Management of Multiple Myeloma

Diagnostic Workup, Staging and Transplant Strategy

Stem Cell Transplantation

Systemic Therapy Issues: Regimen Selection, Dexamethasone Dosing, Maintenance Therapy, Bisphosphonates

Clinical Case Presentations

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A Survey Comparing Practices of Clinical Investigators, Practicing Oncologists and Fellows

PowerPoint files of the graphics contained in this document can be downloaded at ResearchToPractice.com/POCMM109.
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ABBREVIATIONS OF TREATMENT REGIMENS IN AUDIO PROGRAM AND GRAPHICS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CyBorD</td>
<td>Cyclophosphamide/bortezomib/dexamethasone</td>
</tr>
<tr>
<td>FC</td>
<td>Fludarabine/cyclophosphamide</td>
</tr>
<tr>
<td>FCR</td>
<td>Fludarabine/cyclophosphamide/rituximab</td>
</tr>
<tr>
<td>MD</td>
<td>Melphalan/dexamethasone</td>
</tr>
<tr>
<td>MP</td>
<td>Melphalan/prednisone</td>
</tr>
<tr>
<td>MPR</td>
<td>Melphalan/prednisone/lenalidomide</td>
</tr>
<tr>
<td>MPT</td>
<td>Melphalan/prednisone/thalidomide</td>
</tr>
<tr>
<td>MPV</td>
<td>Melphalan/prednisone/bortezomib</td>
</tr>
<tr>
<td>PAD</td>
<td>Bortezomib/doxorubicin/dexamethasone</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>Rituximab/cyclophosphamide/doxorubicin/ vincristine/prednisone</td>
</tr>
<tr>
<td>Rd</td>
<td>Lenalidomide/low-dose dexamethasone</td>
</tr>
<tr>
<td>RD</td>
<td>Lenalidomide/high-dose dexamethasone</td>
</tr>
<tr>
<td>RVD</td>
<td>Lenalidomide/bortezomib/dexamethasone</td>
</tr>
<tr>
<td>TD</td>
<td>Thalidomide/dexamethasone</td>
</tr>
<tr>
<td>VAD</td>
<td>Vincristine/doxorubicin/dexamethasone</td>
</tr>
<tr>
<td>VD</td>
<td>Bortezomib/dexamethasone</td>
</tr>
<tr>
<td>Vdox</td>
<td>Bortezomib/liposomal doxorubicin</td>
</tr>
<tr>
<td>VdoxD</td>
<td>Bortezomib/pegylated liposomal doxorubicin/dexamethasone</td>
</tr>
<tr>
<td>VT</td>
<td>Bortezomib/thalidomide</td>
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<tr>
<td>VTD</td>
<td>Bortezomib/thalidomide/dexamethasone</td>
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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 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 optimal approach may be suboptimal.

This program focuses on the self-described treatment approaches used by randomly selected medical oncologists and hematology-oncology fellows in a variety of key clinical scenarios in multiple myeloma. Also included are the parallel treatment approaches recommended by clinical investigators in addition to expert commentary and references addressing these topics. This CME program will provide oncologists and hematologists with information on national cancer patterns of care to assist oncologists and fellows to be aware of similarities and differences between their patterns of cancer care and those of other community practitioners and multiple myeloma clinical investigators.

Learning Objectives
- Compare treatment strategies employed by community oncologists, hematology-oncology fellows and cancer clinical investigators, and apply this knowledge to the routine management of multiple myeloma (MM).
- Evaluate clinical issues for which relative agreement and heterogeneity exist in patterns of MM care, and make treatment decisions considering this information.
- Counsel patients with MM about the benefits and risks of multiple acceptable treatment options when they exist.
- Recognize the rate at which practice-changing clinical research impacts physician decision-making, and explain how this affects patient access to standard and novel therapies.
- Identify current approaches to stem cell transplant for eligible patients with symptomatic MM, and recommend evidence-based induction regimens to facilitate long-term outcomes.
- Recall the design and eligibility criteria for ongoing clinical trials in newly diagnosed and relapsed MM, and consider appropriate patients for study participation.

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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 Richardson — Advisory Committee and Speakers Bureau: Celgene Corporation, Millennium Pharmaceuticals Inc.
- Dr Vesole — Advisory Committee: Celgene Corporation; Speakers Bureau: Celgene Corporation, Millennium Pharmaceuticals Inc, Ortho Biotech Products LP; Stock Ownership: Amgen Inc, Biogen Idec, Bristol-Myers Squibb Company, Celgene Corporation, Eli Lilly and Company.
- Dr Farber — Advisory Committee: Biogen Idec, Genentech BioOncology; Speakers Bureau: Alexion Pharmaceuticals, Bayer Pharmaceuticals Corporation, Centocor Ortho Biotech Services LLC.
- Dr Lonial — Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Ortho Biotech Products LP.

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ABOUT THIS SURVEY
This survey was completed in April 2009 by 100 community-based medical oncologists, 50 hematology-oncology fellows and 25 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>Name</th>
<th>Position and Institution</th>
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<tbody>
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</tr>
<tr>
<td>Guido Tricot, MD</td>
<td>Professor of Medicine, Division of Hematology and Stem Cell Transplantation, University of Utah School of Medicine, Salt Lake City, Utah</td>
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<tr>
<td>Ravi Vij, MD</td>
<td>Associate Professor of Medicine, Washington University School of Medicine, Section of Stem Cell Transplantation and Leukemia, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina</td>
</tr>
<tr>
<td>Peter Voorhees, MD</td>
<td>Associate Professor of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, Illinois</td>
</tr>
</tbody>
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* One participant has chosen to remain anonymous
Editor’s Note: Some answers…and a lot more questions

Although not often openly acknowledged, ‘cure vs control’ is the dominant philosophical difference behind many of the strategies, trials, and debates related to the management of myeloma…Outside of a clinical trial setting, I prefer disease control as the treatment goal, except in selected high-risk patients…Although cure is the ultimate goal of our long-term research, we need more data from randomized trials before resorting to highly intense therapy that is more toxic and unlikely to lead to a cure outside the setting of a clinical trial.

S Vincent Rajkumar, MD

Vincent and I argue about this almost weekly, and our divergence in perspective reflects that there is no right answer. I believe that we have the opportunity at some point in the near future — and I’m not saying we’re there now — to make major inroads in survival for this disease. For me, that means cure. We may be able to do that with some of the drugs that we have or some of the drugs that are coming out now. One of the arguments that the control people always make (control versus cure) is that even patients who experience a CR will experience relapse. So you’re not really curing them, even if you get them to a CR. My counterargument is that you can’t cure patients until you get them to a CR. So that’s the first step.

Sagar Lonial, MD
Patterns of Care Multiple Myeloma 2009;1(1).

**KEY FINDING 1**

Oncologists are quite interested in learning more about the patient care implications of new clinical research in all aspects of myeloma and, in fact, are as interested in myeloma as they are in breast cancer.

Along with 25 clinical investigators specializing in myeloma, we recruited 100 oncologists who had been in community practice for a median of 11 years, and 50 hem-onc fellows (two first-, 32 second-, 14 third- and two fourth-year fellows) to complete the web-based survey that is the basis of this monograph. In addition to many case-oriented questions, we also asked these clinicians about their interest in and need for education on a number of different topics.

It was somewhat striking to see that the participating fellows and practicing physicians rated their interest in myeloma as comparable to their interest in more common tumors, such as breast and colon cancer, and also about the same as their desire for information focusing on another less common cancer where clinical research is exploding: renal cell cancer.
A number of important disparities are apparent in how physicians use bisphosphonates in myeloma (Figures 19-21, pages 22-23). Some of the most interesting variations in practice in this survey relate to the choice of bisphosphonate, duration of treatment and schedule. The “q month versus q3 month” debate reminds me of breast cancer and the use of LHRH agonists for premenopausal women, with which physicians must weigh the inconvenience of monthly office visits against theoretical concerns about the effectiveness of ovarian suppression near the end of three months.

Hopefully, ongoing and future research in the use of bisphosphonates in myeloma will soon provide some definitive answers to these significant and relevant uncertainties.
**KEY FINDING 4**

In contrast to investigators, fellows and the International Myeloma Working Group Guidelines, about one third of practicing oncologists did not consider FISH and metaphase cytogenetics a standard part of the diagnostic workup for patients with myeloma (Figure 3).

This was a shocker in the survey, and if we had been smart enough to anticipate these responses, we could have asked people why. Don’t worry, we’ll get to the bottom of this, and have already started seeking feedback and perspectives.

On the accompanying audio program, Paul Richardson speculates that in the past, some oncologists in practice grew weary of hearing about prognostic factors because previous correlations didn’t pan out, and that these individuals might now be skeptical of recent claims of the clinical worth of such assays.

It could also be that these busy practitioners have not been able to stay up to speed with recent developments in myeloma and that if provided with relevant data and perspectives, they might change their practice patterns (Figure 4).

Another hypothesis is that some physicians have decided that regardless of risk or cytogenetic status, bortezomib will be part of up-front therapy, often combined with an IMiD® and small or large “D” as in the increasingly utilized “RVD” (or “VRD”) (lenalidomide, bortezomib, dexamethasone) platform presented on several occasions by Dr Richardson and the subject of a critical ongoing Phase III study.

Others, such as Dr Lonial, generally use the same induction regimen (RVD again) regardless of cytogenetics but consider cytogenetics to decide on a post-transplant maintenance therapy.

We will keep working on this one, folks, and hopefully document what’s going on and maybe report back in the future a change in this particular pattern of care.
FIGURE 3

55-year-old patient with newly diagnosed multiple myeloma. Which of the following do you consider a standard part of the workup?

- FISH studies: 92%
- Serum beta-2 microglobulin: 96%
- Metaphase cytogenetics: 63%
- Bone marrow biopsy: 92%

FIGURE 4

Guidelines for standard investigative workup: Report of the International Myeloma Workshop Consensus Panel 3

“A patient with suspected multiple myeloma should undergo a unilateral bone marrow aspirate and/or biopsy and the diagnosis is confirmed when over 10% clonal plasma cells are detected...

Standard metaphase cytogenetics should be included in the initial assessment of a patient with high suspicion of multiple myeloma. Despite the low yield of this method (20% or less), it can provide useful prognostic information by separating hyperdiploid from non-hyperdiploid patients and can capture uncommon additions, deletions and translocations.

Furthermore patients should undergo fluorescent in situ hybridization (FISH) preferably after sorting of plasma cells with probes that include chromosome 17p13, t(4;14), and t(14;16).

While some tests are not required for the diagnosis of myeloma, they are important for prognosis or staging. As such the following tests are recommended: serum β2 microglobulin which reflects tumor burden and forms the basis for the International Staging System and serum LDH which has an independent prognostic significance in several studies...”

SOURCE: Dimopoulos MA et al. XIIth International Myeloma Workshop, February 2009.

SELECT PUBLICATIONS


Bergsagel PL. A kinder, gentler way: Control of the proliferative tumor compartment, not cosmetic complete response, should be the goal of myeloma therapy. Leukemia 2008;22(4):873-5. No abstract available


Diagnostic Workup, Staging and Transplant Strategy

**FIGURE 5**

**Clinical Scenario 1:** A local primary care physician has referred a 55-year-old patient to you for evaluation of anemia (10.4 g/dL), fatigue, elevated creatinine (2.0 mg/dL) and hypoalbuminemia (3.2 g/dL). You obtain a serum protein electrophoresis with immunofixation (SPEP with IFE) that reveals a monoclonal protein found to be an IgG K gammopathy: 5.8 g/dL.

What additional tests would you generally order to complete this patient’s diagnostic workup for multiple myeloma? (check all that apply)

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical investigators (CI)</th>
<th>Practicing oncologists (PO)</th>
<th>Hematology-oncology fellows (HOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum beta-2 microglobulin</td>
<td>96%</td>
<td>86%</td>
<td>98%</td>
</tr>
<tr>
<td>Serum immunoglobulins</td>
<td>88%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase (LDH)</td>
<td>76%</td>
<td>57%</td>
<td>68%</td>
</tr>
<tr>
<td>FISH studies</td>
<td>92%</td>
<td>63%</td>
<td>92%</td>
</tr>
<tr>
<td>Metaphase cytogenetics</td>
<td>88%</td>
<td>60%</td>
<td>92%</td>
</tr>
<tr>
<td>Bone marrow aspirate</td>
<td>96%</td>
<td>86%</td>
<td>96%</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>92%</td>
<td>90%</td>
<td>98%</td>
</tr>
<tr>
<td>Serum free light chains</td>
<td>92%</td>
<td>75%</td>
<td>86%</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>36%</td>
<td>17%</td>
<td>14%</td>
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<tr>
<td>24-hour urine collection (UPEP with IFE)</td>
<td>92%</td>
<td>75%</td>
<td>84%</td>
</tr>
<tr>
<td>Urine free light chains</td>
<td>16%</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>Skeletal survey (plain radiographs)</td>
<td>88%</td>
<td>88%</td>
<td>94%</td>
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<tr>
<td>MRI</td>
<td>32%</td>
<td>7%</td>
<td>8%</td>
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<tr>
<td>Bone scan</td>
<td>4%</td>
<td>2%</td>
<td>8%</td>
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**Diagnostic Workup**

**DR PAUL G RICHARDSON:** The guidelines generated at the International Myeloma Workshop were intended to help practitioners make sense of the potential myriad of tests that may be required for patients.

As a basic assessment, the standards remain CBC, chemistry profile, serum protein electrophoresis, immune fixation and urine immunoelectrophoresis. Free light chain testing may be less commonly appreciated, but that’s a useful tool in my experience and is reasonable to use at diagnosis.

Beta-2 microglobulin is essential because it helps us with staging and, along with serum albumin, helps assess proliferative thrust. Plasma cell labeling index is reasonable but not required because you can obtain an assessment of plasma cell labeling index from beta-2 microglobulin and serum albumin results.

One additional test I should mention is serum lactate dehydrogenase, which we routinely order. Assessment of C-reactive protein is an optional test.

When we are dealing with a tumor within the marrow, we require hematomorphology to assess the degree of cellular infiltration. Very importantly, cytogenetic tests including FISH are recommended.

It is good to see that no one was sold on the bone scan (Figure 5), and that’s an important practice point because myeloma is an osteoclast activating disease and an osteoblast suppressing disease through DKK1 (dickkopf homolog 1) and another pathway. In that context, the bone scan is absolutely not useful because it will not detect lytic lesions in the classic myeloma case.

**DR SAGAR LONIAL:** A number of important tests listed here are absolute requirements (Figure 5), certainly according to the new International Myeloma Working Group consensus guidelines. These include beta-2 microglobulin for staging, serum free light chain, bone marrow biopsy, FISH and 24-hour urine collection.
The guidelines don’t require more than a skeletal survey for bone evaluation but suggest that an MRI may be more useful clinically. They also do not recommend the urine free light chain assay, and some discordance is apparent in the responses here. Less than 20 percent of clinical investigators recommend that test, but 52 percent of practicing oncologists and 40 percent of fellows recommend it (Figure 5). A lot of variability occurs in the test and it’s not as useful as the serum free light chain.

FISH studies and bone marrow are clearly important, and almost everyone selected the biopsy. FISH is considered an important part of the initial diagnostic workup as it may help us to decide about maintenance therapy and the absolute benefit of high-dose therapy down the road. I suspect that the reason only 63 percent of practicing oncologists selected that test, but 52 percent of practicing oncologists and 40 percent of fellows recommend it (Figure 5). A lot of variability occurs in the test and it’s not as useful as the serum free light chain.

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I’m also surprised to see the discordance in responses on metaphase cytogenetics. Whereas 88 percent of investigators and 92 percent of fellows chose this, only 60 percent of the practicing oncologists did so. I understand not ordering it for every patient because of the cost, but we’re starting to understand that the course of disease in patients with metaphase cytogenetic abnormalities is notably different from the course of disease in patients who don’t have abnormalities by routine metaphase analysis.

For example, we know that patients with hyperdiploid myeloma by FISH tend to fare well, similar to observations made in acute lymphocytic leukemia. What’s interesting is that the outcomes are not as good for patients whose metaphase cytogenetic test results for hyperdiploid are positive. Clearly hyperdiploid detected by FISH and hyperdiploid detected by routine metaphase cytogenetics are different, so these data are important.

**DR DAVID H VESOLE:** Whether to repeat cytogenetics and FISH analysis at first relapse was a point of significant debate on the consensus panel. They also debated whether we ever need to repeat a bone marrow, because if a patient is followed with protein studies, then what additional information does the bone marrow provide, except for the one percent or less of patients who have nonsecretory myeloma?

The final recommendation was that in progressive disease, prognostic markers, particularly the FISH studies, may change as the disease evolves and that the clinician should be aware of those changes. However, how to use that information is a matter of debate.

**Staging**

**DR VESOLE:** Serum beta-2 microglobulin is essential for staging using the ISS, and it’s a significant prognostic indicator. Bone marrow aspirates certainly should be performed at diagnosis, and whether they should be repeated in follow-up was part of a consensus panel discussion point.

In the ISS, stage is based predominately on the beta-2 microglobulin level.
If the beta-2 microglobulin is less than 3.5 mg/L and the albumin is greater than or equal to 3.5 g/dL, that’s Stage I, and if it’s greater than 5.5 mg/L, that’s Stage III. Any beta-2 microglobulin result from 3.5 to 5.5 mg/L is classified as Stage II, so this case is clearly at Stage II (Greipp 2005).

It’s distressing that none of the respondent groups did well with this question (Figure 6). Clearly some clinicians need more education on this and, depending on their age, may still be relying on the Durie-Salmon staging system and not the ISS.

**DR LONIAL:** What struck me about these responses was the number of clinicians who called this disease Stage III by ISS, which is not correct. This represents a learning curve more than anything else and the need to realize that the criteria have changed.

Proper staging is important because patients come in and say, “I read on the web that I have myeloma and I’m going to die in two and a half years.” Accurately staging the myeloma based on the ISS gives us a more up-to-date way to educate patients regarding their prognosis.

For example, patients with ISS Stage I disease, no cytogenetic abnormalities and normal or hyperdiploid FISH panels have a median survival between eight and 10 years based on some of the more modern series. These are the patients that Dr Barlogie from the University of Arkansas will claim he’s curing because they’re living for 10 years. We also have a handful of patients classified with Stage I disease by ISS who have lived 10-plus years.

**DR LONIAL:** The disease in Clinical Scenario 2 is Stage II according to the ISS for myeloma, which was created by the International Myeloma Working Group and identifies three subsets based on the level of serum beta-2 microglobulin and albumin. Still, some respondents categorized the case as Stage I or Stage III, a few more among the practicing oncologists than among the investigators (Figure 7).

While the albumin does play a role, we know that serum beta-2 microglobulin is an independent prognostic feature and probably one of the most powerful in patients with myeloma. I would argue that beta-2 alone is probably not the optimal way to identify high risk versus low risk, but it’s simple, reproducible, cheap and doable around the world.

Concern exists regarding the relationship between renal function and the beta-2 microglobulin level. Even though patients with renal insufficiency present with high beta-2 levels, that may be a negative prognostic feature in itself. On the other hand, if a patient presents with renal insufficiency caused by 30 years of hypertension, then I believe all bets are off.

**DR CHARLES M FARBER:** I believe that the serum beta-2 microglobulin level is great for identifying patients who are destined to fare poorly, if the patients have normal renal function. However, many of these patients have renal insufficiency, which influences the beta-2 microglobulin, so for a number of patients I find this measurement of limited value.
We see some discordance regarding how to treat a 55-year-old patient with poor-risk features (Figure 8). Only 32 percent of investigators would have recommended a transplant up front, whereas 63 percent of practicing oncologists and 62 percent of fellows would have done so. More of the clinical investigators favored induction followed by transplant depending on response, and I believe that reveals a shift in the management pattern.

I'm not sure that every patient at high risk should undergo a transplant up front, considering that the duration of remission may be shorter. If induction therapy does not result in a complete response (CR), then transplant may be a way to achieve that, administering a novel agent afterward as maintenance. That's the shift I am seeing here.

In our practice, we collect cells from every patient after four cycles of therapy, so we achieve a sense of their status. Our approach is to treat based on response. We routinely administer an induction regimen to every patient, and if they achieve a complete response, we collect cells and then offer them delayed transplant. Probably 50 percent of my patients don’t go to early transplant, and the median delay is approximately two years. If we don’t see a complete response, then we always recommend a transplant early on, although that is not the standard at this point. I believe either way is reasonable. With the new regimens, by four cycles most patients will have a major response. If they don’t, in many ways that’s telling me something biologically and I may not be able to achieve what I want to achieve.

**DR VESOLE:** One of the 55-year-old patients in this clinical scenario (Figure 8) has no bone lesions and the FISH and cytogenetic results are normal.

I would select induction treatment followed by transplant for this patient. I find the discrepancy between clinician groups interesting regarding the option of an induction regimen followed by transplant.

The question is, if the patient achieves a complete remission, should we proceed...
with a transplant? Unfortunately, no one has the answer and it’s a highly controversial issue. One of the major topics of discussion among myeloma experts right now is when to perform a transplant and at what level of response to refer for transplant rather than using another approach to try to achieve a complete response. The data still tell us that one of the standard approaches is to perform a transplant. I would probably perform a transplant for a healthy 70- or 75-year-old. The treatment of a 55-year-old with an adverse cytogenetic profile is another highly controversial area. If you review the Mayo Clinic’s algorithm and mSMART.org, you’ll find they say that patients with poor prognostic features, such as the translocation 4;14, should not undergo transplants because the duration of remission is inferior to that for patients without that prognostic feature.

That being said, bortezomib can apparently overcome this poor prognostic feature, and those patients who receive induction regimens containing it apparently have much better outcomes when they receive transplants. Therefore, I would still induce this patient, proceed to transplant and then initiate maintenance therapy.

DR FARBER: This is one of the situations in which management has changed during the past couple of years. In the past, if we had a younger, or even an older, patient with high-risk disease, we’d expect the patient not to fare well and feel we needed to do something drastic, such as a transplant. Only two years ago, my primary goal was to achieve some form of remission in patients, not damage their bone marrow too badly and find them a transplant.

Now we recognize that patients with high-risk disease who go through transplants don’t fare well in the short or long run. In addition, we have more agents...
with which to manage the disease up front, and for those who experience a good initial response, we tend to delay transplant until treatment fails.

The triplet regimens are particularly active, and the response rates are phenomenal.

When patients achieve remission, I attempt to harvest cells, and then I may administer additional treatment and monitor their condition before referring them for transplant. I would consider maintenance therapy or simply observing them after we achieve a remission, similar to our approach for individuals with follicular lymphoma. Of course, if a patient experiences a rapid recurrence, then I go ahead and make the referral for transplant.

Transplant has evolved from being the primary treatment strategy to one that we’re holding in reserve for patients for whom the up-front treatments fail. With the use of bortezomib and some of the other agents and combinations, autologous transplant has moved a little further back in line as treatment for patients at high risk.

**DR VESOLE:** I’ve performed transplants in two or three 76-year-old patients, and that’s probably my upper age limit (Figure 10). The oldest patient I know who has undergone a transplant was 82. It has to do with physiologic organ function. The data with older patients don’t show quite as long an improvement in progression-free survival as the data with younger patients. However, I’ve published studies on this, and my interpretation of the data is that it still provides them with the longest remission duration.

**SELECT PUBLICATIONS**


Dimopoulos M et al. International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. Leukemia 2009;[Epub ahead of print]. Abstract


Hari PN et al. Is the international staging system superior to the Durie-Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. Leukemia 2009;[Epub ahead of print]. Abstract


**DR RICHARDSON:** Autologous stem cell transplant remains a gold standard without too much debate.

My viewpoint on tandem transplants is less positive because the evidence, in aggregate, suggests that tandem transplants, particularly with the advent of novel therapies and especially bortezomib-based treatment, are not conveying that much benefit.

**DR VESOLE:** For transplant-eligible patients who are younger than age 65, I collect sufficient cells for tandem transplant.

The decision whether to perform a single or tandem transplant is based on small, retrospective, ad hoc evaluations performed by the French Myeloma Group, in addition to an Italian study.

These analyses found that the patients who did not achieve a very good partial remission in the French study or near-complete remission in the Italian study are the ones who would benefit from a second transplant.

That’s in the absence of some type of maintenance or consolidative therapy. Still, for a patient who has not achieved close to a very good partial remission — 90 percent tumor paraprotein reduction — I would be inclined to perform a second transplant. If patients are hesitant to undergo transplant, I would administer some type of maintenance therapy, which is probably further consolidative therapy.

One study, from Abdelkefi in Tunisia, randomly assigned 195 patients to either two transplants or one transplant followed by six months of thalidomide and then a second transplant at the time of...
The patients who underwent one transplant followed by thalidomide fared better. One way to interpret those data is to argue that thalidomide maintenance/consolidation was sufficient or comparable to a second transplant, but it's difficult to understand how six months would have been sufficient because usually with immunomodulatory drugs we have to continue therapy or the diseasereactivates.

Those were the results, but to this day those data are confusing, and the myeloma transplant community still cannot interpret them adequately (Figure 11).

**Impact of Lenalidomide or Bortezomib on Stem Cell Collection**

**DR VESOLE:** I would probably respond that lenalidomide has a moderate impact on stem cell mobilization and/or collection. Two similar papers are coming out from the International Myeloma Working Group discussing small retrospective case reports that essentially show this. I published one of the reports with 20-some patients.

Although I am aware of the lenalidomide data, I'm surprised that the practicing oncologists and fellows are aware of this effect (Figure 12). On the other hand, bortezomib, to the best of my knowledge and in my own experience, does not negatively affect the ability to collect stem cells.

**Preferred Induction Regimen**

**DR LONIAL:** I find it interesting that for the younger patients, over one third of the clinical investigators chose RVD as their preferred induction regimen and another third chose lenalidomide and dexamethasone (Figure 13). Among the community oncologists, the responses are somewhat more evenly spread across the different choices.

I believe this reflects the fact that for the young patient with standard-risk disease, no one superior regimen stands out. I believe that three or four up-front induction regimens are reasonable for the average patient, so clinicians can use whichever one they are comfortable with.

The choice between using lenalidomide/dexamethasone and using RVD is debatable and related to whether we are seeking cure or control. Those seeking control favor the lenalidomide/dexamethasone approach, and those aiming for cure prefer triple therapy.

Differences are apparent in the side-effect and quality-of-life profiles for these two approaches. With the addition of bortezomib, the patient has to come in for treatment more frequently, and the risk of neuropathy is higher than with lenalidomide/dexamethasone alone. On the other hand, triplets clearly dwarf the doublets in terms of response, including very good partial responses (VGPRs) and CRs.

**DR VESOLE:** I participated in Paul Richardson’s study of up-front bortezomib, lenalidomide and dexamethasone, and...
Which is generally your preferred pre-ASCT induction regimen for a 55-year-old patient with newly diagnosed multiple myeloma in the following situations?

**Standard risk**

- RVD: 44%
- Rd: 24%
- RD: 14%
- VD: 17%
- VTD: 11%
- CyBorD: 4%
- PAD/VdooxD: 10%
- TD: 10%
- Other: 3%

**Poor risk**

- RVD: 52%
- VD: 24%
- RD: 11%
- CyBorD: 8%
- PAD/VdooxD: 16%
- VAD: 5%
- Other: 4%
Which is generally your preferred pre-ASCT induction regimen for a 70-year-old patient with multiple myeloma in the following situations?

**Standard risk**

- **Rd**: 22% (26%)
- **RVD**: 9% (8%)
- **VD**: 16% (14%)
- **RD**: 12% (11%)
- **TD**: 4% (2%)
- **CyBorD**: 0% (0%)
- **PAD/VdooxD**: 0% (2%)
- I would not consider a transplant for a person of this age: 20% (20%)
- Other: 5% (7%)

**Poor risk**

- **VD**: 22% (20%)
- **RVD**: 16% (16%)
- **Rd**: 8% (11%)
- **CyBorD**: 0% (0%)
- **PAD/VdooxD**: 0% (0%)
- I would not consider a transplant for a person of this age: 20% (24%)
- Other: 8% (8%)
the response rate was astonishingly high. It was 100 percent, including approximately 75 percent who were achieving a very good partial remission.

That’s one of the highest rates of response we’ve ever seen. It’s better than what we saw in the old days with regular induction therapy and a transplant. This is an extremely potent regimen, so for 55- and 70-year-old patients who are at standard risk and will undergo transplant, for the sake of convenience as much as for quality of life, I would use that regimen.

As for the dose of dexamethasone, I was a co-principal investigator on the ECOG trial. Vincent Rajkumar has presented at repeated national conferences, which showed that one- and two-year survival rates are superior with low-dose dexamethasone compared to the high dose. I prefer the lenalidomide/low-dose dexamethasone combination because it’s easiest to tolerate and has a 70 percent response rate.

As for the patient with an adverse cytogenetic profile, approximately 20 percent of all patients with myeloma have an adverse feature, such as translocations of 4;14 and 14;16 and 17p deletion. The current data imply that bortezomib can overcome adverse prognostic factors, particularly for the 15 percent of patients who have translocation of 4;14. This is based on earlier data with bortezomib in the relapsed setting and, more recently, with the up-front data from the VISTA trial using MPV, which showed that patients with and without 4;14 abnormalities had essentially the same response rate, progression-free survival, and overall survival.

This suggests that bortezomib-based regimens may be more potent and effective in the adverse prognostic group compared to other treatment regimens. I have treated all of my patients in the adverse prognostic group with a bortezomib-based regimen, and I would probably use RVD in this case.

**SELECT PUBLICATIONS**

Cavo M et al. Superior complete response rate and progression-free survival after autologous transplantation with up-front Velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma. *Proc ASH 2008; Abstract 158*.

Cavo M et al. Superior rate of complete response with up-front Velcade-thalidomide-dexamethasone (VTD) versus VAD as induction treatment prior to autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (MM): Updated results of the IFM 2005/01 Trial. *Proc ASH 2007; Abstract 450*.


Kumar S et al. Stem cell mobilization following initial therapy with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma. *Proc ASH 2008; Abstract 3467*.


Rajkumar SV et al. Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome. *Proc ASCO 2008; Abstract 8504*.


Rosolino L et al. Thalidomide/dexamethasone (TD) vs bortezomib (Velcade®)/thalidomide/dexamethasone (VTD) vs BMB/C/VBAD/ Velcade® as induction regimens prior to autologous stem cell transplantation (ASCT) in younger patients with multiple myeloma (MM): First results of a prospective Phase III PETHEMA/Gem trial. *Proc ASH 2008; Abstract 654*.

Roussel M et al. Bortezomib (BOR) and high dose melphalan (HDM) as a conditioning regimen before autologous stem cell transplantation (ASCT) for de novo multiple myeloma (MM): Final results of the IFM Phase II study VEL/MEL. *Proc ASH 2008; Abstract 160*.


Zonder JA et al. Superiority of lenalidomide (L) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma: Results of the randomized, double-blinded, placebo-controlled SWOG trial S0232. *Proc ASH 2007; Abstract 77*. 

**DR RICHARDSON:** For transplant-eligible patients, we have top-line Phase III data to support bortezomib-based induction therapy. I would refer physicians to the updated NCCN guidelines.
Systemic Therapy Issues: Regimen Selection, Dexamethasone Dosing, Maintenance Therapy, Bisphosphonates

DR LONIAL: The responses for preferred systemic regimens after ASH 2007 are pretty evenly spread among lenalidomide/low-dose dexamethasone (Rd), MPV and MPT (Figure 15). The biggest discordance appears in the higher proportion of clinical investigators using Rd for the nontransplant-eligible patient.

I believe the use of Rd in this population is based on the survival data from the ECOG trial with older patients, which were encouraging.

However, we need to be cautious and not fall into the same trap we fell into five or six years ago with induction thalidomide/dexamethasone, when it essentially eclipsed MP, even for older, nontransplant-eligible patients. We now know from the Austrian Myeloma Group study that MP is actually superior to thalidomide/dexamethasone.

So we need completed trials to prove whether the combination of lenalidomide and dexamethasone is better than some of the other available treatments, or at least equivalent. I believe it will be, but we need to prove it.

DR FARBER: It’s important to realize that in some ways we stopped using melphalan for a time. Instead, we were using thalidomide with dexamethasone and then lenalidomide/dexamethasone. The use of melphalan has increased in an effort to use triplet regimens and incorporate more agents, particularly for older patients or those at low risk, and I believe this is reasonable.

**FIGURE 15**

In general, what are your top 3 preferred systemic regimens for a patient with active multiple myeloma who is not a candidate for transplant (eg, due to age, comorbidity, etc)?

**Prior to 2007 ASH meeting**

- Clinical Investigators
  - MPT: 60%
  - Rd: 56%
  - MP: 52%

- Practicing Oncologists
  - TD: 65%
  - MP: 52%
  - MPT: 43%

- Fellows
  - MP: 62%
  - TD: 58%
  - MPT: 40%

**After 2007 ASH meeting**

- Clinical Investigators
  - Rd: 72%
  - MPV: 64%
  - MPT: 48%

- Practicing Oncologists
  - MPT: 51%
  - VD: 41%
  - Rd: 40%

- Fellows
  - Rd: 42%
  - MPT: 40%
  - VD: 38%

* American Society of Hematology Annual Meeting

**Dosing Dexamethasone**

DR LONIAL: When physicians ask me treatment questions and I recommend dexamethasone, they say, “What’s the dexamethasone dose we’re using this week? You guys keep changing your mind.”

I base my dose decision on a number of factors. I use high-dose dexamethasone for patients who are fit, have a high tumor burden and need a quick response. I believe the lenalidomide and high-dose dexamethasone regimen is safe and reasonable in the right patient population (Figure 16). I also believe that if you use combinations, you’re less likely to need as much high-dose dexamethasone.

In the ECOG trial comparing low-dose to high-dose dexamethasone, the
survival advantage was most marked in the older population, but those aren’t the patients I generally consider to be eligible for dexamethasone. In many ways, that trial confirmed what the Europeans published five years ago, which is that high-dose dexamethasone in an older patient population is simply not tolerable.

In older patients, we see profound fatigue and generalized weakness, particularly in the hip and shoulder muscles, with high-dose dexamethasone. I also see weight loss in these patients, despite the fact that weight gain is typical with steroids. I’ve had a number of patients who lost 10 or 15 pounds in the first cycle of therapy.

**DR FARBER:** In combination with lenalidomide, many patients experience significant cytopenias, so when they come in with low platelet counts, I hold therapy or dose reduce. The toxicity experienced by older patients precludes using the 40-mg dose on days one to four, nine to 12, and so on, but for the younger patient who needs a rapid response, I would not shy away from the high-dose dexamethasone schedule.

**DR RICHARDSON:** Currently, high-dose dexamethasone has a relatively limited role in multiple myeloma. In my experience, a short exposure to high-dose dexamethasone is reasonable for some patients, especially younger patients and particularly in combination with drugs such as bortezomib.

Unfortunately, in combination with the IMiDs, particularly lenalidomide, high-dose dexamethasone is simply not indicated because of the toxicity difference between it and low-dose dexamethasone (Figure 16). The toxicology appears less pronounced with thalidomide and high-dose dexamethasone, and that is the FDA-approved combination, so it is reasonable to consider. However, in my practice I have tended to use less. You have to talk with patients about using lower doses of dexamethasone because it truly is a double-edged sword.

I use less dexamethasone and I use other drugs in combination. For example, if I have a patient at high risk in whom I need quick cyto reduction and prompt reduction of the paraprotein,
then I administer a steroid, an IMiD and a proteosome inhibitor. Using this combination, you can achieve the depth and quality of response needed while forgoing high-dose dexamethasone.

**Maintenance Therapy**

**DR RICHARDSON:** In the clinical trial HOVON-65/GMMG-HD4, the German Intergroup evaluated induction therapy with PAD followed by bortezomib maintenance versus VAD induction followed by thalidomide maintenance. No surprises were evident in the comparison of induction therapies — PAD trounced VAD.

What I found intriguing was that the bortezomib-based maintenance therapy continued to improve response over time. Thalidomide did the same on the PAD arm, so it wasn’t that bortezomib was better than thalidomide. However, the difference was far greater in the bortezomib-based arm because the patients were starting from a better point, if you will, considering the superior response to PAD versus VAD.
We believe that IMiD-based maintenance is important (Figures 17, 18). I anticipate that we will see data at ASH this year from the French showing a benefit with lenalidomide. I also expect that data will be augmented over time as we learn more about the maintenance role of bortezomib.

All of this is speculative, and we’ll be conducting randomized trials to nail down the respective roles of these agents. Still, my take is that the randomized Phase III trials clearly show that novel therapies make a difference, that VAD probably has no role in induction therapy pretransplant and, importantly, that maintenance therapy appears to matter.

**Bisphosphonates**

**DR RICHARDSON:** I believe that pamidronate is the best-tolerated bisphosphonate in terms of renal toxicity (Figure 19). Zoledronic acid is clearly potent, and if a patient has bone disease, is tolerating zoledronic acid and doesn’t have any contraindications to its use, then we continue it after transplant.

Essentially, the duration of bisphosphonate administration that we consider off protocol is driven by the status of bone disease in the patient (Figures 20, 21). For patients in remission post-transplant, we typically consider up to two years of therapy on differing schedules. Obviously we are likely to use the monthly schedule for patients with bone disease, especially if they’re not in remission. We consider less fre-
When you initially administer a bisphosphonate to a patient with multiple myeloma, what dosing interval do you use for a patient with multiple lytic lesions?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Clinical investigators (CI)</th>
<th>Practicing oncologists (PO)</th>
<th>Hematology-oncology fellows (HOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly</td>
<td>96%</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>Every 3 months</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Every 6 months</td>
<td>0%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Once per year</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

If you administer a bisphosphonate monthly in this setting, how long do you generally continue this strategy?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Clinical investigators (CI)</th>
<th>Practicing oncologists (PO)</th>
<th>Hematology-oncology fellows (HOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>18%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>24 months</td>
<td>74%</td>
<td>67%</td>
<td>61%</td>
</tr>
<tr>
<td>Indefinitely</td>
<td>0%</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
<td>8%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Recent administration for patients who are in complete remission with relatively modest or minimal bone disease who is in complete remission. For patients with bone disease, one has to be careful, particularly if they’re tolerating treatment well and have no side-effect issues, such as renal dysfunction or osteonecrosis of the jaw.

**SELECT PUBLICATIONS**


Hulin C et al: Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients ≥75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01/01. Proc ASCO 2007; Abstract 75.


Morgan GJ et al: Maintenance thalidomide may improve progression free but not overall survival: Results from the Myeloma IX maintenance randomisation. Proc ASCO 2008; Abstract 656.

Palumbo A et al: Bortezomib-doxorubicin-dexamethasone as induction prior to reduced intensity autologous transplantation followed by lenalidomide as consolidation/maintenance in elderly untreated myeloma patients. Proc ASCO 2008; Abstract 159.


Rajkumar SV et al: Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome. Proc ASCO 2008; Abstract 8504.


Clinical Case Presentations

**Case 1:** A 55-year-old patient presents with fatigue/anemia (HGB 9.5 g/dL). Total protein = 7.7 g/dL (globulin: 4.1 g/dL, serum albumin: 3.6 g/dL). Calcium and creatinine: Normal. SPEP with IFE: IgG κ. Monoclonal gammopathy: 2.2 g/dL. Quantitative immunoglobulins: Total IgG 3,000 mg/dL, with concomitant suppression of IgM and IgA. β2-microglobulin: 3.9 mg/L. Bone marrow: 32% infiltration of plasma cells. Skeletal survey: Osteopenia, no obvious lytic lesions. FISH and cytogenetics: Normal.

The patient undergoes induction with VTD followed by a single ASCT and remains asymptomatic. HGB is 13.6 g/dL, creatinine is 1.1 mg/dL and no M-protein is detected. Bone marrow plasmacytosis is 2%. Which would be your most likely approach to post-transplant management for this patient?

<table>
<thead>
<tr>
<th>Surveillance only</th>
<th>Clinical investigators (CI)</th>
<th>64%</th>
<th>Practicing oncologists (PO)</th>
<th>31%</th>
<th>Hematology-oncology fellows (HOF)</th>
<th>42%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates alone</td>
<td></td>
<td>24%</td>
<td></td>
<td>30%</td>
<td></td>
<td>34%</td>
</tr>
<tr>
<td>Thalidomide alone (with or without bisphosphonates)</td>
<td>8%</td>
<td>10%</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib/thalidomide (with or without bisphosphonates)</td>
<td>4%</td>
<td>1%</td>
<td></td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide alone (with or without bisphosphonates)</td>
<td>0%</td>
<td>15%</td>
<td></td>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide or thalidomide (with or without bisphosphonates)</td>
<td>0%</td>
<td>9%</td>
<td></td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>0%</td>
<td></td>
<td>4%</td>
<td></td>
<td>4%</td>
</tr>
</tbody>
</table>

The patient was treated with a bisphosphonate for 18 months with no other maintenance therapy. He now has a rising paraprotein level at 1.2 g/dL. HGB is 11.2 g/dL. Creatinine and calcium: Normal. Bone marrow: 15% plasma cells. Skeletal survey: Persistent osteopenia, 2 new lytic lesions.

Which would be your preferred treatment for this patient in first relapse?

<table>
<thead>
<tr>
<th>Rd</th>
<th>Clinical investigators (CI)</th>
<th>64%</th>
<th>Practicing oncologists (PO)</th>
<th>41%</th>
<th>Hematology-oncology fellows (HOF)</th>
<th>40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD</td>
<td></td>
<td>20%</td>
<td></td>
<td>9%</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>RD</td>
<td></td>
<td>8%</td>
<td></td>
<td>15%</td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td>VTD</td>
<td></td>
<td>4%</td>
<td></td>
<td>2%</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>VD</td>
<td></td>
<td>4%</td>
<td></td>
<td>14%</td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>0%</td>
<td></td>
<td>19%*</td>
<td></td>
<td>10%†</td>
</tr>
</tbody>
</table>

* PO PAD/VdorD 7%, TD 4%; † HOF PAD/VdorD 2%, TD 2%
the patients who’d achieved a complete response gained little to no benefit from the use of maintenance therapy, and the patients who had not achieved a complete response did gain benefit from maintenance thalidomide. Bisphosphonates did not appear to have a major impact in terms of skeletal events or progression-free survival.

I would have chosen bisphosphonates in this case (Figure 22). It’s debatable, but we usually treat patients with bisphosphonates for approximately one year post-transplant and then check bone mineral density for ongoing osteopenia.

DR FARBER: I believe the role of maintenance therapy is undefined, and I don’t use it routinely. If I have a patient with a rising paraprotein level after a transplant, I try several maneuvers that I believe are beneficial. I have put several patients on maintenance therapy in that setting who are now two to three years out with stable disease. It’s remarkable.

Treatment at Relapse

DR LONIAL: For patients who experience relapse after transplant, the questions I ask are, how long was that first remission, which induction therapy did they receive and what response was achieved (Figures 22, 23)?

If patients are in an unmaintained remission, they experience relapse and they received RVD up front, then you can consider a doublet combination — bortezomib/pegylated liposomal doxorubicin (PLD), bortezomib/dexamethasone or lenalidomide/dexamethasone.

The utility of bortezomib/PLD has been established in the relapsed setting, with an improvement in survival compared to bortezomib alone. Data are also emerging for PLD in combination with lenalidomide.

In the up-front setting, a couple of trials have evaluated bortezomib/PLD and dexamethasone, or bortezomib/PLD alone, which is a steroid-sparing induction regimen that can be attractive for patients with diabetes.

In a trial through the Multiple Myeloma Research Consortium, we’re combining PLD with the RVD regimen to determine whether we can proceed to a four-drug CHOP-like regimen that will result in a significantly higher rate of complete remissions.

Treatment at Relapse

Which would generally be your next therapeutic choice for this patient who is approximately 21 months post-ASCT?

<table>
<thead>
<tr>
<th>Choice</th>
<th>Clinical investigators (CI)</th>
<th>Practicing oncologists (PO)</th>
<th>Hematology-oncology fellows (HOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I would not proceed to transplant but salvage with additional systemic therapy</td>
<td>33%</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>A second ASCT</td>
<td>21%</td>
<td>45%</td>
<td>58%</td>
</tr>
<tr>
<td>Full-intensity or miniallogeneic stem cell transplant</td>
<td>21%</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>Reinitiate treatment with RD</td>
<td>13%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>12%*</td>
<td>8%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* Bortezomib-based regimen 4%

DR FARBER: I totally agree with Dr Lonial’s approach. Treating a patient at high risk with triple-drug therapy is the correct tactic, to find out whether we can reach a plateau or achieve a good initial response.

DR RICHARDSON: In the past two years, the most important series of studies for transplant-eligible patients comes primarily from the Europeans. Jean Luc Harousseau presented an update at ASH that showed an improvement in progression-free survival, for which bortezomib is fairly active in the up-front setting (Figure 24). I believe — and this is an area of some debate — that the advantage of combining drugs in myeloma is that we obtain synergistic interactions.

As I joke with my lung cancer colleagues, this is not like combining carboplatin with paclitaxel, with which one plus one equals a half. This is bortezomib and an IMiD, either lenalidomide or thalidomide, with which one plus one probably equals three or four.

This patient with aggressive disease, a high tumor burden, renal insufficiency and the risk of progressive renal dysfunction is the type I would treat with triple therapy. I would use either VTD or RVD in order to use all three of the most active drug classes we have.

Treatment at Relapse

DR LONIAL: For patients who experience relapse after transplant, the questions I ask are, how long was that first remission, which induction therapy did they receive and what response was achieved (Figures 22, 23)?

Case 2 - Initial Therapy

DR LONIAL: The top three choices in this question — VTD, RVD and VD — all contain bortezomib, and I believe that relates to the fact that this patient has high-risk disease and renal insufficiency, for which bortezomib is fairly active in the up-front setting (Figure 24). I believe — and this is an area of some debate — that the advantage of combining drugs in myeloma is that we obtain synergistic interactions.

As I joke with my lung cancer colleagues, this is not like combining carboplatin with paclitaxel, with which one plus one equals a half. This is bortezomib and an IMiD, either lenalidomide or thalidomide, with which one plus one probably equals three or four.

This patient with aggressive disease, a high tumor burden, renal insufficiency and the risk of progressive renal dysfunction is the type I would treat with triple therapy. I would use either VTD or RVD in order to use all three of the most active drug classes we have.

Treatment at Relapse

DR LONIAL: For patients who experience relapse after transplant, the questions I ask are, how long was that first remission, which induction therapy did they receive and what response was achieved (Figures 22, 23)?
free survival for induction bortezomib-based therapy compared to VAD, which usually translates to a survival advantage.

I believe that this study will become a landmark trial, and it had several important endpoints. The message from this study was clear: Bortezomib-based therapy outperformed VAD in depth and quality of response, and that benefit continued after transplant.

The quality of post-transplant response was significantly higher for the bortezomib-based therapy and, most importantly, after transplant in terms of continued response.

Another study from Michele Cavo and the Italians demonstrated that the depth and quality of response correlated with a progression-free survival benefit in their comparison of induction VTD to TD.

It’s intuitive that the triplet would be better than the doublet in terms of induction, but the benefit was also seen in terms of continued response.

Another important take-home message came from the analysis of patients with poor cytogenetics (e.g., del 13 and/or trans 4;14), for whom again VTD was superior to TD, and the doublet was unable to overcome the adverse impact of these poor-risk cytogenetics.

A final piece of information from this trial came from the correlative science studies, which demonstrated that...
the depth and quality of response was so profound that the proportion of stringent CR, which was PCR-negative in this particular study, was higher with VTD compared to TD.

**DR LONIAL:** A couple of key differences are clear between RVD and RD. Obviously, with RVD the patient has to come in more frequently, and the risk of neuropathy is higher.

If you conduct a cross-trial comparison of RVD to RD head to head, the triplet regimen dwarfs the doublet, no matter how you view it, in terms of depth of VGPRs and CRs. Of course, you can argue that this depth of response may not be as important for a patient at standard risk.

**Case 2 - Approach to Transplant**

**DR LONIAL:** Few clinicians chose an allogeneic stem cell transplant, which I believe is the subject of a current or recently completed clinical trial (Figure 25). That would not be my first choice, either, for these patients.

**DR FARBER:** I don’t believe that we have to commit to a single or a tandem autologous stem cell transplant right up front. We can wait to see the response, and if it’s particularly good, we can delay the second transplant. If it’s intermediate, we do get some mileage out of it and if we’ve helped the patient, we might proceed with a tandem transplant at that point.

**DR RICHARDSON:** Autologous stem cell transplant remains a gold standard without too much debate. The use of allogeneic stem cell transplant is a different issue and remains in the purview of clinical trials because the treatment-related mortality associated with its use in the fully ablated setting is prohibitive.

The broader direction of allogeneic transplant in the field is reduced-intensity allogeneic or nonmyeloablative allogeneic transplant, and we are actively pursuing that approach under protocol-directed conditions.

Some interesting data have been published recently. For example, the Italian group, led by Dr Bruno from Turin, published in *The New England Journal of Medicine* the results of their study in which they randomly assigned patients to either autografting or autografting followed by miniallografting if they had a sibling donor available. They showed nicely a survival advantage for the autografting followed by miniallografting, although some limitations are evident in that trial.

My viewpoint on tandem transplants is less positive because the evidence, in aggregate, suggests that tandem transplants, particularly with the advent of novel therapies and especially bortezo-
**FIGURE 26**

**Case 3: A 71-year-old patient presented with hip pain and fracture to the acetabulum related to multiple lytic lesions.** HGB was 10 g/dL, creatinine was 1.5 mg/dL, IgG λ was 5.2 g/dL and β2-microglobulin was 6.5 mg/L. Bone marrow: 54% infiltration of plasma cells. The patient had an adverse cytogenetic profile (eg, del 13 and/or trans 4;14).

<table>
<thead>
<tr>
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<tr>
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<td>18%</td>
<td>20%</td>
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<tr>
<td>MPT</td>
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<td>4%</td>
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<tr>
<td>Other</td>
<td>8%</td>
<td>15%*</td>
<td>18%†</td>
</tr>
</tbody>
</table>

* VdOxD 7%, RD 4%; † VdOxD 4%, RD = 8%

**If you selected a nonmelphalan regimen, did you select this regimen because you would consider ASCT for this patient?**

<table>
<thead>
<tr>
<th></th>
<th>Clinical investigators (CI)</th>
<th>Practicing oncologists (PO)</th>
<th>Hematology-oncology fellows (HOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>69%</td>
<td>51%</td>
<td>53%</td>
</tr>
</tbody>
</table>

**mib-based treatment, are not conveying much benefit. Considering the real issue of increased toxicity and, importantly, increased myelosuppression subsequent to the second transplant, a lot of centers are no longer performing tandem transplants.**

We performed tandem transplants on protocol only, and we have no current active studies in that regard. We do collect stem cells and we’ll perform a second transplant for selected patients later, but we’re not routinely performing tandem transplantation.

**Case 3 - Induction Therapy; Adverse Cytogenetics**

**DR RICHARDSON:** We were particularly pleased with the performance of upfront RVD in the multicenter Phase II study. The response rate, particularly in the context of its favorable tolerability, was remarkable. The rate of partial response (PR) or better among 65 evaluable patients was 100 percent. Our CR/near-CR rate was 44 percent, and our rate of VGPR or better was 74 percent.

It was particularly good to see those results corroborated by the Mayo group, who were leading the EVOLUTION trial, in which Shaji Kumar showed nicely that the combination of RVD and cyclophosphamide was also able in the Phase I portion of the trial to engender a response rate of 100 percent PR or better in evaluable patients and similar qualities of response — a CR rate of approximately 35 percent and a VGPR rate of approximately 68 percent.

Another important aspect of the RVD data is that risk profile may matter in terms of cytogenetics. We conducted an analysis of risk profile by the International Staging System criteria and the presence or absence of adverse cytogenetics, particularly 4;14 translocation and chromosome 13 deletion. RVD was able to engender a similar response rate in all of these subgroups.

**DR LONIAL:** My preferred induction regimen is RVD, which is a combination of our most active drugs: lenalidomide, bortezomib and dexamethasone (Figure 26). I believe that the real power of RVD lies in the high responses reported with that regimen. The overall response rate was 98 percent in the Phase II portion of the trial evaluating that regimen, and the VGPR or better rate for induction was higher than 70 percent.

My second-preferred regimen, VTD, was evaluated in the Cavo trial, which compared VTD to TD. A number of trials have evaluated thalidomide/dexamethasone versus VAD or dexamethasone as induction therapy. Although the response rates with TD were better up front, after transplant they were all nullified.

Cavo reported that the CR/near-CR...
rates were significantly higher for VTD up front — almost 36 percent. This also translated to better post-transplant CR/near-CR rates.

This was the second trial to report that the agents administered as induction therapy affect post-transplant outcomes. The question we are now asking is, do all patients who achieve a CR up front need to proceed to transplant? For some of the patients we’ve treated, we’ve elected to delay the transplant but not completely omit it. We’re critically evaluating the timing of the transplant — early versus late.

Case 4 - Bisphosphonates; Mild Osteopenia

DR VESOLE: Three different sets of guidelines exist for the use of bisphosphonates: one from ASCO, another from Mayo Clinic and a third from the International Myeloma Working Group. They are relatively similar but not exactly the same. The best data we have for answering this question are from a maintenance study by the French Myeloma Group. They conducted a three-arm trial to evaluate the impact of thalidomide on progression-free and overall survival in addition to the effect of bisphosphonates during a long period of time. The three arms consisted of one group receiving pamidronate, the second group receiving pamidronate and thalidomide and the third group simply being observed. The patients who received thalidomide demonstrated a better progression-free and overall survival. However, a subgroup analysis revealed that only those patients who had not achieved a very good partial remission and had low beta-2 microglobulin levels were the ones who benefited from the thalidomide maintenance therapy, which is why I believe thalidomide is consolidative therapy.

Case 4 - Bisphosphonates; Mild Osteopenia

Which would be your recommended approach regarding continued zoledronic acid treatment beyond 1 year for this patient in each of the following settings?

**Case 4: A 65-year-old patient with newly diagnosed, mildly symptomatic, intermediate-risk multiple myeloma was treated with induction therapy and ASCT, yielding a partial response post-transplant. He then began maintenance thalidomide. The patient was treated with monthly zoledronic acid for 1 year. Creatinine clearance is normal.**
Case 4 - Bisphosphonates; Osteolytic Lesions

DR VESOLE: The two patients in Case 4 are quite similar except that one patient has multiple lytic lesions rather than mild osteopenia (Figure 27). I would stop the zoledronic acid at one year. The majority of respondents who chose to continue bisphosphonates were ingrained in us years ago, beginning with Jim Berenson’s study of conventional chemotherapy with or without a bisphosphonate for patients with advanced multiple myeloma who did not undergo transplant.

Unfortunately, the strategy to continue bisphosphonates was ingrained in us years ago, beginning with Jim Berenson’s study of conventional chemotherapy with or without a bisphosphonate for patients with advanced multiple myeloma who did not undergo transplant.

The initial report was published with nine months of follow-up in The New

The other finding, which relates to this question, was that no differences in skeletal events appeared between those patients who received a bisphosphonate and those who did not. One year of a bisphosphonate for patients who had undergone transplant and were in remission did not provide benefit beyond that period. The International Myeloma Working Group recommends one year of monthly bisphosphonate after transplant if the patient achieves a remission. For patients who have not received a transplant or those with only stable disease post-transplant, the guidelines recommend two years of bisphosphonate therapy.

Thus, in my mind, only patients who have persistently active bone disease, not simply mild osteopenia, should receive bisphosphonates beyond that one-year period. I would not treat this patient with a bisphosphonate (Figure 27). As for the choice to decrease the frequency to every three months or every six months, no data whatsoever are known to support that.

The initial report was published with nine months of follow-up in The New

Which prophylactic anticoagulation therapy would you most likely recommend for this patient starting treatment with VTD?*

<table>
<thead>
<tr>
<th>Therapy</th>
<th>CI (%)</th>
<th>PO (%)</th>
<th>HOF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted-dose warfarin (target INR 2.0-3.0)</td>
<td>55</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>Low-molecular-weight heparin at a prophylactic dose†</td>
<td>21</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>Aspirin 325 mg/day</td>
<td>8</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Adjusted-dose warfarin (target INR of 1.5)</td>
<td>8</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Fixed low-dose warfarin (1.0-1.25 mg/day)</td>
<td>4</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Low-molecular-weight heparin at a therapeutic dose‡</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Low-dose aspirin (81-100 mg/day)</td>
<td>0</td>
<td>12</td>
<td>14</td>
</tr>
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</table>

* Physicians who would recommend prophylactic anticoagulation, CI n = 24, PO n = 99, HOF n = 50; † Equivalent of enoxaparin 30 mg twice daily or 40 mg once daily; ‡ Equivalent of enoxaparin 1.0 mg/kg twice daily or 1.5 mg/kg once daily

In my practice, a history of deep venous thromboembolism is a contraindication to the use of lenalidomide and thalidomide.

<table>
<thead>
<tr>
<th>Opinion</th>
<th>CI (%)</th>
<th>PO (%)</th>
<th>HOF (%)</th>
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</thead>
<tbody>
<tr>
<td>Agree</td>
<td>0</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>In between</td>
<td>8</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td>Disagree</td>
<td>92</td>
<td>49</td>
<td>76</td>
</tr>
</tbody>
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The other finding, which relates to this question, was that no differences in skeletal events appeared between those patients who received a bisphosphonate and those who did not. One year of a bisphosphonate for patients who had undergone transplant and were in remission did not provide benefit beyond that period. The International Myeloma Working Group recommends one year of monthly bisphosphonate after transplant if the patient achieves a remission. For patients who have not received a transplant or those with only stable disease post-transplant, the guidelines recommend two years of bisphosphonate therapy.

Thus, in my mind, only patients who have persistently active bone disease, not simply mild osteopenia, should receive bisphosphonates beyond that one-year period. I would not treat this patient with a bisphosphonate (Figure 27). As for the choice to decrease the frequency to every three months or every six months, no data whatsoever are known to support that.

Case 4: A 67-year-old smoker with high-risk multiple myeloma will be treated with VTD. Three years ago, the patient experienced a deep-vein thrombosis without known precipitating factors, which was managed with 1 year of full-dose warfarin.
In England Journal of Medicine in 1996, and in 1998 they published the 21-month analysis in the Journal of Clinical Oncology. Both data sets showed that the patients who continued therapy had fewer fractures and less pain.

With those data, the myeloma community assumed that patients should receive bisphosphonates forever. It wasn’t until we received these newer data showing an increased risk of osteonecrosis to the jaw with prolonged treatment that people felt the need to reassess these guidelines. The data from the French group may not have filtered down, which is apparent to me. We believed that the French study was significant and, with that in mind, we recommend the one year of therapy after transplant for patients who achieve a remission.

**Case 5 - Anticoagulation**

DR VESOLE: Guidelines on prophylactic anticoagulation, including recommendations from the International Myeloma Working Group published in December 2007 in *Leukemia*, divide patients into low-risk and high-risk groups. This patient would be at high risk because he has already experienced a deep-vein thrombosis, for whatever reason, and now he’s receiving a thalidomide/dexamethasone regimen.

I would fully anticoagulate this patient, with a target INR between two and three. Sixty percent of the clinical investigators agree with that approach and only a third of the oncologists or fellows do, but I believe they will learn from experience (Figure 28).

**DR RICHARDSON:** I believe that anticoagulation is required for patients treated with an IMiD, and it’s particularly essential with IMiD-based combination therapy (Figure 29).

Lenalidomide monotherapy is well tolerated and it’s an excellent agent in my experience, and we would always use aspirin at a minimum — likewise with thalidomide. With patients for whom the risk of thrombosis is real — whether from prior history, family history or other concomitant factors — the use of more aggressive anticoagulation, including low-molecular-weight heparin, is an important consideration.
It is interesting that data from Europe suggest that aspirin is the gold standard. In a series of well-executed studies, Antonio Palumbo showed that aspirin was essentially as effective as full-dose warfarin and perhaps as effective as prophylactic low-molecular-weight heparin.

If you combine an IMiD with bortezomib, clear evidence from randomized trials indicates that the thrombotic risk is reduced. So a nice synergy occurs in terms of toxicology, by which bortezomib can protect against thrombosis to some extent, but you must still have an anticoagulant or aspirin on board.

The International Myeloma Working Group published a good guideline in Leukemia last year, and I do believe some form of anticoagulation or antithrombotic prophylaxis is essential.

**Case 6 - Peripheral Neuropathy**

DR RICHARDSON: In myeloma, it is clear that neurotoxicity is part of the illness and is probably driven partly by an inflammatory cytokine effect, which has become better understood. Obviously steroids will blunt that to some extent, but it's important to recognize that the IMiDs are potent inhibitors of IL-6 and potent inhibitors of TNF-alpha, for example. It may well be that the anti-inflammatory effects of the IMiD in concert with the proteasome inhibitor act to reduce that component of neurotoxicity that's driven by inflammation. That's why the IMiD and proteasome inhibitor in combination are less neurotoxic than you might expect, and the cardinal example, of course, is VTD.

DR FARBER: Dating back to the early approval of bortezomib, many patients were treated with the single agent only or in combination with steroids. Even when we had to reduce the dose of bortezomib, I was impressed with the response rates we saw with the lower dose, and we still see impressive responses (Figure 30).

**Case 7 - RVD-Associated Neuropathy**

DR LONIAL: It’s important to point out that this is not a garden-variety
case. Rather it’s a patient with high-risk myeloma. This is a practical and important question because it arises in the real world. Patients do develop neuropathy from RVD.

I would favor reducing the dose of bortezomib, allowing that neuropathy to improve, and then continuing on for an additional two cycles to give the patient a chance to respond.

The responses among the three groups are similar, with the majority choosing to discontinue bortezomib but continue lenalidomide and dexamethasone for at least two more cycles (Figure 31). While discontinuing bortezomib is a reasonable choice and may improve the overall peripheral neuropathy, I believe that we lose some of the synergy that we may gain by combining bortezomib with an IMiD.

DR RICHARDSON: In our experience with the RVD regimen, we do not see significant neurotoxicity, particularly when the bortezomib dose is reduced. The other point is that if you have combinations that work, you can afford to use lower doses of the bortezomib and you will see less neurotoxicity. In a nutshell, the neurotoxicity question is complicated but we’re observing that certain combinations may be less neurotoxic than others.

DR LONIAL: I suspect that the reason so many of the respondents have not used induction RVD is the large number of available choices (Figure 31). I call it the “confusing collection of consonants.” It’s difficult to know which regimen is best. Is it VTD? Is it RD? Is it VD? Is it bortezomib and liposomal doxorubicin? We don’t have enough data to say outright that RVD is the best choice.

I do believe that we have enough data to say that certain regimens are not the right answers. VAD is essentially dead. Dexamethasone alone, in my mind, is dead. Also, I don’t believe that we get enough mileage out of thalidomide/dexamethasone for it to be a reasonable option.
**Case 8:** A 65-year-old patient was previously treated with induction therapy and ASCT for intermediate-risk myeloma. The patient achieved a near-complete response after transplant and received monthly bisphosphonates for 1 year. The patient presents after 6 months of observation alone (18 months post-transplant) with increasing paraprotein, slowly progressive anemia and a rise in bone marrow plasma cells from 2% to 7%. Creatinine is 1.5 mg/dL.

**Which systemic treatment would you most likely recommend now if this patient received...**

### TD as induction therapy

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<tr>
<td>Other</td>
<td>12%*</td>
<td>19%†</td>
<td>22%‡</td>
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* CI CyBorD 4%; † PO TD 5%, Vdoox 4%, VTD 3%; ‡ HOF TD 10%, VTD 8%

### RD as induction therapy

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<tr>
<td>Other</td>
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<td>11%*</td>
<td>22%†</td>
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* PO MPV 4%; † HOF RD 12%

### RVD as induction therapy

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<tr>
<td>Other</td>
<td>8%</td>
<td>20%*</td>
<td>24%‡</td>
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</table>

* PO VTD 8%, MPV 3%, VAD 3%; † HOF VTD 6%, MPV 6%, MPR 6%
DR FARBER: I have administered induction RVD to a couple of newly diagnosed patients, and I’ve seen dramatic responses. It’s a highly active regimen.

Case 8 - Treatment of Relapsed Multiple Myeloma

DR RICHARDSON: One important practice point is to recognize that unlike with epithelial neoplasms, we’re revisiting a class of drug to which a patient has already been exposed. Patients with epithelial neoplasms may be unlikely to benefit from re-treatment with the same agent, but that paradigm doesn’t apply in myeloma. You can revisit backbone agents or platform drugs, such as proteasome inhibitors and IMiDs as a combination (Figures 32, 33).

The use of additional drugs makes sense, and the data to support it are best exemplified by Bob Orlowski’s work with liposomal doxorubicin and bortezomib (Figure 34). He showed in his randomized trial that liposomal doxorubicin and bortezomib administered at relapse within 12 months of a transplant produced superior outcomes compared to bortezomib monotherapy.

Therein lies an important clue that if you have a patient with aggressive relapse relatively soon after intensive therapy, you should consider combinations. This would include agents that the patient may have received before but also agents with which he or she has not been treated. You can revisit combinations, but be innovative. The good news is that we have a constellation of new agents.

Off protocol, in the relapsed/refractory setting it’s wise to consider revisiting an alkylator in combination with an IMiD and proteasome inhibitor. I won’t in any way downplay the challenge of relapsed/refractory disease.

We’re excited because patients are living longer. Median survivals are now extending out to five to seven years. Having said that, relapsed/refractory patients are still seriously sick and face great challenges.

Case 9 - Waldenström Macroglobulinemia

DR VESOLE: The fact that the 70-year-old patient in Case 9 who has Waldenström macroglobulinemia is experiencing...
neuropathy and headaches is worrisome, although the serum viscosity is only four (Figure 35). We become concerned about hyperviscosity syndrome if patients have headaches related to their IgM gammopathy.

This patient’s IgM is high at 7,300, even though the serum viscosity seems to be disproportionately low at four, and the bone marrow shows the typical lymphoplasmacytoid cells with the appropriate flow cytometric markers. This patient indeed has Waldenström macroglobulinemia, and we have data for a number of regimens that can be used in treating such patients.

Rituximab with bortezomib and dexamethasone is one of the choices, and Steve Treon at Dana-Farber has data demonstrating the efficacy of rituximab. Data also exist for CVP, CHOP and R-CHOP (Figure 35).

The Waldenström’s Working Group lists a whole series of options available to treat these patients, including chlorambucil, which has demonstrated activity, but I don’t think I would use it considering that this patient may have some hyperviscosity.

I would treat this patient with R-CHOP and possibly change after a few cycles when his hyperviscosity symptoms resolve.

Even if this patient were 55 years old, I still would not recommend transplant — and I’m a transplanter.

The 68-year-old patient with a plasmacytoma in Case 11 is a little different because the other one may or may not be extramedullary plasmacytoma, but this one is obviously a plasmacytoma in bone (Figure 37). The long-term outcome is different depending on whether they’re extramedullary or solitary plasmacytomas in bone. One has a high cure rate and the other has a low cure rate.

I would order MRIs of the entire head, spine and pelvis and a PET scan for this patient before initiating treatment. If no additional findings were made, then I would use radiation therapy alone. I would not administer bisphosphonates. This is not a lytic bone disease process, so I don’t believe that would be an appropriate treatment for this patient. Whether to administer steroids if significant swelling occurs depends on what is causing the swelling. If it’s truly mechanical and not from swelling of the optic nerve, I would probably use radiation therapy.

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Text continued on page 38
Case 10: A 68-year-old patient developed paraspinal soft tissue swelling centered 6 centimeters to the right of his T10 vertebral body. Imaging studies, including bone and skeletal x-ray series, revealed a solitary abnormality. Blood work revealed an IgG \( \lambda \) monoclonal protein level of 1.3 g/dL, \( \beta_2 \)-microglobulin of 3.9 mg/L and a normal calcium level. A biopsy of the mass revealed sheets of plasma cells with IgG \( \lambda \) surface markers. Bone marrow studies were normal. The patient was diagnosed with plasmacytoma.

Which would be your most likely approach to initial therapy for this patient?

<table>
<thead>
<tr>
<th></th>
<th>Clinical investigators (CI)</th>
<th>Practicing oncologists (PO)</th>
<th>Hematology-oncology fellows (HOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation therapy with or without steroids</td>
<td>80%</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>Radiation therapy with bisphosphonates with or without steroids</td>
<td>16%</td>
<td>34%</td>
<td>44%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>7%</td>
<td>4%</td>
</tr>
</tbody>
</table>

If this patient were 55 years old, would you generally recommend a transplant?

<table>
<thead>
<tr>
<th></th>
<th>Clinical investigators (CI)</th>
<th>Practicing oncologists (PO)</th>
<th>Hematology-oncology fellows (HOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>8%</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>No</td>
<td>92%</td>
<td>77%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Case 11: A 68-year-old patient with a history of right eye trauma developed acute onset of right orbital swelling and pain. MRI revealed a destructive bone lesion. Blood work revealed an IgG \( \lambda \) monoclonal protein level of 1.3 g/dL, \( \beta_2 \)-microglobulin of 3.9 mg/L and calcium of 11.3 mg/dL. Urine electrophoresis was negative, and serum K light chains were minimally elevated. Bone marrow study results were normal. The patient was lucid, and a bone survey revealed no additional abnormalities. A biopsy of the orbital bone revealed infiltration with plasma cells. PET/CT was negative for other abnormalities. The patient was diagnosed with plasmacytoma.

Which would be your most likely approach to initial therapy for this patient?

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
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<tr>
<td>Radiation therapy with or without steroids</td>
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<td>43%</td>
<td>40%</td>
</tr>
<tr>
<td>Radiation therapy with bisphosphonates with or without steroids</td>
<td>40%</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Other</td>
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<td>7%</td>
<td>0%</td>
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If this patient were 55 years old, would you generally recommend a transplant?

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<td>8%</td>
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<td>20%</td>
</tr>
<tr>
<td>No</td>
<td>92%</td>
<td>78%</td>
<td>80%</td>
</tr>
</tbody>
</table>
we may still see a mass on the MRI but be unable to determine whether or not it’s an active plasmacytoma.

On the other hand, the PET scan, assuming the plasmacytoma is PET avid, would provide us with that information.

SELECT PUBLICATIONS


Bensinger W et al. A Phase II study of bortezomib (Velcade®), cyclophosphamide (Cytoxan®), thalidomide (Thalomid®) and dexamethasone as first-line therapy for multiple myeloma. Proc ASH 2008; Abstract 94.


Cavo M et al. Superior complete response rate and progression-free survival after autologous transplantation with up-front Velcade-thalidomide-dexamethasone compared with thalidomide-dexamethasone in newly diagnosed multiple myeloma. Proc ASH 2008a; Abstract 152.

Cavo M et al. Superior rate of complete response with up-front Velcade-thalidomide-dexamethasone versus thalidomide-dexamethasone in newly diagnosed multiple myeloma is not affected by adverse prognostic factors, including high-risk cytogenetic abnormalities. Proc ASH 2008b; Abstract 1662.


Harousseau JL et al. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM); Updated data from IFM 2005/01 trial. Proc ASCO 2008; Abstract 8505.


Morgan GJ et al. Maintenance thalidomide may improve progression free but not overall survival: Results from the Myeloma IX maintenance randomisation. Proc ASH 2008; Abstract 656.

Orlowski RZ et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: Combination therapy improves time to progression. J Clin Oncol 2007;25(25):3892-901. Abstract


Palumbo A et al. Bortezomib-doxorubicin-dexamethasone as induction prior to reduced intensity autologous transplantation followed by lenalidomide as consolidation/maintenance in elderly untreated myeloma patients. Proc ASH 2008; Abstract 159.


Rajkumar SV et al. Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group. Abstract 94.


San Miguel JF et al. Longer duration of treatment and maintenance of best response with lenalidomide and dexamethasone prolongs overall survival in patients with relapsed or refractory multiple myeloma. Proc ASH 2008b; Abstract 3702.

San Miguel JF et al. Updated follow-up and results of subsequent therapy in the Phase III VISTA trial: Bortezomib plus melphalan-prednisone versus melphalan-prednisone in newly diagnosed multiple myeloma. Proc ASH 2008a; Abstract 650.

Sonneveld P et al; DOXIL-MMY-3001 Study Investigators. Combined pegylated liposomal doxorubicin and bortezomib is highly effective in patients with recurrent or refractory multiple myeloma who received prior thalidomide/lenalidomide therapy. Cancer 2008;112(7):1529-37. Abstract


Treon SP et al. Primary therapy of Waldenström's macroglobulinemia with bortezomib, dexamethasone and rituximab: Results of WMC TG clinical trial 05-180. Proc ASCO 2008; Abstract 8510.


Zonder JA et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as consolidation for newly diagnosed multiple myeloma (NDMM): Results of the randomized, double-blinded, placebo-controlled SWOG Trial S0232. Proc ASH 2007; Abstract 77.
EDUCATIONAL ASSESSMENT AND CREDIT FORM: Patterns of Care Vol 1 · 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

BEFORE completion of this 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>
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</thead>
<tbody>
<tr>
<td>Staging of multiple myeloma based on the International Staging System</td>
<td>4 3 2 1</td>
<td></td>
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<tr>
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<tr>
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<tr>
<td>Indications for and selection of maintenance therapy</td>
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</table>

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

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

☐ Yes ☐ 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 LEARNER statements 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 = Learning objective 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 employed by community oncologists, hematology-oncology fellows and cancer clinical investigators, and apply this knowledge to the routine management of multiple myeloma (MM) .............................................................. 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
• Counsel patients with MM about the benefits and risks of multiple acceptable treatment options when they exist .............................................................. 4 3 2 1 N/M N/A
• Recognize the rate at which practice-changing clinical research impacts physician decision-making, and explain how this affects patient access to standard and novel therapies .............................................................. 4 3 2 1 N/M N/A
• Identify current approaches to stem cell transplant for eligible patients with symptomatic MM, and recommend evidence-based induction regimens to facilitate long-term outcomes .............................................................. 4 3 2 1 N/M N/A
• Recall the design and eligibility criteria for ongoing clinical trials in newly diagnosed and relapsed MM, and consider appropriate patients for study 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?
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 _______________________________

Medical License/ME Number: ___________________________ Last 4 Digits of SSN (required): _______________________

Street Address: ___________________________________ Box/Suite: ___________________________

City, State, Zip: ___________________________________

Telephone: ___________________________ Fax: ___________________________

Email: __________________________________

Research To Practice designates this educational activity for a maximum of 5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

Diagnostic Workup, Staging and Transplant Strategy

Stem Cell Transplantation

Systemic Therapy Issues: Regimen Selection, Dexamethasone Dosing, Maintenance Therapy, Bisphosphonates

Clinical Case Presentations

Editor
Neil Love, MD

Contributing Editors
Paul G Richardson, MD
David H Vesole, MD, PhD
Charles M Farber, MD, PhD
Sagar Lonial, MD

A Survey Comparing Practices of Clinical Investigators, Practicing Oncologists and Fellows

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