapy (45 Gy or more) to the involved field and/or surgery.

Follow-up and surveillance for both solitary plasmacytoma and extraosseous plasmacytoma consist of blood and urine tests done every 4 weeks initially to monitor response to the radiation therapy. If the patient achieves complete disappearance of the paraprotein then the frequency could be reduced to every 3-6 months and as clinically indicated. If the protein persists, then the monitoring should continue every 4 weeks.

If progressive disease emerges, then the patient should be re-evaluated for recurrent extraosseous plasmacytoma or myeloma, with systemic therapy administered as indicated.”

SELECT PUBLICATIONS


Palumbo A et al. A Phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma. ASH 2009;Abstract 613.


Case 4 (Continued)

FIGURE 18

Case 4 continued: The patient receives Rd, achieves a very good partial response (VGPR*) and has no personal or family history of either venous or arterial thromboembolic events.

Which thromboprophylaxis, if any, would you recommend for this patient while he receives lenalidomide-based therapy?

<table>
<thead>
<tr>
<th>Option</th>
<th>Continue Rd</th>
<th>Stop Rd and administer an alternative maintenance therapy</th>
<th>Stop Rd and do not administer maintenance therapy</th>
<th>Lenalidomide alone as maintenance</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin either 81 mg or 325 mg</td>
<td>61%</td>
<td>18%</td>
<td>7%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Therapeutic-dose warfarin (target INR 2-3)</td>
<td>54%</td>
<td>20%</td>
<td>24%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Prophylactic doses of low molecular weight heparin</td>
<td>11%</td>
<td>10%</td>
<td>1%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Low-dose warfarin (target INR ~ 1.5)</td>
<td>7%</td>
<td>7%</td>
<td>0%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Combination of the above choices</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>No prophylactic anticoagulation</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR at least a 90% reduction in serum M-protein with a urine M-protein <100 mg/24 h

The patient remains in VGPR after 6 months of therapy with Rd. Which of the following would be your approach to further management?

FIGURE 19

Phase III study evaluating lenalidomide maintenance in elderly patients with multiple myeloma

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MPR-R (n = 152)</th>
<th>MPR (n = 153)</th>
<th>MP (n = 154)</th>
<th>p-value (MPR-R vs MP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>77%</td>
<td>67%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>18%</td>
<td>13%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>32%</td>
<td>33%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR</td>
<td>45%</td>
<td>34%</td>
<td>37%</td>
<td>—</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>Not reached</td>
<td>Not reported</td>
<td>13 months</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 Measured using EBMT criteria; 2 Immunofixation-negative with or without bone marrow confirmation; 3 VGPR: >90% reduction in M-protein
M = melphalan; P = prednisone; R = lenalidomide; CR = complete response; VGPR = very good partial response; PR = partial response

Palumbo A et al. Proc ASH 2009; Abstract 613

POCMM110_Book_Final.dn.indd 18 6/11/10 2:26:38 PM
Case 5: A 41-year-old woman is diagnosed with myeloma after a bone marrow evaluation for presumptive leukemia.

CASE 5: A 41-year-old woman initially presents with a 6-month history of fatigue and symptoms of pneumonia. Lab results are normal. A couple of months later, she develops pancytopenia and is at first presumed to have acute leukemia. A bone marrow evaluation shows 95% plasma cells. Albumin level is 3.9 g/dL and beta-2 microglobulin is 3.6 mg/L. A skeletal survey reveals small lucencies in the calvarium and humeri, and cytogenetic studies reveal t(4;14) translocation.

— Irene M Ghobrial, MD

Do you routinely stage patients with multiple myeloma?

Which staging system do you use for your patients with multiple myeloma?

How would you categorize this patient’s multiple myeloma by ISS staging?

FIGURE 21

International Staging System (ISS) for multiple myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>% Patients</th>
<th>ISS criteria</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>28%</td>
<td>Serum beta2-microglobulin &lt; 3.5 mg/dL&lt;br&gt;Serum albumin ≥ 3.5 g/dL</td>
<td>62 months</td>
</tr>
<tr>
<td>II</td>
<td>33%</td>
<td>Neither Stage I nor Stage III</td>
<td>44 months</td>
</tr>
<tr>
<td>III</td>
<td>39%</td>
<td>Serum beta2-microglobulin ≥ 5.5 mg/L</td>
<td>29 months</td>
</tr>
</tbody>
</table>

Case 5 (Continued)

**Staging multiple myeloma**

DR GHOBRIAL: In staging multiple myeloma, we use both the International Staging System (ISS) and the Durie-Salmon staging system. That’s in part because we participate in many clinical trials and it’s still required to use the Durie-Salmon staging system. In practice, I believe it’s fine to use the ISS alone. It’s prognostic and it gives you the information you need.

This patient has ISS Stage II disease, yet only half of the practicing oncologists categorized it that way. The physicians who did not stage this case correctly may not be familiar with the ISS. It’s a simple staging system that includes albumin and beta-2 microglobulin levels. We may need to educate physicians on this further, but the most important element for them to remember is the beta-2 microglobulin.

In this patient, the beta-2 microglobulin was 3.6 mg/L, and the cut-off for Stage I is <3.5, so it barely made it to Stage II. Her albumin was normal and she looked healthy. However, she did have other prognostic factors that increased her risk. She had translocation 4;14, which is one of the worst prognostic factors we have in myeloma, and her bone marrow evaluation shows 95 percent plasma cells. Assessing whether a patient is at high risk is a matter of putting everything together.

**Novel agents and poor-risk cytogenetics**

Whether patients have certain risk features, such as 4;14 translocations or 13q deletions, or have no abnormal cytogenetics is becoming more and more of a patient care issue because it affects treatment decisions. We select some drugs specifically for patients with poor cytogenetic features, especially novel agents such as bortezomib and lenalidomide.

For example, we already use bortezomib in some patients who have specific poor prognostic features, such as 13q deletion. As for 4;14 translocations, some papers say bortezomib can overcome this, whereas others say it can’t. A paper that’s coming out soon indi-
icates that bortezomib cannot overcome it completely, but it does still have some effect on it.

The patient’s risk affects both induction and maintenance treatment decisions. In patients at high risk we use combinations that include agents such as bortezomib and lenalidomide. In patients expected to undergo transplant, one has to question whether transplant will help those who are at high risk or will they relapse within six months. We’re already using a lot of maintenance therapy, especially for patients with high-risk features. One may even potentially consider bortezomib for maintenance therapy for some of those patients.

Assessing the patient’s risk already makes a difference in treatment decisions. In the future we will have more and more individualized therapy and we’ll see specific trials for specific subsets of patients. One example is FGFR3, which can occur in patients with 4;14 translocations, and we now have some new drugs that target FGFR3. We’ll probably see this more now in the new era of novel agents in myeloma.

Using only the ISS, this patient’s risk is intermediate. However, other features, including the cytogenetic information, must be considered. The 4;14 translocation alone is enough to place her at high risk, and she has a packed marrow. If the marrow had been that way for months or years without problems, one could say it potentially is a slower growing myeloma. However, she presented quite fast with a packed bone marrow, so we can see this was a fast-growing myeloma. That along with the translocation definitely places her at high risk.

**Triplet and quadruplet induction therapy**

We treated her with RVD, the most common choice by respondents, and she had a good response to therapy. The CyBorD regimen is also an excellent combination that has a high response rate.

Shaji Kumar, from Mayo Clinic, presented data at ASH 2009 from the randomized Phase II study of bortezomib/dexamethasone/cyclophosphamide (VDC) versus bortezomib/dexamethasone/lenalidomide (VDR) versus the four-drug combination bortezomib/dexamethasone/cyclophosphamide/lenalidomide (VDCR) for patients newly diagnosed with multiple myeloma.

Patients in all three arms fared well. They had good responses and the toxicity profiles were similar. We expected to see a higher response rate in the four-drug arm. They have now changed the dose of cyclophosphamide in that arm, adding an extra week, and they’re beginning to see a higher complete response rate and stringent complete remission.

I believe we’ll see more data from this randomized study, but for now I believe CyBorD, VDR or VDCR are perfectly fine combinations.
Although I believe lenalidomide/dexamethasone alone is okay, I like to add bortezomib for patients with a 4;14 translocation, light chain myeloma, IgA myeloma or anything that places them at high risk. For such patients, using both novel agents — lenalidomide and bortezomib — together would be a good idea.

Bortezomib/thalidomide/dexamethasone (VTD) is also fine, but the risk of neuropathy is high when thalidomide and bortezomib are administered together. So why not replace thalidomide with lenalidomide, given Paul Richardson’s data showing that RVD has high responses and less toxicity, especially less neurotoxicity?

I see that some physicians select the combination of bortezomib and dexamethasone, which is also a good option. However, RVD is well tolerated and we’re seeing high responses with this regimen.

Immediate versus delayed transplant

Although a number of physicians indicate here that they would have held off from transplant, this patient is young and after we discussed all the risks and benefits of transplant, she chose transplant up front. She went on to receive a stem cell transplant and had a good response to it, and then she received lenalidomide maintenance.

It is interesting that people are starting to perform fewer and fewer transplants. This is a new trend in myeloma. I believe that had you asked the same question three years ago, 100 percent of physicians would have chosen stem cell transplant. Now we’re considering alternatives, such as whether we could mobilize and store, or should we treat with maintenance lenalidomide maintenance.

We are initiating a large study with the French study group Intergroupe Francophone du Myelome (IFM), in which patients will be randomly assigned to a transplant or no-transplant group. Half of the patients will undergo mobilization and then proceed to maintenance therapy, whereas the other half will go...
to transplant followed by maintenance. The reason to conduct such a trial is that in this era of novel agents, we don’t know whether transplant adds to the efficacy of a combination like RVD that already has a high response rate and an excellent depth of response.

**Impact of Response Failure with IMiD-Containing Induction Therapy on Outcomes After Stem Cell Transplantation**

“Unlike patients in reports published previously — before immunomodulatory drugs — patients who do not achieve partial remission have a significantly shorter overall survival from transplantation (73.5 vs 30.4 months) and a shorter progression-free survival (22.1 vs 13.1 months; P < 0.001). Absence of a response to induction therapy with thalidomide or lenalidomide predicts a poorer outcome after high-dose therapy.”


**Importance of pretransplant response**

I believe it’s important to note that today patients need to achieve a good response before transplant. In the old days, we used to say that even if we didn’t achieve an excellent response, we should simply perform the transplant and we’ll get a good response. Morie Gertz recently published a retrospective study in *Blood* in which we basically see that patients who received lenalidomide and dexamethasone and did not achieve at least a partial response did not fare well with the transplant.

**Maintenance lenalidomide**

This patient has been on lenalidomide maintenance for almost a year and is currently in near-complete remission. The maintenance trials with lenalidomide continued for two years. We have patients who participated in the Phase I/II trials and are still on lenalidomide six or seven years later, so it’s not a safety concern. As long as we monitor her carefully and she’s faring well.
and has no toxicities, then I will continue the therapy. Two large studies conducted with lenalidomide maintenance were presented at ASH 2009 and I hope we’ll see more results this year. We participated in the CALGB 100104 study, in which patients were randomly assigned to low-dose lenalidomide versus placebo post-transplant. The French study had a similar study design. Both trials demonstrated a progression-free survival benefit with lenalidomide. The CALGB study was stopped after an interim analysis, and patients on placebo were offered lenalidomide maintenance. We don’t have overall survival data yet in those studies.

**Duration and schedule of bisphosphonates**

This issue of bisphosphonate use will get more confusing soon because so many studies are coming out now saying that particularly long-term use of bisphosphonates is causing more problems with fractures in some patients because of a lack of bone remodeling. So we might have to change the guidelines again.

Although it’s controversial, what I currently do is administer a once-a-month bisphosphonate treatment for the first year and then in the second year I switch to every three months as long as patients have a good response and no new lesions or myeloma relapse. It’s hard to know what to do after the second year. Some physicians treat indefinitely, which is what we did in the old days. After two years, if they have no new lytic lesions and they’re in an excellent remission, I prefer to stop treatment rather than continue on forever.

Several ongoing clinical trials are evaluating this issue. The Z-MARK study randomizes between therapy once a month versus every three months after the initial year of treatment to determine whether the every three-month treatment is beneficial. Some studies use NTX levels to see how long one will need to treat those patients with bisphosphonates. In addition, so many other new drugs are coming out — anti-DKK-1 and RANK
ligand inhibitors — and all of those will probably play a big role in treatment of bone disease in myeloma.

SELECT PUBLICATIONS


**FIGURE 29**

Do you ever administer maintenance therapy (other than bisphosphonates) to your patients who:

<table>
<thead>
<tr>
<th>Received ASCT?</th>
<th>Did not receive ASCT?</th>
</tr>
</thead>
<tbody>
<tr>
<td>% answering yes</td>
<td>% answering yes</td>
</tr>
</tbody>
</table>

In general, has your approach to maintenance therapy after induction changed in the past year for patients with multiple myeloma who are:

<table>
<thead>
<tr>
<th>Transplant candidates?</th>
<th>Not transplant candidates?</th>
</tr>
</thead>
<tbody>
<tr>
<td>% answering yes</td>
<td>% answering yes</td>
</tr>
</tbody>
</table>

**FIGURE 30**

Z-MARK: A Phase IV study of zoledronic acid treatment every 4 or 12 weeks to prevent skeletal complications in advanced multiple myeloma

Protocol ID: CZOL446EUS129
Target Accrual: 120 Primary Completion Date: December 2010
Eligibility: Patients with multiple myeloma and stable renal function who have received 1 to 2 years of zoledronic acid or pamidronate. Bisphosphonate therapy initiated for osteolytic lesion, bone fracture, spinal cord compression or osteopenia due to multiple myeloma.

- NTX < 50nM-q12wk
- NTX > 50nM-q4wk
- NTX < 50nM-Obs
- NTX > 50nM-Rx

n = 120 NTX directed q4 or 12 wk Obs or NTX directed

Primary efficacy endpoint: Time to first skeletal-related event

NTX = N-telopeptide of type I collagen

Case 6: A 65-year-old man with myeloma seeks a second opinion after attaining PR with Rd induction

Dr. Fonseca:

This patient came to us after his initial therapy for a second opinion. The primary reason for the consultation was for consideration of an autologous stem cell transplant. The patient presented around the time of the first published French data suggesting that pretransplant response does matter with regard to post-transplant results.

So, this is not an uncommon situation — one in which a patient receives effective therapy — but perhaps without the depth of response one might want to have in a pre-transplant setting.

The questions are: Is that a reflection more of the biology? And should we do something more with the therapy in an attempt to achieve a higher quality of response?

As it turned out, this patient was very active physically and was not keen on proceeding with a stem cell transplant. We presented several alternatives, the first being continuation of Rd therapy. Data reported by Ruben Niesvizky indicate that if you continue therapy over the long term, the quality of responses continues to increase.

The other option presented to the patient was treatment with a combination such as RVD. The presumption here would be that addition of bortezomib may induce a better-quality response or at least may not push the patient toward stem cell transplant since this patient is not keen on moving to stem cell transplant.

One comment on top of all these considerations is that if one is to consider the lenalidomide over a longer period, the issue is what time one should consider the collection of the stem cells.

We discussed with the patient and opted to switch to the RVD combination. At this time stem cells were harvested, but the patient at this point declined to receive high-dose melphalan. Again, this patient was active, had a great life, felt good and was not symptomatic at that point with the exception of the peripheral neuropathy. He proceeded with stem cell collection but declined moving on to stem cell transplant.

**Bortezomib-Based Front-Line Therapy**

“Front-line therapy for multiple myeloma is rapidly evolving with the development of new, highly active regimens based on novel agents such as bortezomib. Bortezomib-based regimens are demonstrating substantial efficacy both as induction prior to stem cell transplantation and as treatment for patients ineligible for transplant, offering rapid and durable responses with consistently high rates of complete response, a surrogate end point for improved overall survival. Combinations of bortezomib plus established and novel agents, such as melphalan-prednisone, dexamethasone, doxorubicin, thalidomide-dexamethasone and, most recently, lenalidomide-dexamethasone, are proving superior to or more promising than previous standards of care.”


**Bortezomib-associated peripheral neuropathy**

With regard to the patient’s neuropathy, I try to emphasize that the

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**Quality of response to front-line therapy**

**DR FONSECA:** This patient came to us after his initial therapy for a second opinion. The primary reason for the consultation was for consideration of an autologous stem cell transplant. The patient presented around the time of the first published French data suggesting that pretransplant response does matter with regard to post-transplant results.

So, this is not an uncommon situation — one in which a patient receives effective therapy — but perhaps without the depth of response one might want to have in a pre-transplant setting.

The questions are: Is that a reflection more of the biology? And should we do something more with the therapy in an attempt to achieve a higher quality of response?

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The other option presented to the patient was treatment with a combination such as RVD. The presumption here would be that addition of bortezomib may induce a better-quality response or at least may not push the patient toward stem cell transplant since this patient is not keen on moving to stem cell transplant.

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**FIGURE 31**

**CASE 6: A 65-year-old man is diagnosed with multiple myeloma, which is treated with Rd by his oncologist. A PR is achieved after 3 cycles of Rd and the patient comes to you for a second opinion.**

— Rafael Fonseca, MD

<table>
<thead>
<tr>
<th>What would be your preferred treatment approach at this time?</th>
<th>CI (n = 27)</th>
<th>PO (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add bortezomib for 2 to 3 cycles, then harvest stem cells and offer high-dose melphalan with ASCT</td>
<td>48%</td>
<td>45%</td>
</tr>
<tr>
<td>Harvest stem cells now and offer immediate high-dose melphalan with ASCT</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>Continue Rd for 2 to 3 additional cycles and then harvest stem cells and offer high-dose melphalan with ASCT</td>
<td>15%</td>
<td>27%</td>
</tr>
<tr>
<td>Harvest stem cells now, then continue Rd for 2 to 3 additional cycles and offer high-dose melphalan with ASCT</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>6%</td>
</tr>
</tbody>
</table>
The best treatment for neuropathy is always prevention. We have used a number of agents to try to ameliorate the symptoms. Whenever we treat neuropathy, it’s treating the painful component. You cannot treat the sensory component. I believe that’s an important point.

People use agents such as gabapentin or pregabalin for the treatment of some of the symptoms. Administration of these agents did help in this case. We’ve also used a topical cream containing ketamine that is mixed by an apothecary. We combine that with clonidine, and I believe it also can be combined with lidocaine. It’s a dissociative anesthetic agent that, in a topical fashion, has helped some patients with painful peripheral neuropathy. I believe it helped this patient with his symptoms, and overall he was allowed to recover more from the painful event.

Patients’ acceptance of transplant in an era of novel agents

After we had collected the patient’s stem cells and, based on the fact that he had responded to lenalidomide and did not want to proceed with stem cell transplant, we went back to the original treatment. We placed him back on chronic lenalidomide treatment, and he continues to fare well and is recovering from his peripheral neuropathy.

I believe cases such as this one pose a unique challenge we are currently facing — a young individual who is aware of the literature, who does not wish to undergo stem cell transplant and who realizes that lenalidomide is a reasonable option. This makes our discussion more challenging. I believe this is something we will probably see more and more moving forward — whether everyone should go through stem cell transplant as frontline therapy. I believe transplant remains a key option for patients with myeloma, but sometimes, as was the case in this particular individual, we opted not to use that approach.

SELECT PUBLICATIONS

In your view, what is the clinical impact of maintenance therapy for a patient who:

**Has not received ASCT**
- It improves progression-free survival (PFS) but does not affect overall survival (OS): 52% prefer improvement in PFS over OS, 49% prefer maintenance therapy regardless of OS.
- It improves both PFS and OS: 33% prefer improvement in both PFS and OS, 27% prefer improvement in PFS and no change in OS, 0% prefer no change in PFS and improvement in OS.
- It does not affect either PFS or OS: 0% prefer no change in PFS or OS, 6% prefer improvement in OS regardless of PFS, 15% prefer improvement in PFS regardless of OS, 18% are not sure.
- I am not sure: 27% are not sure.

**Has received ASCT**
- It improves PFS but does not affect OS: 33% prefer improvement in PFS over OS, 34% prefer maintenance therapy regardless of OS.
- It improves both PFS and OS: 48% prefer improvement in both PFS and OS, 40% prefer improvement in PFS and no change in OS, 0% prefer no change in PFS and improvement in OS.
- It does not affect either PFS or OS: 0% prefer no change in PFS or OS, 5% prefer improvement in OS regardless of PFS, 19% prefer improvement in PFS regardless of OS, 21% are not sure.
- I am not sure: 27% are not sure.

**Phase III Trials of Maintenance Lenalidomide versus Placebo**
- CALGB-100104: 58% improvement in event risk (HR = 0.42)\(^1\)
- MM-015: 75% reduction in PFS risk (HR = 0.245, \(p < 0.001\))\(^2\)
- IFM 2005-02: 54% improvement in 3-year PFS (HR = 0.46, \(p < 10^{-6}\))\(^3\)

CALGB and IFM: Maintenance lenalidomide after ASCT

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Case 7: A 23-year-old man presents to an emergency room with hypercalcemia and acute renal failure

**Risk stratification**

**DR LONIAL:** It’s clearly important to classify patients according to their risk. In my practice, the risk data are critical in helping me define if and how I will use maintenance after initial induction therapy. For example, in patients with 4;14 translocation, maintenance with a proteasome inhibitor appears to overcome at least a part of the poor-risk features associated with that disease.

Physicians who are not routinely evaluating risk may not be seeing enough patients with myeloma to have that Pavlovian reflex to order FISH and cytogenetics. For a large number of the patients I consult with, this is being done — it’s the rare patient for whom it’s not.

Management of hypercalcemia

The management of hypercalcemia is often driven by the hospital-based pharmacy — physicians don’t want to administer bisphosphonates to patients with acute renal failure, but I believe they can’t see the forest for the trees. You are never going to make the hypercalcemia better until you treat with bisphosphonates. Bisphosphonate-induced renal failure is not an acute issue but a chronic issue and occurs with multiple months of administration. So you’ll almost never go wrong with a single dose.

What we have started to push now among the house staff and the fellows is to hydrate the patient as best we can, treat with a bisphosphonate and observe how the results settle. Then we can decide on subsequent doses and frequency of bisphosphonates, but it shouldn’t be withheld simply because a patient has a high creatinine level.

In this kind of an acute setting, one dose is usually sufficient. We can use agents like calcitonin to bring the calcium down a lot quicker. This patient received reduced-dose pamidronate.

**Triplet induction therapy**

This patient received lenalidomide/bortezomib/dexamethasone (RVD) on
Case 7 (Continued)

**FIGURE 35**

**Case 7 continued:** The patient receives IV hydration, steroids and reduced-dose IV bisphosphonates. The hypercalcemia and renal dysfunction improve. Cytogenetics and FISH results are normal.

**Which induction regimen would you use?**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD</td>
<td>29%</td>
</tr>
<tr>
<td>VTD</td>
<td>25%</td>
</tr>
<tr>
<td>CyBorD</td>
<td>21%</td>
</tr>
<tr>
<td>VD</td>
<td>20%</td>
</tr>
<tr>
<td>Rd</td>
<td>17%</td>
</tr>
<tr>
<td>VdoxD</td>
<td>12%</td>
</tr>
<tr>
<td>Other</td>
<td>16%</td>
</tr>
</tbody>
</table>

**Case 7 continued:** The patient is started on RVD induction on a clinical trial. After 1 cycle, a CR (complete response) is achieved.

**Would you harvest this patient’s stem cells and if so, at what point?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, after 4 to 6 cycles of RVD</td>
<td>79%</td>
</tr>
<tr>
<td>Yes, now</td>
<td>14%</td>
</tr>
<tr>
<td>No</td>
<td>25%</td>
</tr>
</tbody>
</table>

study, and within 10 days, his back pain and major symptoms were significantly alleviated. He was walking around, despite the compression fractures, and felt significantly better. He achieved complete remission after one cycle of therapy.

With regard to using lenalidomide in a patient with renal dysfunction, this patient’s creatinine had come down to about 1.8. If we had measured his creatinine clearance, it would probably have been right on the border of 50 mL/min, which is the cutoff for full- versus reduced-dose therapy.

For patients in whom I believe renal dysfunction is disease related and will reverse with adequate treatment, I tend to use full-dose therapy to maximize the likelihood of obtaining a response. The downside of that is perhaps we’ll see a little bit more prolonged cytopenias. It’s not that we’ll get more renal failure — it’s that the drug remains around a bit longer. In this case, the patient’s creatinine level came down to less than one after one cycle of therapy.

Looking at the survey responses, it appears we are beginning to see a big shift in the use of RVD. I believe people are more aware of the data and the concept that a triplet is superior to a doublet is gaining more of a foothold. The question then becomes, which triplet should one use? Here RVD, VTD and CyBorD are the three most often selected.

CyBorD is a combination of oral cyclophosphamide with bortezomib and dexamethasone that was pushed forward by the Mayo Scottsdale folks and is now being tested in Europe in a couple of trials as the experimental induction arm.

I believe the triplets make a lot of sense. Personally, I like the idea of non-cross-reacting combinations, as we use in treating lymphoma, Hodgkin disease and in many other success stories in oncology. The real question is the duration of triplet therapy. Although I believe we get more value when we put three drugs together, all patients don’t need all three drugs until disease progression. The toxicity of RVD is fairly significant, but if we can achieve a complete response
(CR) in 40 percent of patients up front, to me, that is a sizable impact, at least as the first step.

In treating plasma cell neoplasia, you’ll never have another shot like the first shot. I believe it’s clear from gene sequencing and gene expression profiles that even a patient at low risk at first relapse has acquired so many new mutations in his or her plasma cells that we’ll never get the same response rate from sequential therapy that we will with a combination up front.

What’s different in treating hematologic cancer as opposed to solid tumors is that synergy occurs when we combine an IMiD and a proteasome inhibitor, whereas it does not, necessarily, when we combine carboplatin and paclitaxel. In that situation we get an additive benefit, but I don’t believe we get the same magnitude of synergy.

**Harvesting stem cells**

As for harvesting stem cells, in this case we elected to do so after four cycles of therapy. He tolerated therapy well. I believe no one knows whether we should collect stem cells immediately after CR or not.

We know that with lenalidomide-based inductions, earlier is probably better than later, but four cycles seems to be more than sufficient to be able to successfully collect cells. In this case, that’s what we ended up doing.

This patient’s cells were collected with growth factor mobilization without incident.

This patient received radiation therapy for pain control, and the kyphoplasty was done in an attempt to restore a little bit of height. Pain was his biggest issue and the short course of radiation therapy and kyphoplasty made a big difference.

After eight cycles of RVD, he was in CR and he went on single-agent lenalidomide maintenance.

He has essentially stayed in CR for over two years now and has fared well. He is back to work and has no major limitations. His biggest practical issue is that he needs to see us once a month. For thromboprophylaxis, he started aspirin

**FIGURE 36**

**Case 7 continued:** The patient undergoes radiation therapy and kyphoplasty to involved vertebrae and the pain improves. Three additional cycles of RVD are administered and then stem cells are collected. Subsequently the patient receives 4 more cycles of RVD (total of 8 cycles), remains in CR and receives monthly IV bisphosphonates.

**What would be your next treatment choice for this patient?**

<table>
<thead>
<tr>
<th>Option</th>
<th>CI</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose melphalan with stem cell transplant</td>
<td>54%</td>
<td>60%</td>
</tr>
<tr>
<td>Lenalidomide maintenance</td>
<td>29%</td>
<td>20%</td>
</tr>
<tr>
<td>Observation</td>
<td>3%</td>
<td>12%</td>
</tr>
<tr>
<td>Continue RVD</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**The patient has been receiving maintenance lenalidomide along with IV bisphosphonates for the past 18 months. How long would you continue to administer the monthly bisphosphonates?**

<table>
<thead>
<tr>
<th>Option</th>
<th>CI</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>For an additional 6 months and then reduce frequency to q2-3m indefinitely</td>
<td>39%</td>
<td>53%</td>
</tr>
<tr>
<td>For an additional 6 months (total of 24 months) and then stop</td>
<td>18%</td>
<td>36%</td>
</tr>
<tr>
<td>Indefinitely</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>For an additional 6 months and then reduce frequency to q6m indefinitely</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>I would discontinue bisphosphonates</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>7%</td>
</tr>
</tbody>
</table>
**Case 7 (Continued)**

initially and has continued it while on lenalidomide maintenance.

**Immediate versus delayed transplant**

As we do with most of our patients when they achieve that quick a response, we offered this man the option of early transplant. Interestingly, about 50 percent of the patients want to have the transplant and be done with treatment, while the other half want to continue what they’re doing and stay on maintenance therapy.

We are participating in a study that randomly assigns patients to immediate versus delayed transplant. This was not available when this patient started therapy over two years ago, but we would have presented it to him if it had been. The study is evaluating early versus late transplant and whether there is an impact on patient outcomes by delaying transplant. This was not available when this patient started therapy for 18 months. In this case and in others for whom we have delayed transplant, it’s important to realize that we cannot necessarily stop therapy once the patient has achieved a CR. I believe that is clear. Four cycles of RVD and no further treatment doesn’t last terribly long. On the other hand, four cycles of RVD, followed by consolidation or maintenance therapy, is a different situation. We made the decision early on that we would delay transplant for this patient and that he needed to remain on active therapy.

**Duration of bisphosphonates**

As for bisphosphonates, our approach is essentially two years of therapy. Then at the two-year mark — usually at one year post-transplant — we will perform a bone-mineral density assessment. In patients who have essentially normal bone density and are in complete remission, we will stop bisphosphonates at that point. In patients who still have low-bone density, we will likely continue bisphosphonates, but change the frequency to every three months.

**SELECT PUBLICATIONS**


**FIGURE 37**

**Activity of lenalidomide, bortezomib and dexamethasone (RVD) in newly diagnosed multiple myeloma**

<table>
<thead>
<tr>
<th></th>
<th>≥PR</th>
<th>CR + nCR + VGPR</th>
<th>CR + nCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N = 66)</td>
<td>100%</td>
<td>67%</td>
<td>39%</td>
</tr>
<tr>
<td>Phase II population (N = 35)</td>
<td>100%</td>
<td>74%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Confirmation for all response categories required 2 assessments at least 6 weeks apart, per EBMT criteria.

“This phase I/II study, the first prospective investigation of the regimen of lenalidomide–bortezomib–dexamethasone in newly diagnosed MM, has shown the combination to have favorable tolerability over a lengthy period, with no treatment-related mortality. This regimen is the first of its kind to result in a 100% response rate… and may represent the basis of future standards-of-care in this setting. Phase III studies are comparing bortezomib–dexamethasone with or without lenalidomide (NCT00522392) and lenalidomide–dexamethasone with or without bortezomib (NCT00644228) to assess the benefit of the three-drug approach. An international prospective study is planned to assess this combination with or without ASCT, followed by maintenance.”

PR = partial response; CR = complete response; nCR = near-complete response; VGPR = very good partial response; ASCT = autologous stem cell transplant

Richardson PG et al. *Blood* 2010;[Epub ahead of print].

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**SELECT PUBLICATIONS**


Case 8: A 63-year-old man presents with sixth nerve palsy and is diagnosed with multiple myeloma with extensive disease in the base of the skull. No extracranial lytic disease is evident.

— Rafael Fonseca, MD

Considering the baseline sixth nerve palsy, would you recommend a bortezomib-based treatment regimen for this patient?

<table>
<thead>
<tr>
<th>% answering yes</th>
<th>CI n = 27</th>
<th>PO n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For those who responded no to the previous question: Would you recommend a bortezomib-based treatment regimen if the patient did not have the nerve palsy?

<table>
<thead>
<tr>
<th>% answering yes</th>
<th>CI n = 4</th>
<th>PO n = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>73%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Would you administer IV bisphosphonates to this patient without the presence of lytic lesions?

<table>
<thead>
<tr>
<th>% answering yes</th>
<th>CI n = 27</th>
<th>PO n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>59%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>58%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bortezomib-based therapy for aggressive multiple myeloma

DR FONSECA: We had a chance to participate early on in the care for this patient, although without access to all of the patient's information from the get-go I had concern that this patient would be considered at high-risk.

No lytic lesions were identified, which in my mind is worrisome because occasionally we might see extensive disease and no lytic bone lesions in some of the more aggressive variants of the disease.

With regard to nerve palsy and the recommendation for use of a bortezomib-based treatment regimen for this patient, we do not have a lot of data. I have not seen toxicity with regard to development of nerve palsies. I presume they are possible or maybe even have been reported, but it's not a common occurrence.

My take on the survey results is that most respondents felt that they had to quickly control the disease and would thus opt to administer a bortezomib-based treatment regimen for this particular patient for that reason alone.

IFM 2005-01: Induction VD (Bortezomib/Dexamethasone) versus VAD (Vincristine/Adriamycin®/Dexamethasone) Before ASCT in Newly Diagnosed Multiple Myeloma (MM)

“...These data suggest that induction with VD might partially overcome the poor prognosis associated with ISS Stage III MM, and presence of t(4;14) ± del17p. In conclusion, in this trial achievement of at least VGPR after induction appears to be a major prognostic factor. Apparent improvement in PFS obtained with VD vs VAD induction might be related to higher ≥VGPR rate, across all prognostic subgroups including patients with poor-risk characteristics.”

Case 8 (Continued)

This patient received one cycle of VD elsewhere, with which he had a dramatic response. It was at this point that he came to us for a second opinion. A bone marrow analysis had previously been performed, but the sample had not yet been sent for cytogenetic analysis. We were unable to perform the genetic testing because there were not enough plasma cells. At that point we assumed, without specifics, that he probably had a more high-risk variant of myeloma.

A repeat bone marrow analysis indicated disappearance of the plasma cells. We then continued therapy for the patient. With such a good response, we continued the patient on therapy with the bortezomib combination and we also provided him with radiation therapy to the base of the skull. Our radiation oncologist felt this could be done safely with a narrow field, and the patient fared well over the next several weeks to months. He had complete resolution of the palsy, went on to complete six cycles of bortezomib/dexamethasone treatment and was able to resume a more normal life.

Post-transplant maintenance therapy

Because of the young age of the patient and the lack of added information, we did offer him an autologous stem cell transplant, which he completed successfully with no major toxicity issues. The patient fared well post-stem cell transplant — he had a complete response and was not placed on maintenance treatment. We monitored the patient regularly. A year after the transplant, he subsequently developed a pathologic femur fracture, for which he required surgical correction. At that time he was placed on lenalidomide maintenance therapy and his disease seems to be reasonably well controlled.

Today I would probably have placed this patient on immediate post-transplant lenalidomide maintenance, although we didn’t do that at the time. Some of the surveyed physicians would put the patient on bortezomib maintenance of some sort, which would be reasonable given his good response initially.
I believe what this part of the survey indicates is that people are thinking along the same lines, that despite the lack of genetic studies, this patient has high-risk disease. That is the case for the clinical investigator group.

**SELECT PUBLICATIONS**


Loiseau HA et al. Induction with Velcade®/dexamethasone partially overcomes the poor prognosis of t(4;14), but not that of del(17p), in young patients with multiple myeloma. *Proc ASH 2009;Abstract 957.*


Neki NS et al. Multiple myeloma presenting as proptosis and sixth nerve palsy. *J Assoc Physicians India 2001;49:1116-7.*

Palumbo A et al. Phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma. *ASH 2009;Abstract 613.*


**ASH Evidence-Based Guidelines: Role of Bortezomib Maintenance Therapy**

“Bortezomib has been used in maintenance therapy following stem cell transplantation in a large phase III randomized study...

Current studies using weekly bortezomib maintenance therapy after 8 cycles of therapy, such as in the phase I/II trial of bortezomib, lenalidomide and dexamethasone study conducted by Richardson et al and the phase I/II study of bortezomib, lenalidomide, cyclophosphamide and dexamethasone conducted by Kumar et al, will help delineate the role of bortezomib in maintenance therapy.”


---

**FIGURE 40**

*Case 8 continued:* The patient additionally receives high-dose melphalan with stem cell transplant and a stringent CR is attained.

**What would you most likely offer the patient at this time?**

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI n = 27; PO n = 100</td>
<td></td>
</tr>
<tr>
<td>41%</td>
<td>45%</td>
</tr>
</tbody>
</table>

**For those who would recommend maintenance therapy, which would be your preferred regimen?**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CI n = 16; PO n = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide with or without steroids</td>
<td>82%</td>
</tr>
<tr>
<td>Bortezomib with or without steroids</td>
<td>6%</td>
</tr>
<tr>
<td>Thalidomide with or without steroids</td>
<td>6%</td>
</tr>
<tr>
<td>Steroid alone</td>
<td>6%</td>
</tr>
</tbody>
</table>

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PoCMM110_Book_Finaldn.indd   35
6/11/10   2:26:49 PM
Case 9: A 61-year-old woman with IgM MGUS and slowly rising M-protein is cared for with active surveillance

**CASE 9: Surveillance for IgM MGUS**

**DR GHOBRIAL:** This patient presented to her physician with some shoulder pain. Her x-rays were normal, but a chemistry profile revealed an elevated protein level. On further workup, a serum protein electrophoresis showed a small M-spike. Her IgM level was 313 milligrams per deciliter, which is only slightly elevated. A bone marrow biopsy was performed and she had six percent plasma cells. She had not developed any of the CRAB criteria for symptomatic myeloma (ie, anemia, lytic lesions, renal failure or hypercalcemia). So by definition, with less than 10 percent plasma cells and a M-spike less than three grams, she had an IgM monoclonal gammopathy of undetermined significance (MGUS).

When she was diagnosed, she went online and thought that she had myeloma. She was scared, so she came to us for a second opinion and wanted to know what exactly she should be doing. We classify patients like this with an M-spike of less than three grams, plasma cells less than 10 percent and no symptoms or signs of disease as MGUS. We now consider other factors, like the serum free light chain assay, and even with smoldering myeloma, we’re starting to classify them as high risk versus low risk.

This patient had a relatively low M-spike and low number of plasma cells, and her free light chains were normal, so she had none of the high-risk features for MGUS progression. If you consider all patients with MGUS and do not risk stratify and simply use Bob Kyle’s data from Mayo Clinic, in which he followed patients in Olmsted County for years and years, a one percent chance of progression to a malignant neoplasm is expected per year. In 20 years, which is what we have here, it’s a 20 percent chance of progression. Now, if you consider the high-risk features, the high-risk cases usually progress a little bit faster.

---

**What do you estimate to be the likelihood that this patient will develop multiple myeloma within the next 20 years?**

![Median likelihood graph](image)

**What would be your approach to monitoring this patient?**

![Monitoring approach chart](image)
In our practice, we usually follow their numbers every six months for the first year and then once a year thereafter. We usually monitor the serum free light chain and the M-spike, check their blood counts and make sure that they’re faring well while watching for any new symptoms or signs. We continued to follow her, but because her IgM kept increasing every time we checked it, we began following her more closely. She had no symptoms at all, but she was worried that her IgM had increased to 1,220 milligrams per deciliter within a couple of years.

**Case 9 continued:** The patient has been monitored with serial M protein and free light chain assays. The M spike is slowly rising. The IgM level was 548 mg/dL in 2008, 876 mg/dL in February 2009 and 1,220 mg/dL in October 2009. The patient remains asymptomatic, with normal calcium, renal function and hemoglobin.

**What would be your approach to monitoring this patient?**

<table>
<thead>
<tr>
<th>Approach</th>
<th>CI</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue surveillance with free light chain assay/M-protein/CBC/kidney function tests every 3 months</td>
<td>50%</td>
<td>28%</td>
</tr>
<tr>
<td>Continue surveillance with free light chain assay/M-protein/CBC/kidney function tests every 3 months and <strong>periodic skeletal surveys</strong></td>
<td>25%</td>
<td>39%</td>
</tr>
<tr>
<td>Continue surveillance with free light chain assay/M-protein/CBC/kidney function tests every 3 months and <strong>periodic skeletal surveys and periodic bone marrow evaluations</strong></td>
<td>14%</td>
<td>31%</td>
</tr>
<tr>
<td>Periodic bone marrow with or without cytogenetics and PET/CT scans</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Case 9 continued:** Results of a skeletal survey are normal, and bone marrow evaluation is deferred until symptoms or other suggestions of active myeloma occur.

**What is the diagnosis of the patient at this point?**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CI</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive MGUS</td>
<td>43%</td>
<td>44%</td>
</tr>
<tr>
<td>Smoldering myeloma</td>
<td>4%</td>
<td>22%</td>
</tr>
<tr>
<td>Information is insufficient to make a distinction between MGUS and smoldering myeloma</td>
<td>34%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Even though she was asymptomatic, her IgM was increasing significantly, and therefore we increased follow-up to every three months, which is how others responded in the survey. The most common response among the clinical investigators was to repeat the CBC, M-protein, and serum free light chain every three months and not the skeletal survey. We, too, don’t usually repeat the skeletal surveys every three months — we usually recommend performing those every six or 12 months.

It’s interesting that twice as many community oncologists as clinical investigators selected bone marrow evaluation to monitor patients. We don’t routinely perform a lot of bone marrow biopsies because of the discomfort to the patients.

"Monoclonal gammopathy of undetermined significance (MGUS) was identified in 3.2% of 21,463 residents of Olmsted County, Minnesota, 50 years of age or older. The risk of progression to multiple myeloma, Waldenstrom’s macroglobulinemia, AL amyloidosis or a lymphoproliferative disorder is approximately 1% per year. Low-risk MGUS is characterized by having an M protein of 15 g/l, IgG type and a normal free light chain (FLC) ratio. Patients should be followed with serum protein electrophoresis at six months and, if stable, can be followed every 2–3 years or when symptoms suggestive of a plasma cell malignancy arise."

Kyle RA et al. *Leukemia* 2010;[Epub ahead of print].

**Case 9 continued:**

Results of a skeletal survey are normal, and bone marrow evaluation is deferred until symptoms or other suggestions of active myeloma occur.

What would be your approach to monitoring this patient?

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**Case 9 continued:** The patient has been monitored with serial M protein and free light chain assays. The M spike is slowly rising. The IgM level was 548 mg/dL in 2008, 876 mg/dL in February 2009 and 1,220 mg/dL in October 2009. The patient remains asymptomatic, with normal calcium, renal function and hemoglobin.

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<td>34%</td>
<td>53%</td>
</tr>
</tbody>
</table>
In an ITT analysis (n=40), based on IMWG criteria, the overall response rate was 90%, including 53% PR, 21% VGPR, 11% CR and 5% sCR. If we select the group of 16 patients who completed the nine cycles, the ORR was 100%, including 27% VGPR, 13% CR and 7% sCR. After a median follow-up of 16 months (range:12-20), no disease progression was observed in the Len-dex arm, while 8 patients progressed to active MM in the therapeutic abstention arm with a median TTP from inclusion in the trial of 17.5 months (p<0.002). It should be noted that 6 of these 8 patients developed bone lesions as a symptom of active MM.

In conclusion, these preliminary results show that in sMM patients at high-risk for progression to active MM, delayed treatment is associated with early progression (median time 17.5 months) with bone disease, while so far Len-dex has been able not only to prolong the TTP (without any progression so far) but also to induce CRs with a manageable and acceptable toxicity profile.

PR = partial response; VGPR = very good partial response; CR = complete response; sCR = stringent CR; ORR = overall response rate; TTP = time to disease progression.


I believe following their M-spike and their light chain carefully is helpful and, if she develops anemia or any other signs, we would perform the bone marrow biopsy at that time.

We did not choose to treat her, but rather to continue monitoring her carefully. I did tell her that even if she had smoldering multiple myeloma, which means a serum M-spike ≥3 g/dL and bone marrow plasma cells ≥10 percent, we still don’t treat those patients.

Dr Mateos, with the Spanish group, did present data at ASH 2009 from a Phase III trial comparing lenalidomide/dexamethasone to placebo in patients with smoldering multiple myeloma at high risk for progression to symptomatic MM. The lenalidomide/dexamethasone delayed progression to active myeloma and the development of bone lesions.

However, most of us have not applied this to the clinic yet. We are planning a lot of other studies for high-risk smoldering myeloma, but if a patient is not on a study, we usually simply watch them. No data suggest that if you’re not watching them carefully you will change the progression or the survival of those patients in any way.

**SELECT PUBLICATIONS**


Chiecchio L et al. Gain of Igq21 does not predict for immediate progression in MGUS. Proc ASH 2009;Abstract 123.

Chng WJ et al. MYC activation is a common transformation event in myeloma and associated with poor prognosis. Proc ASH 2009;Abstract 834.


Kyle RA et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010;[Epub ahead of print].


Mateos MV et al. Multicenter, randomized, open-label, phase III trial of lenalidomide/dexamethasone (Len-dex) versus therapeutic abstention in smoldering multiple myeloma at high risk of progression to symptomatic MM: Results of the first interim analysis. Proc ASH 2009;Abstract 614.


EDUCATIONAL ASSESSMENT AND CREDIT FORM: Patterns of Care Vol 2 · Issue 1

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th>Topic</th>
<th>4 = Excellent</th>
<th>3 = Good</th>
<th>2 = Adequate</th>
<th>1 = Suboptimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk stratification of multiple myeloma based on cytogenetics/FISH analysis</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pivotal research supporting the clinical use of triple-agent induction regimens in multiple myeloma</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact of lenalidomide on stem cell mobilization and/or collection</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rational clinical use of maintenance therapy for patients who have or have not received transplant</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of bortezomib-associated neuropathy</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommendations for monitoring MGUS</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes  ☐ No

If no, please explain: .................................................................................................................

Will this activity help you improve patient care?

☐ Yes  ☐ No  ☐ Not applicable

If no, please explain: .................................................................................................................

Did the activity meet your educational needs and expectations?

☐ Yes  ☐ No

If no, please explain: .................................................................................................................

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

<table>
<thead>
<tr>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
</table>

AS A RESULT OF THIS ACTIVITY, I WILL BE ABLE TO:

• Compare treatment strategies used by community oncologists/hematologists and cancer clinical investigators, and apply this knowledge to the routine management of plasma cell disorders ............4 3 2 1 N/M N/A
• Evaluate clinical issues for which relative agreement and heterogeneity exist in patterns of MM care, and make treatment decisions considering this information ........................................4 3 2 1 N/M N/A
• Use clinical and molecular factors to risk stratify and select optimal treatment for patients with plasma cell disorders ........................................4 3 2 1 N/M N/A
• Recognize practice-changing clinical research, and incorporate it into decision-making where applicable ........................................................................................................4 3 2 1 N/M N/A
• Communicate the benefits and risks of evidence-based induction regimens to patients with MM who may or may not be eligible for transplant ........................................4 3 2 1 N/M N/A
• Optimize the management of MM through rational integration of emerging data in the maintenance setting ..................................................................................................................4 3 2 1 N/M N/A
• Counsel appropriately selected patients about the availability of ongoing clinical trial participation .................................................................................................................................4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

What additional information or training do you need on the activity topics or other oncology-related topics?
EDUCATIONAL ASSESSMENT AND CREDIT FORM (Continued)

Additional comments about this activity:

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.  ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty for this educational activity

To what extent do you feel the faculty members' comments were helpful or not helpful?

Please be as specific as possible about individual faculty.

Please recommend additional faculty for future activities:

Other comments about the faculty for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: _______________________________ Specialty: _______________________________

Professional Designation:

☐ MD    ☐ PharmD    ☐ NP
☐ DO    ☐ RN    ☐ PA    ☐ Other: _______________________________

Street Address: _______________________________ Box/Suite: _______________________________

City, State, Zip: _______________________________

Telephone: _______________________________ Fax: _______________________________

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I certify my actual time spent to complete this educational activity to be ______________ hour(s).

Signature: _______________________________ Date: _______________________________

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Management of Multiple Myeloma

Survey of 100 Practicing Medical Oncologists and 28 Clinical Investigators on 9 Cases Presented by Contributing Faculty Members

Faculty
Rafael Fonseca, MD
Irene M Ghobrial, MD
Sagar Lonial, MD

Editor
Neil Love, MD

Faculty Interviews and PowerPoint Slides Included on Enclosed CD

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