AXIS Medical Education

Tumor Board:
Challenging Cases in Multiple Myeloma Patient Care

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This activity is supported by educational funding provided by Amgen.

Activity Information

Release date: May 13, 2016
Expiration date: May 12, 2017
Educational credits: 1.0 *AMA PRA Category 1 Credit(s)™*
Estimated time to complete activity: 60 minutes

TARGET AUDIENCE

This activity is designed for hematologists, medical oncologists, and other healthcare professionals who treat or manage patients with multiple myeloma.

PURPOSE

The goal of this activity is to identify and close knowledge, competence, and performance gaps by providing clinicians with appropriate context and practical application of the latest evidence-based data and guidelines on established and emerging agents and regimens for the treatment of patients with multiple myeloma to improve the quality of care delivery.

ACTIVITY OVERVIEW

The treatment armamentarium for MM has expanded significantly in recent years, with 4 new therapies approved by the FDA in 2015 alone. With so many agents and regimens to choose from, and more emerging therapies in clinical trials, it is crucial for oncology/hematology healthcare professionals to understand current treatment approaches for newly diagnosed and relapsed/refractory MM.

In this activity, a faculty panel will come together to discuss real-world patient cases leveraging their expertise and perspectives in a tumor board style exercise. The faculty panel will address some of the most pressing questions facing clinicians today when formulating the most appropriate treatment plans for their patients with MM. Current and emerging evidence-based updates will be integrated to assist in translating this array of information into real-world treatment scenarios and shed light on the progress toward answering many of the clinical challenges faced in MM treatment.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should better be able to:

- Identify the differential diagnosis, prognostic factors, and cytogenetics of multiple myeloma (MM)
- Evaluate current treatment modalities, in combination or alone, for newly diagnosed and relapsed/refractory MM to optimize patient outcomes
- Assess recent clinical trial data on novel and emerging therapies for the treatment of MM and the implications of these agents on clinical practice
- Explain appropriate strategies to manage adverse events and toxicities in patients with MM

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FEE

There is no fee for this educational activity

OVERVIEW OF MULTIPLE MYELOMA AND TREATMENT APPROACHES

Paul G. Richardson, MD:

Welcome to this CME-certified activity. Dr. Giralt, Dr. Kumar, and I will be using a case-based approach to discuss multiple myeloma (MM) treatment. First, we will briefly discuss the pathophysiology, epidemiology, diagnosis, staging, and risk assessment for MM.

Sergio A. Giralt, MD, FACP:

One of the things that I'm getting more and more calls about is what's happening with the new diagnosis of MM and smoldering myeloma. With the new criteria—myeloma-defining events such as clonal bone marrow plasma cell percentage ≥60%, more than 1 focal lesion on magnetic resonance imaging (MRI), and an involved versus uninvolved serum free light chain ratio of ≥100—we know these people are at high risk of developing end-organ damage known as the CRAB criteria, which includes hypercalcemia, renal insufficiency, anemia, and bone lesions. The new definition of smoldering MM requires both criteria to be met: serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg/24 hr and/or clonal bone marrow plasma cells 10% to 60%, and the absence of myeloma-defining events or amyloidosis (Rajkumar et al, 2014). According to the new guidelines, patients who meet these criteria actually require treatment now, and they require the same treatment as patients with stage I symptomatic myeloma. The International Myeloma Working Group (IMWG) revised diagnostic criteria for MM and smoldering MM no longer requires patients to exhibit end-organ damage before treatment is initiated (Rajkumar et al, 2014).

Dr. Kumar and I were speaking with community physicians at a large meeting recently and we realized that these new guidelines change their treatment paradigm a bit. In a sense, it does make things a little bit more straightforward. There are patients who they were very concerned about that may experience rapid disease progression, and now physicians have clear guidance that the patients should be treated. But the physicians were unclear about how the patients should be treated. We were making the case that these patients need to be treated as if they had symptomatic myeloma, with triple induction, consolidation, and maintenance therapy, if they were not going to participate in a clinical trial.

In the context of pathophysiology, although we're learning more and more about the biology of this disease, about the issue of clonal type and clonal waves, for all practical purposes we still are treating patients more or less all the same way.

Shaji Kumar, MD:

True. I think quite a bit has changed with respect to the diagnostic criteria. But again, taking a step back and just looking at the epidemiology of the disease, and the fact that we understand it's a spectrum of diseases, we are drawing the lines at a little different time point compared to what we were before. However, more than just the fact that the criteria changed, there is a consensus among every one of us in the field that we could actually start treating patients before something bad happens. I think that is really a paradigm shift for the disease overall. And that's not something we would have thought about 10 years ago when we did not have all the drugs that we have today.

I think a lot of it is driven by the ability for us to deliver effective regimens with less toxicity than we used to before. However, clearly, in terms of understanding the disease biology, I think we're certainly making great strides, especially understanding the genomic complexity and the understanding that we are not dealing with a single disease but rather a heterogeneous group of diseases probably driven by different underlying mechanisms but with a common phenotype.

Dr. Richardson:

Next, please let's comment on what we're seeing in terms of myeloma epidemiology because we are seeing increases in incidence globally and particularly in certain countries.

Dr. Giralt:

I think environmental exposures definitely play a role. I also think, remember the population is definitely getting older, and to a certain degree—thanks to wonderful work that you and others, the Multiple

Myeloma Research Foundation, and the IMWG in educating primary care providers—I definitely think there's much more awareness now about myeloma. So, when an older patient comes in with recurrent pneumonia, we are thinking that maybe this patient has underlying immune suppression, and we start thinking about myeloma.

Dr. Kumar:

I think overall we are seeing more patients with myeloma, but again when you look at age-adjusted population basis it may not be such a dramatic change over the years. But I think it's certainly understood more in terms of environmental exposures, in terms of ethnicity, how it's 2- to 3-fold higher in the black population compared to whites, less so in Hispanics or Asians (Greenberg et al, 2012). We also have, I think, a better understanding about the familial risk of it being 2- to 3-fold higher in first-degree relatives (Vachon et al, 2009). But again, we don't know how much of that is environmental exposures versus genetics in terms of familial risk.

Dr. Richardson:

I think in certain countries they're seeing certain changes. For example, in Taiwan, which has a relatively well-organized national system and in the Chinese population, myeloma is relatively uncommon. However, in the past 25 years, they've seen a 5-fold increase in the incidence of MM, particularly in certain populations, such as agricultural workers and, interestingly enough, healthcare workers (Huang et al, 2007). So, some interesting observational data are emerging.

As we know, there are other epidemiological factors that may be relevant. For example, we know that woodworkers are at risk for this disease, and that workers exposed to radiation and other particular organic chemicals may be at risk for MM (Jagannath et al, 2008). And finally, of course, we are aware now that professional firefighters have an increased risk for this disease, suggesting that chemical exposure associated with large factory- or warehouse-based fires may be more likely to cause the illness.

Dr. Kumar:

One other thing to highlight is risk assessment. We now have the revised International Staging System (R-ISS) from the IMWG that really incorporates a lot of what we have learned about the disease (Palumbo et al, 2015). The fact that genetic abnormality is clearly the major driver for prognosis, and combining that with lactate dehydrogenase (LDH) and the old ISS staging system really does make that staging system more current. The R-ISS combines the ISS with chromosomal abnormalities detected with interphase fluorescence in situ hybridization (FISH) to provide a simple and reliable prognostic staging system to stratify MM (Palumbo et al, 2015).

Dr. Richardson:

I agree, and the increasing use of additional imaging, with MRI and positron emission tomography/computed tomography is helping to distinguish smoldering from active disease.

Dr. Giralt:

I think this is another area where we really do need to do much more work in divulgation, because we still have patients who are being treated outside of an academic center, and many of them don't have beta-2 microglobulins done at the time of diagnosis, or don't undergo a full FISH panel for myeloma performed. I think it's very important that community oncologists understand that this actually now will define what the best treatment is for many patients.

Dr. Richardson:

The treatment armamentarium for MM has expanded significantly in recent years, with 4 new therapies approved by the US Food and Drug Administration (FDA) in 2015 alone, and 1 additional approval for an existing drug as well as two others for expanded indications to a total of 7 in one year. New drugs include panobinostat, the first histone deacetylase inhibitor approved for MM (FDA News Release, 2015a); daratumumab, the first monoclonal antibody approved for MM (FDA News Release, 2015b); ixazomib, the first oral proteasome inhibitor approved for MM (FDA News Release, 2015c); and elotuzumab, a second monoclonal antibody targeting the SLAMF7 protein (FDA News Release, 2015d). Carfilzomib, which was initially approved in 2012, received an additional approval for relapsed MM in 2015 (FDA News Release, 2015e). This adds to the already approved immunomodulatory agents (thalidomide, lenalidomide, pomalidomide), and proteasome inhibitors (bortezomib, carfilzomib). **Table 1** provides a summary overview of currently available therapies for MM.

Table 1
Drugs Used to Treat Multiple Myeloma

Drug Class	Drug Name
Proteasome inhibitor	Bortezomib
	Carfilzomib
	Ixazomib
Immunomodulatory agent	Lenalidomide
	Pomalidomide
	Thalidomide
Monoclonal antibody	Daratumumab
	Elotuzumab
Histone deacetylase inhibitor	Panobinostat
Alkylating agent	Cyclophosphamide
	Melphalan
Corticosteroid	Dexamethasone
	Prednisone
Bisphosphonate	Pamidronate
	Zoledronic acid

DEMYSTIFYING MULTIPLE MYELOMA TREATMENT: HOW CAN CURRENT AND EMERGING EVIDENCE HELP US WITH THE TREATMENT CHALLENGES WE FACE?

Dr. Richardson:

Please let's now turn our attention to the case studies in this activity.

Case Study #1

Dr. Richardson:

The first case is a 56-year-old man previously in good health. He presents with a 4-month history of lower back pain, classic left-sided chest discomfort, and progressive fatigue. His examination is noteworthy for some mild pallor and also some tenderness to palpation and muscle spasm in the lumbosacral region, as well as some tenderness to palpation in the chest wall. After an initial diagnostic workup (shown in **Table 2** and **Figure 1**), MM was diagnosed.

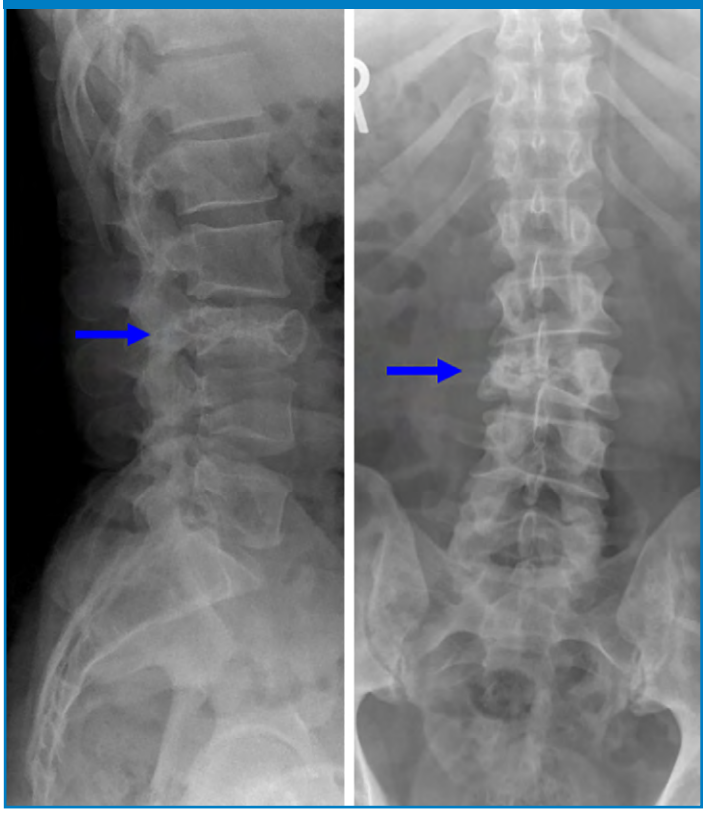
Table 2
Laboratory Findings, SPEP and Bone Marrow Results, Imaging Information, Staging and Prognosis

Laboratory Findings	
CBC	WBC count 5.2 x 10^9/L, hemoglobin 11 g/dL, platelets 125 x 10^9/L
Creatinine	1.37 mg/dL
Calcium	10.8 mg/dL
Beta-2 microglobulin	4.0 mg/L
Serum albumin	3.4 mg/dL
LDH	Normal
SPEP and Bone Marrow	
Serum protein electrophoresis	Serum IgG-lambda protein 4.5 g/dL 24-hr urine collection: lambda light chain M protein measuring 730 mg/L
Bone marrow aspiration and biopsy	Extensive infiltrate of CD 138+ plasma cells with lambda light chain restriction involving approximately 60% of cellularity
Imaging	
Skeletal survey	Extensive lytic lesions Seventh left nondisplaced rib fracture Early compression fracture in lumbar spine
MRI	Abnormal marrow signal thoracolumbar vertebrae Compression fracture of L3 No spinal cord compression
Staging and Prognosis	
Stage	Durie-Salmon: IIIa ISS: II
Other prognostic factors	13q del by metaphase cytogenetics (confirmed on FISH; 17p was not present) LDH normal

FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; SPEP, serum protein electrophoresis; WBC, white blood cell.

Figure 1

Plain radiological images (lateral, left; posterior-anterior, right) show a compression fracture (arrow).



Images courtesy of Paul G. Richardson, MD.

Dr. Richardson:

So, let's discuss some management issues for this patient with newly diagnosed MM, including the choice of initial treatment, the utility of vertebroplasty/kyphoplasty, and the role and timing of autologous transplantation.

Dr. Giralt:

We now have a lot of guidance about what the initial therapy should be with a patient like this who has normal renal function, stage II disease, and whose beta-2 microglobulin is still less than 5 mg/L, with a deletion 13 chromosome abnormality on metaphase cytogenetics.

Many of us think that patients who have abnormal cytogenetics by karyotype are probably a worse group of patients. Obviously this patient has symptomatic disease with bone involvement and other borderline metabolic abnormalities. So he needs treatment with an induction therapy that's effective and that will not affect stem cells to allow for stem cell collection. We now have 4 randomized trials conducted by European investigators comparing bortezomib-containing regimens to non-bortezomib containing regimens. These studies showed that in the context of symptomatic myeloma, the use of bortezomib as part of the induction regimen improved survival and progression-free survival (Kaufman et al, 2010; Rosinol et al, 2012; Reeder et al, 2009; Einsele et al, 2009). The question is, what should bortezomib be combined with—an immunomodulatory drug or the alkylator, cyclophosphamide?

The prospective IFM 2013-04 European trial that was presented at the American Society of Hematology (ASH) 2015 meeting that compared VTD to VCD showed improvement in overall response rates for VTD (92.3% vs 84%). Very good partial response and partial response rates were significantly higher in the VTD arm (*P* values = .04 and .02, respectively; Moreau et al, 2015).

I think many of us in the United States think that the combination that you developed, Paul, with lenalidomide, bortezomib, dexamethasone (RVD), is extremely well tolerated, extremely effective, and allows for the collection of stem cells (Richardson et al, 2010). So I think that would be the choice of initial therapy for this patient. Will the combination of carfilzomib, lenalidomide, dexamethasone (KRD) be better? It is too early to say. Published data on that combination showed very high response rates (Jakubowiak et al, 2012).

As for vertebroplasty and kyphoplasty, I would say that a patient who has a lytic lesion or a compression fracture that's symptomatic should be referred for interventional radiology. We have all been impressed by how these patients come in writhing in pain and suddenly after treatment by the interventional radiologist, their pain is gone; it's miraculous.

I think the role of autologous transplant based on the French IFM/DFCI 2009 trial presented at ASH 2015 should still be considered the standard of care for young patients (Attal et al, 2015). We are waiting to see what the American part of the trial will show, and I think at the end we will have enough data, particularly for patients to achieve minimal residual disease (MRD) negativity, to determine whether patients can opt to defer transplant.

I think patients need to be aware that if they do defer transplant, that there is no guarantee that they may actually get it later on, although two-thirds of the patients in Palumbo's study were able to get a second transplant when they were randomized to deferred transplantation. Transplant is a choice, but I think now we have much more information that patients can make an informed choice.

Dr. Richardson:

I agree and I think that the important message around the role of transplant is that it remains a standard of care in younger patients who are eligible. The issue of timing is very important however, because as patients live longer, and especially in the United States, where there are many salvage options can transplant be kept in reserve. Specifically, the question is, if you use a transplant early versus late, is there a survival benefit? That clearly is an open question and our data from our French colleagues did not give us guidance there yet as importantly there were competing causes of mortality in the French analysis (Attal et al, 2015). On one hand, although there were a higher number of myeloma-related deaths in the delayed transplant arm (83% vs 65%), there were a higher number of toxicity-related deaths, both acute and late, in the transplant arm (16% vs 8%). Hence the overall survival was similar for both arms, at 88% at a follow-up of 3 years (Attal et al, 2015) and 83% for the non-transplant versus 80% for the transplant arm respectively at a median follow up of 4 years. Although the updated analysis was not statistically significant, of course, it's an important observation that in the transplant arm 11% of the deaths were due to secondary acute myeloid leukemia, whereas only one death (2%) was seen in the non-transplant arm (Attal et al, 2015).

Dr. Kumar:

After the SWOG study (Durie et al, 2015) results were presented, it's pretty clear between that data as well as the data from multiple European trials that a proteasome inhibitor plus immunomodulatory agent combination is the best initial therapy for these patients. Obviously some older patients may not be able to tolerate this combination and those patients can do well with lenalidomide/dexamethasone combination. I think for patients who can tolerate it, the proteasome inhibitor/immunomodulatory drug combination is the best choice. Whether it is VTD or whether it is RVD, obviously depends on the availability of the drugs and the cost involved. RVD is the only one that has shown an overall survival benefit compared with the VTD trials, where progression-free survival (PFS) is the only improvement that we have seen so far (Cavo et al, 2010). Having said that, I think VCD may still have some role in situations where cost may be a factor. If renal function is compromised, VCD could be a choice in those groups of patients as well.

Regarding the role of autologous stem cell transplant, I think what really needs to be highlighted is that despite all of these new drugs and combinations with really high efficacy, transplant still has a major role to play. I know we highlighted the increased treatment-related mortality in the transplant arm in the French IFM trial (Attal et al, 2015), but obviously there are variations in the expertise at individual centers, in terms of the total volume of patients with MM they see, and obviously that is one of the fallacies of studies that recruit patients from multiple centers. I know in most of the larger centers, the treatment-related mortality related to transplant in MM is very small. So I think that needs to be taken into consideration.

Nonetheless, I think between what the French trial showed, and what the 2 randomized trials that Dr. Palumbo conducted, it's pretty clear that stem cell transplant can still improve on that response, despite getting combinations of highly effective agents (Attal et al, 2015; Palumbo et al, 2014). Regarding the timing of transplant, I think the French trial still leaves the choice for patients to make if they are so inclined. However, as Dr. Giralt mentioned, we need to collect the stem cells ahead of time, and obviously these patients should try to get their transplant at the time of the first relapse rather than delaying it even further.

Dr. Richardson:

I do agree that the important message around timing is that patients have choices, particularly in the United States, and not least because of our highly effective salvage strategies that are available. I completely concur that early transplant versus late remains a critical question. Of course, in the US trial what remains a fundamental difference versus the French experience is the duration of maintenance therapy (Attal et al, 2015) and what we know from the MRD analyses is that maintenance really matters.

I do think that Dr. Giralt raised a very important point about new combinations building on the proteasome inhibitor, lenalidomide, dexamethasone backbone. In

other words, we have shown that RVD obviously is better than lenalidomide and dexamethasone (RD) alone, with a survival benefit as well as PFS benefit (Durie et al, 2015). I am also impressed by the KRD data (Avet-Loiseau et al, 2015). I think that they are very provocative, particularly the quality of responses over time and the absence of significant neurotoxicity. Thus I do think KRD does offer a very attractive option to patients who are looking for a minimally neurotoxic approach, but also, of course, we do recognize there are some caveats to that with the emerging understanding of the vascular toxicity seen with carfilzomib and its importance in terms of the thrombo-embolic hypertensive, pulmonary, cardiac, and renal side effects encountered. Fortunately, these are uncommon and, in the context of a serious form relatively rare.

Dr. Kumar:

I think the KRD data definitely look very promising. Unlike the transition from RD to RVD, where obviously there are preclinical data suggesting that there is synergy and it's actually a paradigm change; here we are looking at basically tweaking it further by using something that's potentially more efficacious. There are still obviously some concerns about toxicity and the impact on the quality of life; the patient has to come to the hospital twice a week to receive infusions. So I think this is the place where we really have to rely on head-to-head data from phase 3 clinical trials that are currently ongoing before we can say one versus another is definitely the way to go.

Dr. Richardson:

That's very fair, and I completely agree. In the same vein, this important question of the timing of transplant and who benefits from what, when, and the fact that clearly one size does not fit all, will also be answered by current ongoing randomized trials. So I think we've got some very exciting times ahead to further help us tailor treatment.

Dr. Giralt:

There's been dramatic progress in the treatment of patients who have myeloma. But we really think that, particularly for the transplant-eligible patients, it is essential to refer patients early on, to be able to collect enough stem cells, and whether patients opt for an early or late transplantation, a lot of it will depend on their personal factors. The preponderance of data does suggest that at least early transplant will be associated with a PFS benefit (Attal et al, 2015). The cost of treatment will also need to be incorporated into this because I think cost issues are starting to become part of the equation.

Dr. Richardson:

I think while our French colleagues have done a fabulous job of looking at MRD and assessments of MRD, another difference between the French and the US studies is that in the French study, there is no quality-of-life assessment, which we have in the US trial that is ongoing (Richardson et al, 2014). Moreover, we also have a cost analysis in the current study as well, which will hopefully be helpful (Richardson et al, 2014).

Case Study #2

Dr. Richardson:

The second case is a 68-year-old man with a history of hypertension and type 2 diabetes. He presented with progressive fatigue, night sweats, and dyspnea on exertion. This patient was evaluated by his local primary care physician and found to have a hemoglobin level of 8.3 g/dL, and a mean corpuscular volume of 101 fL.

Table 3

Panel Consensus on Controversial Topics and Issues in Newly Diagnosed MM

Question	Panel Consensus
Should MM be considered a chronic disease and is it curable in a subset of patients?	• Cautiously, yes, myeloma is curable • Can be called a chronic disease, with the use of continuous medication • 30% of patients who achieve a complete remission are still in complete remission years later (Stewart et al, 2009); this could increase with the new treatments that are getting more patients into MRD negativity • Can control disease for long periods by sequentially using different regimens • There's still a lot more to do

Table 3 (Continued)

What are some of the important prognostic factors that should be considered to help guide treatment?	• Need to put everything together • Biologic factors related to the disease, ISS staging, cytogenetics • Comorbidities and comorbidity scoring • Socioeconomic factors; access to transplant is only 30% to 40% of potential eligible patients (ASBMT registry data) • Essential to take a very good history and physical (ie, for a patient with renal failure, optimal induction may not be an immunomodulatory drug; and for a patient with neuropathy because of diabetes, we may have to avoid bortezomib and use a second-generation proteasome inhibitor) • Patients with plasma cells, leukemia, and extramedullary disease are starting to stand out
Should patients with high-risk versus low-risk features get the same induction regimen?	• Able to get a very good response in all of these groups of patients with induction regimen that include both classes of drugs • Clinical trials needed to evaluate using a regimen like KRD instead of RVD in patients with high-risk disease • Clinical trials needed to evaluate adding monoclonal antibodies to induction therapy for high-risk disease • Triplet therapy (VCD or RVD) is standard in the US at this time (vs 4 drug regimen); clinical trials needed to evaluate adding a monoclonal antibody or second generation proteasome inhibitor • Participation in clinical trials is a priority
What are the latest updates and clinical considerations for newly diagnosed MM?	• Idea of incorporating a fourth drug may be very attractive (ie, Dr. Shah's presentation on RVD plus panobinostat had quite remarkable results by cycle 4 (Shah et al, 2015) • How do we make it better? Changing the type of drug, adding more drugs, or alternating different regimens? • Results of the EVOLUTION trial and the addition of doxorubicin to RVD show that adding a conventional chemotherapeutic may have some intrinsic hazard, be it added toxicity, whereas adding novel drugs to novel drugs does appear to be somewhat more encouraging in terms of tolerability but again, trials remain relatively small in size (Kumar et al, 2012; Jakubowiak et al, 2011)
Is there an optimal induction regimen prior to autologous stem cell transplant?	• Randomized trials suggest a benefit for bortezomib/immunomodulatory combination over the bortezomib alkylator (Moreau et al, 2015) • Depends on individual patient • Triplet over a doublet is well established at this time (ie, SWOG trial of RVD vs RD; Durie et al, 2015) • Concerns about immunomodulatory drugs having a major impact on stem cell mobilization have largely been offset, particularly with advent of plerixafor • CIBMTR data showed a particular depth of response prior to transplant may not be necessary in these patients (Vij et al, 2015)
What are some of the optimal combination approaches to consider for improving induction response prior to autologous stem cell transplant?	• Excited to see what monoclonal antibodies will bring (ie, 3-drug platform combined with a monoclonal antibody; Richardson et al, 2015) • New protease inhibitor data are exciting; ixazomib is an oral agent (convenient, can give it for prolonged periods without any significant cumulative toxicity): will be well suited for older patients, shouldn't rule it out for younger patient, manageable toxicities, responses and quality of responses were remarkable

CIBMTR, Center for International Blood and Marrow Transplant Research; KRD, carfilzomib, lenalidomide, dexamethasone; MM, multiple myeloma; VCD, bortezomib, lenalidomide, dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone.

Table 4

SPEP and Bone Marrow, Treatment Course, Stem Cell Mobilization, and Harvest Approach

SPEP and Bone Marrow	
SPEP/IFE	2.8 g/dL IgA kappa M spike
Bone marrow	40% infiltration of clonal plasma cells
Imaging	
Skeletal survey	Diffuse osteopenia
Chromosomal Abnormalities	
Metaphase or FISH	None
Treatment Course	
Induction therapy	4 cycles of lenalidomide, bortezomib and dexamethasone
Best response pretransplant	Complete response
Stem Cell Mobilization and Harvest Approach	
Choices	1. Filgrastim (granulocyte colony-stimulating factors) alone 2. Cyclophosphamide and filgrastim 3. Plerixafor and filgrastim

FISH, fluorescence in situ hybridization; IFE, immunofixation electrophoresis; SPEP, serum protein electrophoresis.

With this symptomatic and profound anemia, and macrocytosis, he was referred to a hematology/oncology specialist. **Table 4** shows patient and disease characteristics, his initial treatment course, and his options for stem cell mobilization and harvest, which we will discuss next.

Dr. Giralt:

I think the data suggest that stem cells from this patient might be collected with filgrastim alone (Duhrsen et al, 1988; Weaver et al, 2000; Arora et al, 2004; Giralt et al, 2014; Duong et al, 2014). Most transplant programs are doing just-in-time plerixafor where CD34 level is monitored and if, on the fourth day of filgrastim, it is not over 5 or 10, they each have their algorithm and they'll give plerixafor that night (Smith et al, 2013; Li et al, 2011; Ferzoco et al, 2015). In places where CD34 selection or CD34 monitoring is not available, a lot of transplant programs have gone to upfront plerixafor and filgrastim (DiPersio et al, 2009).

Dr. Kumar:

My institution also has the same risk adapted approach, the just-in-time plerixafor strategy. With that approach, we use plerixafor only in approximately 50% of the patients, and the failure rate is practically 0, maybe 1% at the worst.

Dr. Giralt:

We are doing chemo-mobilization in patients who have more than 10% plasma cells. Data suggest that these are the people who have poor stem cell collections and that the chemo-mobilization actually helps them (Tuchman et al, 2015; Giralt et al, 2014; Duong et al, 2014).

Dr. Kumar:

We have been doing essentially the same thing, but not using bone marrow plasma cell percentage, but presence of circulating plasma cells. In people with significant residual disease and circulating plasma cells, we tend to use cyclophosphamide mobilization.

Dr. Richardson:

We've been more traditional and used cyclophosphamide and granulocyte colony-stimulating factor (G-CSF) because we like the additional cytoreduction that cyclophosphamide can offer. Preclinical data from a number of years ago showed that the viability of circulating tumor cells mobilized during stem cell mobilization was reduced when this was done in the context of cyclophosphamide use (Richardson et al, 2014).

Having said that, I do agree with you about plerixafor plus G-CSF, and G-CSF alone even, but we still do feel comfortable using cyclophosphamide simply because it's such a well-tolerated and potent chemotherapeutic. Generally speaking, we've seen great results when we've used it. To some extent, if there is a bit of a carryover also from the lenalidomide recommendations, which were to use cyclophosphamide to help get across any problems that one might run into with lenalidomide effects on mobilization.

Consolidation

Dr. Richardson:

Now, let's get back to the patient in our case. His mobilization and transplant approach and recovery are outlined in **Table 5,** along with maintenance therapy and consolidation considerations, which we will discuss next.

Table 5

Mobilization Strategy, and Maintenance and Consolidation Considerations

Mobilization and transplant therapy	• Mobilization w/ cyclophosphamide/G-CSF - Collects 6 x 10^6 CD34+ cells/kg • High-dose melphalan 200 mg/m^2 and ASCT • Good post-transplant recovery of bone marrow function
Approach to maintenance therapy and consolidation	• Maintenance or no maintenance? • If maintenance, what agent? Immunomodulatory agent alone or with proteasome inhibitor? • What duration of maintenance therapy? • Would we also consider consolidation? • Consolidation plus maintenance?

ASCT, autologous stem cell transplant; G-CSF, granulocyte colony-stimulating factor.

Dr. Richardson:

The question really is, in this man who's achieved a complete response, maintenance or no maintenance? If maintenance, what agent and what duration of maintenance therapy? Would we also consider consolidation and consolidation plus maintenance? Let's ask that first, consolidation or no consolidation?

Dr. Giralt:

I think the honest answer is that we don't know. The randomized trial from the Blood and Marrow Transplant Clinical Trial Networks (BMT CTN 0702) is asking the question in the context of lenalidomide maintenance, what is the role of consolidation with either a second high-dose melphalan or whether to use 4 more cycles of RVD (Blood and Marrow Transplant Clinical Trials Network, NCT01109004)? It is an important question.

The tandem question has never been answered in the context of modern treatments with a proteasome inhibitor and an immunomodulatory drug. That actually when we look at some randomized trials that were done in Europe, patients who were in countries where they received 2 transplants did better than those who received only 1, and this actually holds for people with high-risk disease (Sonneveld et al, 2012).

I think it is fair to say that in the context of lenalidomide maintenance, we are uncertain what the role of consolidation is. We all know that depth of response is important. This patient has achieved a complete remission. He actually had a complete remission prior to going to transplant. So he may be a patient for whom no maintenance would be appropriate; the group of patients before we had late maintenance lenalidomide were the ones who did the best. This is the hardest conversation I have in clinic today.

Dr. Kumar:

I completely agree. I think the role of consolidation is really hard to determine, but there's enough tangential evidence to suggest that there's a role for additional therapy, whether we use it in a short duration, more intense consolidation versus a more longer duration, less intense maintenance (McCarthy et al, 2012; Attal et al, 2012; Palumbo et al, 2014).

At the end of the day, I think it's probably the additive effect of both of these approaches.

Dr. Richardson:

I agree. We're fairly convinced by the consolidation data, by first of all Michele Cavo's study of VTD versus TD, showing that improvement in response also translated in PFS benefit comparing VTD to TD post SCT (Cavo et al, 2010). A Nordic study group showed that bortezomib consolidation resulted in an improvement in PFS (Mellqvist et al, 2013). Michel Attal and colleagues have become strong advocates of consolidation (Roussel et al, 2014). In that regard, in our prospective trial, the DETERMINATION study, we're looking at RVD for a total of 2 cycles of consolidation post-transplant followed by our maintenance (Dana-Farber Cancer Institute and Richardson, NCT01208662).

In my experience, consolidation is generally very well tolerated after transplant. The one thing to be careful about is the neurotoxicity of bortezomib in this context. Alkylating therapy can increase neurotoxicity across the whole procedure, be it cyclophosphamide or melphalan, and I would argue perhaps that

they're going to be some very interesting data about consolidation with carfilzomib in the future.

Dr. Kumar:

I think we know that carfilzomib is an effective proteasome inhibitor. I think all the new drugs probably should be considered for consolidation, especially the monoclonal antibodies. One could argue monoclonal antibodies should have a role in consolidation because that is an agent that patients would not have been exposed to up until that time. Perhaps a totally different class of drug has much more efficacy as a consolidating agent.

Dr. Richardson:

We've had experience with carfilzomib consolidation. It's been generally very well tolerated from a standpoint certainly of neurotoxicity. I have to say, though, it's not been without issues in terms of fatigue. There also have been some instances of pulmonary hypertension being seen as well as other vascular phenomena (Jakubowiak et al, 2015), but these are limited data so one has to be careful about overinterpreting the results from them.

Dr. Giralt:

We have experience with carfilzomib consolidation, particularly in patients who have suboptimal responses to induction to RVD. These are people who we then put on carfilzomib as consolidation and maintenance. As you say, for the most part it's very well tolerated. However, there is a cardiopulmonary signal that cannot be ignored there.

Dr. Kumar:

We are not using carfilzomib in the setting of consolidation, at least that's not a common practice at my institution. There may be some selected patients in whom we might end up using this approach, especially the younger ones with residual disease, but in general it's not a routine practice for us.

Dr. Richardson:

I would stress that we're only doing this in the context of clinical trials. Specifically, we've done it as part of Andre's study post-transplant with KRD (Jakubowiak et al, 2015). But, again, I've been impressed by the absence of neurotoxicity, but, just as you pointed out earlier, there are other side effect profiles that are important to bear in mind, including this vascular signal which we need to better understand.

Maintenance

Dr. Giralt:

I think the immunomodulatory alone, lenalidomide, has been established as the standard of care based on the CALGB/ECOG/BMT CTN 100104 trial, which showed a PFS difference and a survival difference in the United States (Holstein et al, 2015; NCT00114101). There are other 2 trials where lenalidomide maintenance has been used, showing a PFS difference. We do recognize that in people with high-risk disease based on cytogenetics, lenalidomide alone may not be enough, or is probably not enough. I've been very intrigued from the data that come from Emory with a double maintenance therapy with the immunomodulatory agent and the proteasome inhibitor. Likewise the data coming from the Nordic trial in which prolonged treatment with a proteasome inhibitor, bortezomib, actually reduced, abrogated the bad risk of deletion 17 (Mellqvist et al, 2013).

So I think, although we don't have data from randomized trials to help inform practice, I am routinely using a combination maintenance with bortezomib and lenalidomide for patients with high-risk disease. I'm doing it until progression, until we get a better idea of what MRD negativity means.

Dr. Kumar:

For patients with high-risk disease, our approach has been to give them bortezomib maintenance to progression. Patients with standard-risk disease, with residual disease, we always give lenalidomide-based maintenance and the ones who are in complete response or even MRD negative post-transplant, we have a discussion about the pros and cons of maintenance, and that may be one group that we may not lean as strongly toward maintenance as with other patients.

Dr. Richardson:

Our practice very much reflects Dr. Giralt's in this regard. We use lenalidomide maintenance, typically 3 weeks on, 1 week off, because the continuous dosing we sometimes find more challenging outside of a protocol, and we like to use bortezomib every 2 weeks in high-risk patients (defined by either cytogenetics and/or ISS stage or an inadequate response to initial treatment followed by residual disease post-transplantation). The tolerability profile we found with that is generally fairly good, especially with the every-2-week bortezomib and the use of subcutaneous administration.

Dr. Giralt:

Good point. There is a signal, heard anecdotally, that the syncopated lenalidomide 3 weeks on, 1 week off, not only is better tolerated, but actually may be associated with a lower risk for second primary malignancies.

What's your take on that? Because it's not the way the trials were done (McCarthy et al, 2012; Attal et al, 2012).

Dr. Richardson:

I personally think it is a very interesting point because I think that the continuous dosing does generate the real challenge of tolerance. I can tell you from the French American studies, we are seeing some important differences post-transplant. In other words, the ability to tolerate continuous dosing of lenalidomide on the non-transplant arm does appear to be easier than it is on the transplant arm in our preliminary results from the IFM DFCI 2009 study.

This is fascinating because it does suggest that post-high dose alkylation in autologous transplant, perhaps a better approach would be 3 weeks on, 1 week off. Indeed, a number of studies are now starting to look at that and I think it's a great observation, which requires further evaluation.

Dr. Kumar:

What I found is that patients tend to tolerate it better when you give it 3 weeks on, 1 week off. I agree that's not what the clinical trials have been using, but I am increasingly using that approach in the maintenance setting.

Dr. Richardson:

There are data to support this from the original O14 study in relapsed refractory MM with lenalidomide monotherapy, where we did use a 3-week-on, 1-week-off regimen as part of the continuum of treatment, and tolerability was remarkably good (Richardson et al, 2009). So it's not as if this is a "data-free zone," but I agree, the post-transplant studies have not validated this regimen per se, other than in the context of dose reduction and schedule change for toxicity.

Sergio, where do you think people are going with this syncopated schedule?

Dr. Giralt:

I think the whole issue of maintenance, particularly the duration of maintenance, is going to become the next important question that we have to address. The determination trial with both the French arm compared to the American strategy will help a lot for both our patients and our colleagues to decide whether it should be until progression or not. It will be interesting; we are preparing proposals that we now have a large subset of patients out there who are on lenalidomide maintenance. We now have 2 MRD assessment strategies: one with one next-generation sequencing and the other with multiparameter flow cytometry. We think we need to develop clinical trials looking at what the role of these MRD assessments are.

Dr. Richardson:

Table 6 describes the patient's post-transplant course.

Table 6
Post-Transplant Course

Post-transplant course	• Thrombocytopenia • Continued on lenalidomide maintenance • PFS from initial therapy: 30 months • Worsening cytopenia and lower back pain develop • MRI spine: new fracture; restaging to include bone marrow aspiration and repeat protein measurements confirm relapse (**Figure 2**)

MRI, magnetic resonance imaging; PFS, progression-free survival.

Figure 2

Magnetic resonance image (lateral view) shows new fracture.

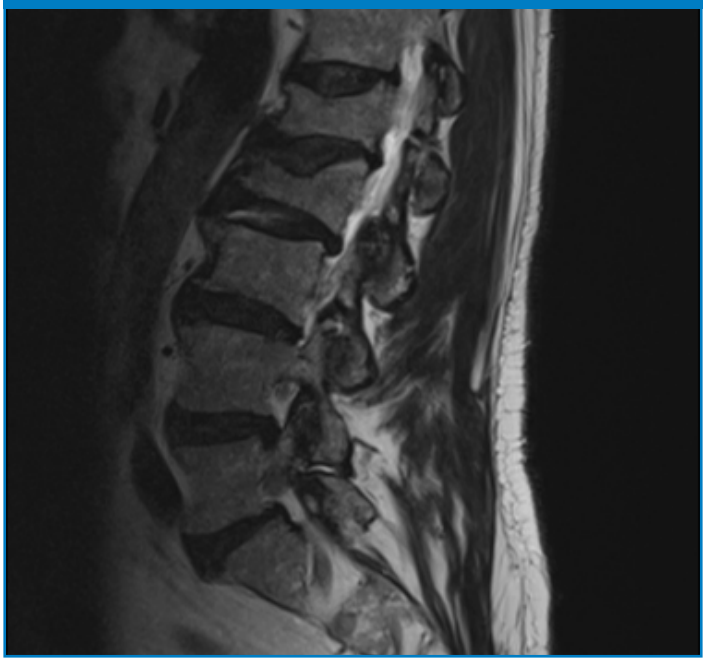


Image courtesy of Paul G. Richardson, MD.

Relapsed/Refractory Treatments

Dr. Richardson:

Table 7 describes the patient's salvage therapy options, which we will discuss next. Remember, this patient was treated with RVD followed by transplantation followed by R maintenance thus far. **Table 8** specifically reviews new agents for relapsed/refractory MM that were approved by the FDA in 2015.

Table 7
Salvage Therapy Options

Salvage therapy options	• Bortezomib + dexamethasone • Lenalidomide + bortezomib + dexamethasone • Thalidomide + dexamethasone • Pomalidomide + dexamethasone • Cyclophosphamide + bortezomib + dexamethasone • Carfilzomib + dexamethasone • Carfilzomib + lenalidomide + dexamethasone • Daratumumab • Elotuzumab + lenalidomide + dexamethasone • Clinical trial

Dr. Kumar:

There is one thing I would like to highlight in this particular patient scenario: a patient who is on lenalidomide maintenance and who experiences disease relapse 30 months after transplant—I would consider them to be relatively high risk considering the median—the clinical trials were showing 44 months with maintenance (McCarthy et al, 2012; Attal et al, 2012). Otherwise, in terms of the particular regimens for these patients, I always like to use something, some class of drugs that they are not receiving. So in my practice, the patients who are experiencing disease relapse on lenalidomide maintenance, I tend to use the VCD combination, if there is no contraindication to using bortezomib in the form of neuropathy and so forth.

The data that we have from phase 3 trials—the ASPIRE trial of KRD, and the ELOQUENT-2 trial of elotuzumab/lenalidomide/dexamethasone (Stewart et al, 2015; Lonial et al, 2015; Dimopoulos et al, 2015)—both of these trials are really not in the group of patients who are experiencing active disease relapse while on maintenance therapy. Extrapolating the data becomes a little bit more difficult. However, my second choice in

Table 8
Highlights of Recent (2015) FDA Approvals for Relapsed/Refractory MM

Drug	Trial; Author(s)	Indication	Data
Panobinostat	PANORAMA 1; San-Miguel et al, 2014	Panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with MM who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent	Median PFS 12.0 vs 8.1 mos (vs placebo plus bortezomib/dexamethasone; $P < .0001$)
Daratumumab	MMY2002 (SIRIUS); Usmani et al, 2015; Lonial et al, 2016	Daratumumab single agent for the treatment of patients with MM who have received at least 3 prior lines of therapy, including a PI and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent	Overall response rate 29.2% (PR or better)
Ixazomib	TOURMALINE-MM1; Moreau et al, 2015	Ixazomib in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least 1 prior therapy	Median PFS 20.6 vs 14.7 mos (vs lenalidomide/dexamethasone; $P = .012$) ORR 78.3% vs 71.5% ($P = 0.035$)
Elotuzumab	ELOQUENT-2; Lonial et al, 2015; Dimopoulos et al, 2015	Elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received 1-3 prior therapies	Median PFS 19.4 vs 14.9 mos (vs lenalidomide/dexamethasone; $P < .001$) Overall response rate 79% vs 66% ($P < .001$)
Carfilzomib	ASPIRE; Stewart et al, 2015	Carfilzomib in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed MM who have received 1-3 prior lines of therapy	Median PFS 26.3 vs 17.6 mos (vs lenalidomide/dexamethasone; $P = .0001$) ORR 87.1% vs 66.7% ($P = .04$)

MM, multiple myeloma; PFS, progression-free survival; PI, proteasome inhibitor; ORR, overall response rate.

this particular patient certainly would be a lenalidomide/dexamethasone-based combination, if you just go by what is available from these phase 3 trials.

Dr. Giralt:

This is an interesting population because we really don't have data from phase 3 trials to inform us. I think we would go with the basic principle that you would like to use drugs that the patient has not been exposed to already. I think a carfilzomib-based salvage with a triplet would be appropriate, for example, KRD (Stewart et al, 2015) or carfilzomib/pomalidomide/dexamethasone (Shah et al, 2015). Another option is actually the bortezomib/dexamethasone/panobinostat triplet. The randomized phase 3 PANORAMA-1 trial of patients who had 1 or 2 prior therapies showed that the combination of bortezomib/dexamethasone/panobinostat did better than bortezomib/dexamethasone in terms of median PFS (San-Miguel et al, 2014). The patient in this case has not received a proteasome inhibitor in a long time.

Obviously, the best thing is to offer these patients is clinical trials (Anderson et al, 2016), the results of which can inform not only the treatment of today, but also the treatment of tomorrow. The patient in our case scenario did have a long remission, more than 12 months from his first transplant. And many of us, based on Gordon Cook's data, would suggest that he may benefit from a second transplant (Cook et al, 2014). One of the things we're learning in every situation is that depth of response is important.

Dr. Richardson:

I agree entirely that pomalidomide and dexamethasone would be a very good treatment option for this man based upon his lenalidomide resistance and having not had an exposure to a second-generation proteasome inhibitor. In that same vein, we have very nice data from the 2015 ASH meeting on the combination of ixazomib and pomalidomide and dexamethasone in the phase 1 Alliance A061202 study, which was well tolerated and very active (Voorhees et al, 2015).

I think the other combination worth mentioning is pomalidomide, bortezomib and dexamethasone—that's the current combination under evaluation in the OPTIMISMM trial (Celgene Corporation, NCT01734928). Then finally, elotuzumab plus bortezomib and dexamethasone is not an unreasonable option based upon Dr. Palumbo's promising randomized phase 2 data presented at ASH 2015 (Palumbo et al, 2015).

Finally, I would like to point out that daratumumab may well be an antibody of choice in combination in this setting in the future (Lokhorst et al, 2015). We really don't have current data to use in the early relapse setting at this point, although intuitively we would expect it to be very effective.

Dr. Giralt:

We get a lot of calls now for people with disease that is failing on lenalidomide maintenance asking about the role of adding elotuzumab.

Dr. Kumar:

There aren't really any data backing that approach. One could argue that all the synergy that we see with elotuzumab is not really the impact of lenalidomide on the tumor cell, but actually on the immune cells. If that is the case, then that should be fine, but unfortunately it has not been tested in that population. I prefer to go

Table 9

Panel Consensus on Controversial Topics and Issues in Maintenance Therapy and Relapsed/Refractory MM

Question	Panel Consensus
What does the evidence point toward for the timing of initiation, appropriate dosing, and duration of maintenance therapy in elderly patients?	• FIRST trial as well as the data from Dr. Palumbo from last year showing the prolonged versus fixed duration of therapy showing an improvement in overall survival (Facon et al, 2013) • Keep on therapy for as long as can be tolerated; most patients cannot stay on therapy until progression
With the array of treatment options available for relapsed/refractory disease, how do we determine the best option?	• Disease may be sensitive again to drugs that have failed in the past (more than 6 mo) • New combination with a core proteasome inhibitor and an immunomodulatory agent • Continue to reuse the drugs, including transplant • Consider what kind of response they had before, how long since they last received it, and what kind of toxicities are persistent • Can revisit drug classes in combination • Ability to add agents with novel mechanisms of action, eg, a monoclonal antibody • Second transplant if adequate progression-free interval (at least 2-3 yrs, or a minimum of 18 mos; Cook et al, 2014)

with something that we know for sure has activity in that setting for somebody who is experiencing active disease relapse on lenalidomide.

Dr. Giralt:

I think in the case we're talking about, an active treatment is essential because this patient has a symptomatic relapse.

Dr. Richardson:

I would agree. And to Shaji's point, this gentleman's progressive disease should be considered a relatively higher-risk relapse because it is within 30 months, while on maintenance, and after having achieved complete remission. The other point to make is that obviously cytogenetic information on this patient's bone marrow would be helpful.

Case Study #3

Dr. Richardson:

Our final case is an 81-year-old woman who presents with bilateral hip pain and anemia and was hospitalized for pain management. Her diagnostic workup and options for therapy are described in **Table 10** and **Figure 3**.

Table 10

Diagnostic Workup and Options of Therapy

Initial Testing	
SPEP	Faint IgG lambda M protein
Serum free light chains	845 mg/L
Beta 2 microglobulin	5.8 mg/L, albumin 2.9 g/dL, LDH 280 U/L
Skeletal survey	Diffuse lytic bone lesions
Bone marrow evaluation	Hypercellular marrow, plasma cells occupy 80% of overall cellularity
Renal function	Normal
Options for Therapy	
Options	• Bortezomib and dexamethasone • Lenalidomide and dexamethasone • RVD-lite: 35-day cycle (O'Donnell et al, 2014) - Lenalidomide 15 mg days 1-21 - Bortezomib 1.3 mg/m^2 weekly SC days 1, 8, 15, and 22 - Dexamethasone 20 mg days 1, 2, 8, 9, 15, 16, 22, and 23 for patients ≤75 yr; days 1, 8, 15, 22 for patients >75 yr

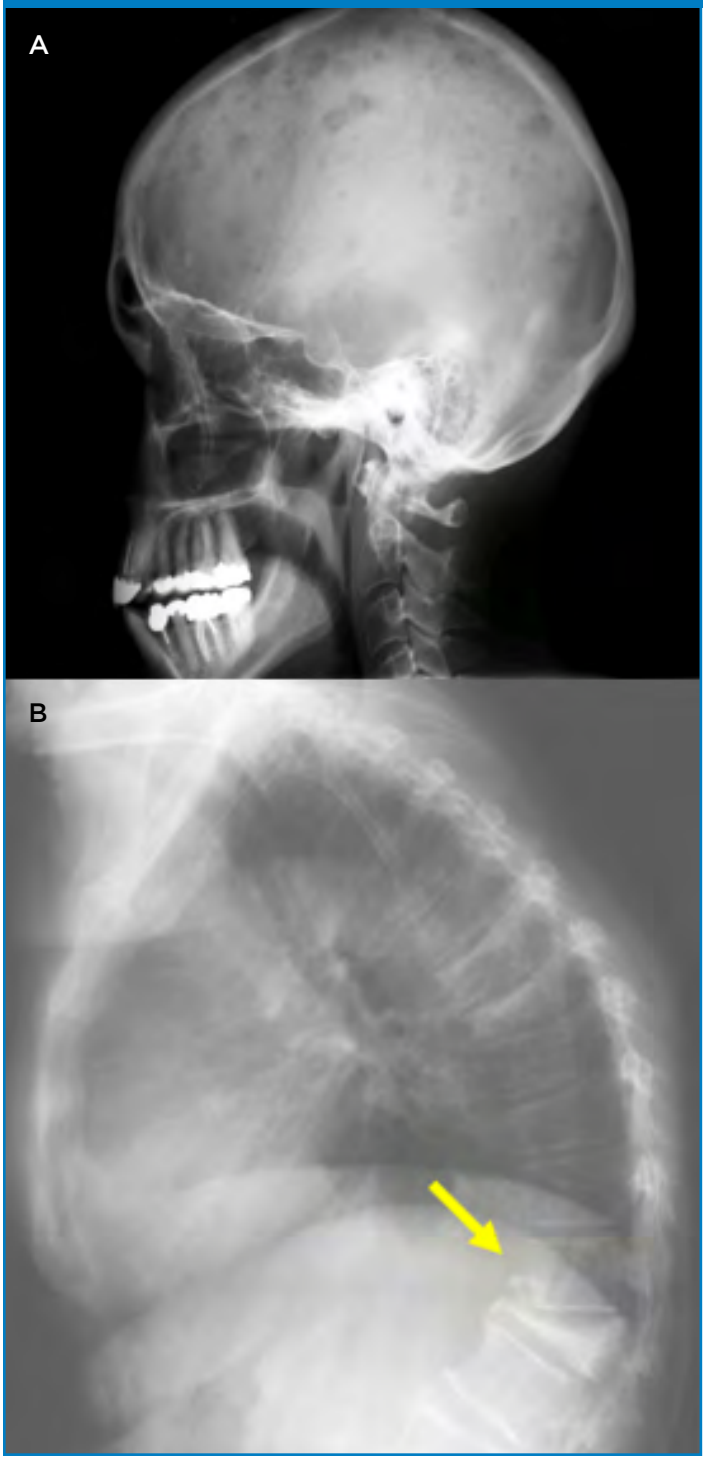
RVD, lenalidomide, bortezomib, dexamethasone.

Dr. Richardson:

There are a number of things to think about here, on protocol and off protocol.

Figure 3

(A) Skull, calvarial view. (B) Skeletal survey shows a compression fracture (arrow).



Images courtesy of Paul G. Richardson, MD.

Dr. Kumar:

We talk about the combination of proteasome inhibitor and an immunomodulatory agent as being the optimal therapy, but this is a patient who is obviously older, likely to be more frail. This is the group of patients where the data from the FIRST trial really are applicable, and I think a lenalidomide/dexamethasone combination would be a very appropriate choice (Facon et al, 2013). At the same time, I consider whether to give older classes of drugs, at reduced doses for both. So, for example, the RVD-lite approach is something that certainly should be considered, and the data from the clinical trials are certainly intriguing (O'Donnell et al, 2014).

Dr. Giralt:

This is a situation where I think if you go with the data from the FIRST trial, lenalidomide/dexamethasone plus prolonged lenalidomide would be the standard (Facon et al, 2013). But I think we're all very intrigued with the RVD-lite (O'Donnell et al, 2014). Here is where comorbidity assessment and frailty assessment are essential because you want to make sure that you can control the disease without making things worse for this older woman.

Dr. Richardson:

I agree and I think the thing that we were struck by in her case is the extent of bone disease. In this context, the RVD-lite data (led by my colleagues Jacob Laubach and Elizabeth O'Donnell) have been really very provocative with high rates of response and excellent tolerability seen (O'Donnell et al, 2014). I also wonder about the role of a drug such as ixazomib emerging in that group of patients.

Dr. Kumar:

The data with ixazomib/lenalidomide/dexamethasone is restricted to the phase 2 study at this point, but I think what was quite striking from the phase 2 trial was the tolerability of the drug (Kumar et al, 2014). Now you think, especially somebody at this age with significant back pain issues, having to come into the clinic once a week, versus being able to come back once a month, can make quite a bit of difference. I think the oral proteasome inhibitors clearly would have some advantage in this particular patient and the ixazomib/lenalidomide/dexamethasone data is certainly interesting.

Dr. Richardson:

I would agree with this as a great option for this patient, particularly if she had a cardiac and/or thrombotic history. In the absence of these worries, I wouldn't rule out carfilzomib, would you?

Dr. Giralt:

No, I would not. This is where each of these patients needs to be evaluated individually. If she has good cardiopulmonary function, carfilzomib is definitely a possibility in the event of failing primary therapy.

Dr. Richardson:

Right. Currently we would have to say that, but in the future with randomized data the highest level of evidences could guide the choices. For example, the CHAMPION study, comparing carfilzomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone, hopefully will give us insights into this. Results from the phase 1/2 CHAMPION-1 trial presented at the 2015 ASH annual meeting showed an overall response rate of 77% with once-weekly carfilzomib at a dose of 70 mg/m^2 with dexamethasone in these patients, and a generally manageable safety profile although there were at least 2 toxic deaths reported, which is a concern (Berenson et al, 2015).

SUMMARY AND FUTURE DIRECTIONS

Dr. Richardson:

So, to review, we hope we've been able to summarize the importance of stem cell transplantation in younger eligible patients. There is excitement around stem cell mobilization and the feasibility of doing this particularly with the advent of newer drugs, such as plerixafor. But critically to talk about the timing and place of transplant and the critical nature of clinical trials in assessing who benefits best from what, when.

In the immunomodulatory drug field, we've talked about lenalidomide and pomalidomide primarily, so please, let's comment briefly also on thalidomide.

Dr. Giralt:

Thalidomide is very nonmyelosuppressive, so people with very poor marrow function. Jatin Shah had a study looking at alternating thalidomide and lenalidomide and there were responses. Thalidomide can be given orally at very low doses, which is an advantage. For people who cannot tolerate lenalidomide because

of myelosuppression, I use every-other-day thalidomide maintenance. However, you cannot give it for a long time.

Dr. Richardson:

I agree. I reach for thalidomide more often than I would have thought I would, after pomalidomide and lenalidomide intolerance and/or failure, simply because I find it so helpful in the context of myelosuppression. In fact I am struck that it, in combination with other platform drugs such as carfilzomib and bortezomib, can be very useful in selected patients. I am also struck by some of the data around its partnering with even some of the newer monoclonal antibodies; for example, the French data would suggest it is very active when given with bortezomib, dexamethasone, and daratumumab (Moreau et al, 2015).

Dr. Kumar:

I think it is mainly the same setting, patients who have significant bone marrow suppression from all of the prior therapies. It is a component of the VTDPACE regimen that we sometimes use in patients with aggressive disease, as a bridge to something else more definitive. I think, though, the combination with monoclonal antibodies may have a uniqueness, especially in the patients with limited marrow reserve, allowing you to deliver 2 or 3 effective agents without causing myelosuppression.

Dr. Richardson:

In the proteasome inhibitor space, we spoke comprehensively about bortezomib. We also touched on the combinations of proteasome inhibitors with immunomodulatory agents, and the excitement around elotuzumab, daratumumab, and ixazomib.

In addition there are some very important new agents in the pipeline. Some of the most exciting are the next-generation histone deacetylase inhibitors, which appear to be better tolerated and very active, particularly ACY-1215 (Raje et al, 2015), and more recently its counterpart which is in oral tablet form, ACY-241—particularly in combination with pomalidomide where early data are very promising for both activity and tolerability (Niesvizky et al, 2015). There is also a new CD38-targeting antibody, isatuximab, which is a promising combination partner with pomalidomide and appears to be very active in a current ongoing phase 1/2 trial (Sanofi, NCT02283775).

Dr. Giralt:

I think another investigational therapy of importance is immunotherapy. I think we were all very impressed with the use of pembrolizumab with lenalidomide that was presented by Jesus San Miguel at the 2015 ASH conference (San Miguel et al, 2015). It brings a whole new and different therapeutic strategy to the treatment of MM, where we know that the immune system is so powerful.

Also, although there have only been case reports, the use of chimeric antigen receptor–modified T cells has been reported: a personalized therapy against a specific target in the malignant plasma cell. I think that is the one that's most exciting; it is actually the one being done by the US National Institutes of Health targeting B-cell maturation antigen.

I'm still skeptical about CD19 as a target for myeloma, although that data need to be seen with a larger number of patients. Now, stellar therapies have been associated with toxicities. I was impressed by how well pembrolizumab was tolerated in the context of lenalidomide/dexamethasone. I think this is where a whole new era is going to open up.

Dr. Richardson:

Checkpoint inhibition in combination with IMiDs as immunotherapy has been stunning. Interestingly, whilst we didn't see much as monotherapy, clearly in combination things are different. Specifically, when you combine with other drugs and immunomodulatory drugs in particular, the results are remarkable.

Dr. Kumar:

I think immunotherapy is definitely the biggest focus, but other small molecules, the BCL2 inhibitor, venetoclax, is pretty exciting, especially for patients with the 11-14 translocation (Kumar et al, 2015; Moreau et al, 2015). The AKT inhibitor (afuresertib) data look pretty interesting in combination with proteasome inhibitors (Spencer et al, 2014). Obviously, that is something that should be going ahead. The selinexor data so far look interesting and that's also in clinical trials (Chen et al, 2014). Then there are data with filanesib, which is a kinesin spindle protein inhibitor (Shah et al, 2015; Lonial et al, 2013). That data look pretty interesting in combination with dexamethasone.

Dr. Richardson:

I do agree and I do think the AC241 platform in combination with pomalidomide is also impressive and well tolerated with the specific targeting of HDAC6, an area of promise. I also concur that the other small molecules are opportunities that are well worth exploring and in aggregate provide our patients and us as their caregivers with exciting and increasingly hopeful treatment options for the future. ●

CLAIM CERTIFICATE

To receive acknowledgment of participation in this CME-certified activity, you must complete the evaluation and posttest.

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REFERENCES

Anderson KC, Alsina M, Atanackovic D, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®). Multiple Myeloma. Version 3.2016. ©National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed April 15, 2016.

Arora M, Burns LJ, Barker JN, et al. Randomized comparison of granulocyte colony-stimulating factor versus granulocyte-macrophage colony-stimulating factor plus intensive chemotherapy for peripheral blood stem cell mobilization and autologous transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2004;10(6):395-404.

Attal M, Lauwers-Cances V, Hilin C, et al. Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial). Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper78452.html. Accessed April 19, 2016.

Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med.* 2012;366(19):1782-1791.

Avet-Loiseau H, Ronseca R, Siegel DS, et al. Efficacy and Safety of Carfilzomib, Lenalidomide, and Dexamethasone Vs Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma Based on Cytogenetic Risk Status: Subgroup Analysis from the Phase 3 Study Aspire (NCT01080391). Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper80240.html. Accessed May 5, 2016.

Berenson J, Cartmell A, Lyons R, et al. Weekly carfilzomib with dexamethasone for patients with relapsed or refractory multiple myeloma: updated results from the phase 1/2 study Champion-1 (NCT01677858). Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper79628.html. Accessed April 19, 2016.

Blood and Marrow Transplant Clinical Trials Network. NCT01109004. Stem Cell Transplant With Lenalidomide Maintenance in Patients With Multiple Myeloma (BMT CTN 0702). https://clinicaltrials.gov/ct2/show/NCT01109004. Accessed May 5, 2016.

Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 2010;376(9758):2075-2085.

Celgene Corporation. NCT01734928. Safety and efficacy of pomalidomide, bortezomib and low-dose dexamethasone in subjects with relapsed or refractory multiple myeloma (OPTIMISMM). https://clinicaltrials.gov/ct2/show/NCT01734928. Accessed April 14, 2016.

Chen CI, Gutierrez M, Siegel DS, et al. Selinexor Demonstrates Marked Synergy with Dexamethasone (Sel-Dex) in Preclinical Models and in Patients with Heavily Pretreated Refractory Multiple Myeloma (MM). ASH 2014, abstract 4773. https://ash.confex.com/ash/2014/webprogram/Paper75658.html.

Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15(8):874-885.

Dimopoulos MA, Lonial S, White D, et al. Eloquent-2 update: a phase 3, randomized, open-label study of elotuzumab in combination with lenalidomide/dexamethasone in patients with relapsed/refractory multiple myeloma - 3-year safety and efficacy follow-up. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper79218.html. Accessed April 19, 2016.

DiPersio JF, Stadtmauer EA, Nademanee A, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood* 2009;113:5720-5726.

Duhrsen U, Villeval JL, Boyd J, et al. Effects of recombinant human granulocyte colony-stimulating factor on hematopoietic progenitor cells in cancer patients. *Blood* 1988;72(6):2074-2081.

Duong HK, Savani BN, Copelan E, et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2014;20:1262-1273.

Durie B, Hoering A, Rajkumar SV, et al. Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777. ASH 2015; abstract 25. https://ash.confex.com/ash/2015/webprogram/Paper79014.html.

Facon T, Dimopoulos MA, Dispenzieri A, et al. Initial phase 3 results of the first (frontline investigation of lenalidomide + dexamethasone versus standard thalidomide) trial (MM-020/IFM 07 01) In newly diagnosed multiple myeloma (NDMM) patients (pts) ineligible for stem cell transplantation (SCT). *Blood* 2013;122(21):2.

FDA News Release. February 23, 2015a. FDA approves Farydak for treatment of multiple myeloma. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435296.htm. Accessed April 19, 2016.

FDA News Release. November 16, 2015b. Daratumumab injection. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm472904.htm. Accessed April 19, 2016.

FDA News Release. November 20, 2015c. Ixazomib. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm473804.htm. Accessed April 19, 2016.

FDA News Release. November 30, 2015d. Elotuzumab. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm474719.htm. Accessed April 19, 2016.

FDA News Release. July 24, 2015e. Carfilzomib/Kyprolis. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm455873.htm. Accessed April 19, 2016.

Ferzoco R, Micallef I, Winters J, et al. Updated results of the Mayo Clinic risk adapted algorithm for peripheral blood stem cell mobilization utilizing G-CSF and plerixafor. *Biol Blood Marrow Transplant*. 2015;21(2):S50-S51.

Giralt S, Costa L, Schriber J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. *Biol Blood Marrow Transplant*. 2014;20:295-308.

Greenberg AJ, Vachon CM, Rajkumar SV. Disparities in the prevalence, pathogenesis and progression of monoclonal gammopathy of undetermined significance and multiple myeloma between blacks and whites. *Leukemia* 2012;26(4):609-614.

Holstein SA, Owzar K, Richardson PG, et al. Updated analysis of CALGB/ECOG/BMT CTN 100104: Lenalidomide (Len) vs. placebo (PBO) maintenance therapy after single autologous stem cell transplant (ASCT) for multiple myeloma (MM). *J Clin Oncol*. 2015;33: abstract 8523.

Huang SY, Yao M, Tang JL, et al. Epidemiology of multiple myeloma in Taiwan. *Cancer*. 2007;110(4):896-905.

Jagannath S, Richardson PG, Munshi NC. Multiple Myeloma and other Plasma Cell Dyscrasias. Cancer Management: A Multidisciplinary Approach – Medical, Surgical & Radiation Oncology. *CMP Media*;2008: 775-796.

Jakubowiak AJ, Griffith KA, Reece DE, et al. Lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone in newly diagnosed multiple myeloma: a phase 1/2 Multiple Myeloma Research Consortium trial. *Blood* 2011;118(3):535-543.

Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 2012;120(9):1801-1809.

Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood* 2012;119(19):4375-4382.

Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. *Lancet Oncol*. 2014;15(13):1503-1512.

Kumar SK, Vij R, Kaufman JL, et al. Safety and Efficacy of Venetoclax (ABT-199/GDC-0199) Monotherapy for Relapsed/Refractory Multiple Myeloma: Phase 1 Preliminary Results. ASH 2015, abstract 4219. https://ash.confex.com/ash/2015/webprogram/Paper78558.html.

Li J, Hamilton E, Vaughn L, Graiser M, Renfroe H, Lechowicz MJ, et al. Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics. *Transfusion* 2011;51:2175-2182.

Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. *New Engl J Med*. 2015;3373:1207-1219.

Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373:621-631.

Lonial S, Shah JJ, Zonder J, et al. Prolonged survival and improved response rates with ARRY-520 (filanesib) in relapsed/refractory multiple myeloma (RRMM) patients with low α-1 acid glycoprotein (AAG) levels: results from a phase 2 study. Presented at: the 2013 American Society of Hematology Annual Meeting; December 7-10, 2013; New Orleans, LA. Abstract 285.

McCarthy PL, Owzar K, Hormeister CC, et al. Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med*. 2012;366(19):1770-1781.

Mellqvist UH, Gimsing P, Hjertner O, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood* 2013;121(23):4647-4654.

Moreau P, Chanan-Khan A, Roberts AW, et al. Safety and Efficacy of Venetoclax (ABT-199/GDC-0199) in Combination with Bortezomib and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Phase 1b Results. ASH 2015, abstract 3038. https://ash.confex.com/ash/2015/webprogram/Paper81394.html.

Moreau P, Pylypenko H, Gorsicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet* 2011;12(5):431-440.

Moreau P, Hulin C, MACRO M, et al. Bortezomib, thalidomide and dexamethasone (VTD) is superior to bortezomib, cyclophosphamide and dexamethasone (VCD) prior to autologous stem cell transplantation for patients with de novo multiple myeloma. Results of the prospective IFM 2013-04 trial. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper81103.html. Accessed April 19, 2016.

Moreau P, Masszi T, Grzasko N, et al. 2015a. Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (IRd), significantly extends progression-free survival (PFS) for patients (Pts) with relapsed and/or refractory multiple myeloma (RRMM): the phase 3 Tourmaline-MM1 study (NCT01564537). Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper79829.html. Accessed April 19, 2016.

National Cancer Institute. NCT00114101. Lenalidomide in treating patients undergoing autologous stem cell transplant for multiple myeloma. https://clinicaltrials.gov/show/NCT00114101. Accessed April 15, 2016.

O'Donnell E, Laubach JP, Yee AJ, et al. A phase II study of modified lenalidomide, bortezomib, and dexamethasone (RVD lite) for transplant-ineligible patients with newly diagnosed multiple myeloma. Presented at the 56th ASH Annual Meeting and Exposition; December 6-9, 2014; San Francisco, California. https://ash.confex.com/ash/2014/webprogram/Paper68619.html. Accessed April 19, 2016.

Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. *J Clin Oncol*. 2015;33:2863-2869.

Palumbo A, Offidani M, Pegourie B, et al. Elotuzumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma: 2-year follow-up. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper79220.html. Accessed April 19, 2016.

Palumbo A, Cavallo F, Gay F, et al. Autologous Transplantation and Maintenance Therapy in Multiple Myeloma. *N Engl J Med.* 2014;371(10):895-905.

Raje NS, Bensinger W, Cole CE, et al. Ricolinostat (ACY-1215), the First Selective HDAC6 Inhibitor, Combines Safely with Pomalidomide and Dexamethasone and Shows Promising Early Results in Relapsed-and-Refractory Myeloma (ACE-MM-102 Study). Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper84847.html. Accessed May 5, 2016.

Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15:e538-e548.

Richardson P, Jagannath S, Hussein M, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. *Blood.* 2009;114(4):772-778.

Richardson P, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;116:679-686.

Richardson PG, Laubach JP, Munshi NC, et al. Early or delayed transplantation for multiple myeloma in the era of novel therapy: does one size fit all? ASH Education Book December 5, 2014 vol. 2014 no. 1; 255-261.

Richardson PG. ASH/FDA Joint Symposium on Late-Breaking Drug Approvals. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida.

Richardson PG, NCT01208662. Randomized trial of lenalidomide, bortezomib, dexamethasone vs high-dose treatment with SCT in MM patients up to age 65 (DFCI 10-106). https://clinicaltrials.gov/ct2/show/NCT01208662. Accessed April 15, 2016.

Roussel M, Lauwers-Cances V, Robillard N, et al. Front-Line Transplantation Program With Lenalidomide, Bortezomib, and Dexamethasone Combination As Induction and Consolidation Followed by Lenalidomide Maintenance in Patients With Multiple Myeloma: A Phase II Study by the Intergroupe Francophone du Myélome. *J Clin Oncol*. 2014;32(25):2712-2717.

San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. *Lancet Oncol.* 2014;15:1195-1206.

San-Miguel J, Mateos MV, Shah JJ, et al. Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): Keynote-023. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper85801.html. Accessed April 19, 2016.

Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. *Blood* 2015;126:2284-2290.

Shah J, Feng L, Thomas SK, et al. Phase 1 Study of the Novel Kinesin Spindle Protein Inhibitor Filanesib + Carfilzomib in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM). Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper82345.html. Accessed May 5, 2016.

Shah JJ, Feng L, Manasanch EE, et al. Phase I/II Trial of the Efficacy and Safety of Combination Therapy with Lenalidomide/Bortezomib/Dexamethasone (RVD) and Panobinostat in Transplant-Eligible Patients with Newly Diagnosed Multiple Myeloma. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper85061.html. Accessed May 5, 2016.

Smith VR, Popat U, Ciurea S, et al. Just-in-time rescue plerixafor in combination with chemotherapy and granulocyte-colony stimulating factor for peripheral blood progenitor cell mobilization. *Am J Hematol*. 2013;88:754-757.

Spencer A, Yoon SS, Harrison SJ, et al. The novel AKT inhibitor afuresertib shows favorable safety, pharmacokinetics, and clinical activity in multiple myeloma. *Blood.* 2014;124(14):2190-2195.

Stewart AK, Richardson PG, San-Miguel JF. How I treat multiple myeloma in younger patients. *Blood*. 2009;114(27):5436-5443.

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2015;372:142-152.

Tuchman SA, Bacon WA, Huang W, et al. Cyclophosphamide-based hematopoietic stem cell mobilization before autologous stem cell transplantation in newly diagnosed multiple myeloma. *J Clin Apher* 2015;30:176-182.

Usmani S, Weiss B, Bahlis N, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated

relapsed or refractory multiple myeloma. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper79029.html. Accessed April 19, 2016.

Vachon CM, Kyle RA, Therneau TM, et al. Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. *Blood*. 2009;114(4):785-790.

Vij R, Kumar S, Zhang MJ, et al. Impact of Pretransplant Therapy and Depth of Disease Response before Autologous Transplantation for Multiple Myeloma. *Biol Blood Marrow Transplant* 2015;21(2):335-341.

Vishnu P, Roy V, Paulsen A, Zubair AC. Efficacy and cost-benefit analysis of risk-adaptive use of plerixafor for autologous hematopoietic progenitor cell mobilization. *Transfusion* 2012;52:55-62.

Voorhees PM, Mulkey F, Hassoun H, et al: Alliance A061202, a phase I/II study of pomalidomide, dexamethasone and ixazomib versus pomalidomide and dexamethasone for patients with multiple myeloma refractory to lenalidomide and proteasome inhibitor based therapy: phase I results. Presented at the ASH 57th Annual Meeting & Exposition; December 5-8, 2015; Orlando, Florida. https://ash.confex.com/ash/2015/webprogram/Paper82846.html. Accessed April 19, 2016.

Weaver CH, Schulman KA, Wilson-Relyea B, et al. Randomized trial of filgrastim, sargramostim, or sequential sargramostim and filgrastim after myelosuppressive chemotherapy for the harvesting of peripheral-blood stem cells. *J Clin Oncol*. 2000;18(1):43-53.

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