
Multiple Myeloma Update

From the XII International Myeloma Workshop (IMW)



TRANSCRIPT

Welcome and Introduction

Anne Quinn Young, MPH

Hello everyone and welcome to the Multiple Myeloma Update from the XII International Myeloma Workshop, or IMW. My name is Anne Quinn Young and I'm program director for the Multiple Myeloma Research Foundation (MMRF).

The MMRF is pleased to provide this update to patients, caregivers, and healthcare professionals. Healthcare professionals will be interested to know that this CME activity is jointly sponsored by the Postgraduate Institute for Medicine (PIM), and AOI Communications, L.P. (AOIC).

I'd also like to thank the Celgene Corporation, Millennium Pharmaceuticals, Inc., and Centocor Ortho Biotech Inc. for their support of this activity through educational grants.

I have the distinct pleasure of speaking with key speakers and moderators here at IMW. I'd like to welcome Dr. Sundar Jagannath from St. Vincent's Comprehensive Cancer Center in New York, NY, and Dr. Sagar Lonial from the Emory Winship Cancer Institute in Atlanta, GA.

Gentlemen, thank you for joining us today.

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Upfront and Induction Therapy

Not Candidates for Transplant

Anne Quinn Young, MPH

Let's begin our discussion with a review of some of the clinical sessions that ended just a few moments ago.

Dr. Lonial, what does the current research tell us about combining agents such as bortezomib, thalidomide, and lenalidomide with therapies such as melphalan and prednisone for the elderly and other individuals who are not eligible for transplant?

Sagar Lonial, MD

Well, I think that the role of induction therapy for patients who are ineligible for transplant has really changed dramatically in the last few years. There have been a number of trials looking at the combination of thalidomide with melphalan and prednisone, two of which have shown significant improvements, not just in progression-free survival but overall survival. There are three that don't show improvements in overall survival but do show improvements in progression-free survival. So I think that the addition of a new agent to the historical standard for these patients, melphalan and prednisone, has really demonstrated significant improvements in outcomes.

The addition of bortezomib to melphalan and prednisone is another example of preclinical science suggesting that alkylators and proteasome inhibitors together are synergistic and demonstrated synergy clinically with complete response rates of 30% and also demonstrated improvements in progression-free and overall survival.

When you look at the addition of lenalidomide to melphalan and prednisone, we really have only one small study that really did that. The Italian study which has so far demonstrated encouraging preliminary data to suggest that you can improve depth of response and duration of response when compared to historical controls but the real test of that regimen is currently being done in the Eastern Cooperative Oncology Group (ECOG) with a melphalan, prednisone, and thalidomide (MPT) versus melphalan, prednisone, and lenalidomide (MPR) randomized phase III trial.

Anne Quinn Young, MPH

Are there any other ongoing trials that are attempting to answer some of these questions?

Sagar Lonial, MD

In the context of nontransplant-eligible patients, there are a number of trials looking at the addition of two novel agents such as Antonio Palumbo, MD's, bortezomib, melphalan, prednisone, and thalidomide (VMPT) regimen, or replacing melphalan with an immunomodulatory agent such as the Spanish trial looking at bortezomib, melphalan, and prednisone (VMP) versus bortezomib, thalidomide, and prednisone (VTP) to find out what is the better partner for bortezomib. Is it an immunomodulatory drug (IMiD) or is it an alkylating agent? And those trials so far I think are a little

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early, but one of the interesting things that has come out of that is the observation that if you change the bortezomib from twice weekly to once weekly, you may be able to maintain some level of efficacy but also significantly minimize the risk of neuropathy in these patients by using the weekly as opposed to the twice weekly bortezomib.

Anne Quinn Young, MPH

So, a question for both of you. What would you classify as the current standard of care or standards of care for this population?

Sagar Lonial, MD

I think the standards of care for the elderly patient population include either melphalan, prednisone plus thalidomide, melphalan, prednisone, and bortezomib, and I think one is starting to make a case given the ECOG data in patients older than the age of 65 that perhaps lenalidomide and low-dose dexamethasone may be a reasonable induction choice for patients ineligible for transplant.

Sundar Jagannath, MD

I just wanted to make a few comments on what was said just now. I believe that melphalan, prednisone with a novel agent is an excellent treatment for people who are ineligible for transplantation or over the age of 70 or 75, our elderly population, however we want to phrase it. But I have a feeling that you presented information that two studies showed survival advantage and progression-free survival advantage. Three other studies from Europe did not show the same thing, especially for survival advantage.

When I asked the actual question to Antonio Palumbo, MD, and to actually the French investigator, Philippe Moreau, MD, when he presented the information, what do you think about it? He made the point that in the other European trials, especially the Nordic trial, as well as the HOVON trial, they give melphalan at a much higher dose, and the tolerance of the drug came down in the elderly patient population and, therefore, the trial really could not show much of an advantage.

The French people have done the study carefully. In people over the age of 75, they further reduced the dose of the melphalan and the thalidomide so their dose reducer made it possible for people to tolerate to keep the quality of life of the patient, the toxicity profile down, so the patient could take the drug for a longer period of time.

Once you address the tolerance of the drugs for the elderly population and pay attention to it, then definitely adding a novel agent improves the life expectancy of these patients. So, I completely agree in what you said, that you would still say that melphalan, prednisone, plus a novel agent is the best.

One other comment, if I may say, combining lenalidomide and melphalan, especially in elderly patients, may not be the best because both of them do give myelosuppression and therefore infection complication will be higher in the elderly patient population. So if you are really talking about transplant-ineligible elderly patient population, then I would rather use lenalidomide and low-

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dose dexamethasone and not worry about combining with melphalan at all. I think there is robust data from ECOG and others to show that lenalidomide and low-dose dexamethasone has benefited elderly patients. Wouldn't you say so?

Sagar Lonial, MD

Yes, I agree.

Anne Quinn Young, MPH

Okay, so switching gears, Dr. Lonial, tell us about some of the interesting phase II and phase III trials for upfront therapy in transplant-eligible patients presented at this meeting.

Sagar Lonial, MD

Yes, I think that there are probably three standards that one can take away as potential induction regimens for patients with newly diagnosed myeloma who are eligible for high-dose therapy. And those are really trials that are based on randomized phase III trials and then there are a couple of phase IIs that I think are encouraging but need additional follow-up in larger trials.

The three standards that I think are reasonable to use are bortezomib and dexamethasone (DEX), as evidenced by the Intergroupe Francophone Du Myelomé (IFM) trial that compared bortezomib and DEX against bortezomib, Adriamycin[®] (doxorubicin), and dexamethasone (VAD) and showed an improvement in progression-free survival as well as an improvement in very good partial remission (VGPR) or better before and after high-dose therapy.

The other standard I think is VTD, bortezomib with thalidomide and dexamethasone, which has been evaluated by the Italian group and shown to be superior to thalidomide and dexamethasone, again with respect to response rates before and after high-dose therapy and has also translated into an improvement in progression-free survival.

And the third I think is lenalidomide and dexamethasone which, again, is based in sort of an indirect way on the ECOG trial which did not look at taking direct, specifically taking patients to transplant as the two European trials did, but I think certainly can make a case that you get deep remissions and that based on the ECOG patients who received four cycles of induction and then went on to transplant, the three-year overall survival for that group is over 90%. So, I think that that would be a third potential standard that one could consider using.

I think that in the phase II settings there are a number of three- and four-drug combinations that have also shown some very encouraging data. The combination of cyclophosphamide with lenalidomide and DEX from the Mayo Clinic is certainly interesting. They did have some problems with myelosuppression and stem cell mobilization, so I think we need more data there.

The combination of bortezomib with lenalidomide and dexamethasone that Paul Richardson, MD, has presented, that both Dr. Jagannath and I participated in with him, is certainly, I think, one of the most encouraging early regimens, and is now being tested as the experimental arm in two large

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US cooperative group trials, the ECOG upfront trial of bortezomib, lenalidomide, and dexamethasone (VRD) versus bortezomib and dexamethasone (VD) and the Southwest Oncology Group (SWOG) upfront trial of VRD versus lenalidomide and dexamethasone (RD). So, I think we'll have more data about the three-drug combination, and there is now a four-drug combination of cyclophosphamide, bortezomib, lenalidomide, and dexamethasone (CVRD). The addition of cyclophosphamide to bortezomib, lenalidomide, and dexamethasone that also was presented by Shaji Kumar, MD, and, I think, looks very encouraging but needs further follow-up.

Anne Quinn Young, MPH

So, this is a large international meeting with quite a few phase III studies being presented from groups abroad. How does practice differ here in the United States (US) versus, say, in Europe?

Sundar Jagannath, MD

Well, in Europe the clinical trials are, I believe, easier to conduct, especially phase III clinical trials. So, they are asking all these very important questions. But, at the same time, outside of the clinical trial, the practice in the community is challenging even in Europe. From talking to people from Spain, I gathered that still quite a number of patients are getting melphalan and prednisone for newly diagnosed myeloma patients.

When the same question was asked in the meeting to the French investigator, Philippe Moreau, MD, so what is the best treatment you give is MPT or melphalan, prednisone, and bortezomib (MPV)? He said, unfortunately, a third of the patients in the French trial are just receiving melphalan and prednisone at this time. So, for him, the first step is to make sure melphalan, prednisone with the novel agent is important. So, the access to the drugs, and the cost of the drugs, are still having an impact how it is being practiced in the community.

But that doesn't say that the questions are important and they need to be answered. And, as Dr. Lonial just said, there are a lot of questions being asked right now. So now the question comes, if I'm the patient who is newly diagnosed with myeloma, and I go to a center that the physician decides to give me a two-drug combination, let us say lenalidomide and low-dose dexamethasone, and then the patient goes into the Internet and finds out there is a three-drug combination, Velcade® (bortezomib), Revlimid® (lenalidomide), and dexamethasone, and maybe the lenalidomide, dexamethasone is not the best treatment they are giving. That is not at all true. I think lenalidomide, low-dose dexamethasone two-drug combination is also very good and these studies have to be done by combining bortezomib, lenalidomide, and dexamethasone whether the outcomes are better, especially long-term outcome are better, because the patient who got lenalidomide and dexamethasone say if their cancer comes back, they can get the bortezomib and dexamethasone afterwards, and their ultimate survival outcome could be the same.

So, clinical trials are asking specific questions to move the field forward. I would recommend that the patients in the United States, they should also be encouraged to participate in clinical trials because under clinical trials the patients are monitored closely, they actually get better medical care, and this also advances the field and we would not know the answer unless clinical trials are

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completed. But, at the same time, if they are with a community oncologist and the oncologist offers this therapy, they should not feel like somehow they are not necessarily getting the best therapy.

So, most important is the fact that these new drugs, especially in the United States, are available to patients. All of them are available widely. You know, we are fortunate in that even if you cross the border to Canada you won't have access to lenalidomide or bortezomib. So in the United States you have access to all the novel drugs plus new drugs are being developed in this country, so patients, whether they are in Missouri or whether they are in New York, everybody's life expectancy has been improved in this country. So, I just want to give that but I'm more than happy to share what are the questions we are asking and what are the exchanges, the investigators who are all gathered together in this symposium are ideas that are being exchanged. But I don't want to leave a message that the patients have to become extraordinarily careful whether they will get the right therapy or wrong therapy.

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Cure or Disease Control

Anne Quinn Young, MPH

Well, you mention a lot of questions are being asked and discussed here. One seems to be this issue of cure versus control. What are each of your thoughts on that?

Sundar Jagannath, MD

Well, you know, the first statement is all of us taking care of cancer patients, you know, as a physician caring for patients, I want to be able to cure my patients. I want my patients to come ten years from now and give me a hug. There is absolutely nothing more rewarding for a physician than the fact that we want a cure. So that is paramount and every physician is looking for a cure.

Okay, having said that, let's look at the history of myeloma. So, we had initially dexamethasone or prednisone, the glucocorticoids, then we have alkylating agents, either melphalan or cyclophosphamide. And the third drug was perhaps with a little bit of activity was anthracycline, Adriamycin.

So, between 1960 to 1990, it didn't matter how we combined these drugs, you know, even if you combined all these drugs and got a little higher response but once the cancer came back, you had to fall back to the same drug so, ultimately, the survival did not improve between 1960 to 1990.

Then in a small group of patients or younger patients who could tolerate high-dose therapy and stem cell transplant, giving melphalan at a high dose one time turned out to be superior rather than giving melphalan in small amounts over a period of a year or longer. So, high-dose therapy, giving melphalan in high dose at one time, turned out to be superior and people who can tolerate that treatment, they lived longer.

So, now since 1998, thalidomide was introduced, then bortezomib or Velcade was approved, and then lenalidomide came into the market; so these have all improved the life expectancy of the patient.

So, now let me put it that the difference between those who think about control versus those who think about cure, this is the paradigm difference. It all depends upon how you look at the work. If you're suddenly stuck and there is no more new drugs that are coming, and these are the only drugs you have, lenalidomide and thalidomide, the immunomodulatory molecule, the proteasome inhibitors. These are the two other compounds that are added to the alkylating agent and steroid. Then whether you combine them all upfront or you give them sequentially, the ultimate outcome will be the same, as long as you have the drug access.

But if we give them all earlier on, and within two years new drug comes in, and another two drugs more new drugs come in, then perhaps it will be changing and eventually, within the next five to ten years, we will have a cure. So, the question is, are we curing myeloma patients now? There is a small subgroup of patients being cured as we speak because we consistently have people beyond ten years now. It is amazing, even in community practice, the community oncologists, sending me

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patients from Long Island, Staten Island, and Connecticut. The physicians, when they call me, they say, “I have this patient who is now ten years out with myeloma. When I started with her in the practice, I thought she wouldn’t make it to three years or something like that.”

So, everywhere patients are living longer, and a small subset of them have no activity of myeloma and in some of them there is still some protein so technically we can’t say they are cured, but operationally they are cured because their life is going on as if there is no cancer because a small amount of protein is not affecting them.

So, I think the information when the clinical researchers, when they discuss this, they are trying to come up with how to distinguish and how to come up with a goal and how to design clinical trials and hardened facts so we can do clinical research and make progress, and we don’t want soft facts. But, at the bedside, it is a totally different picture. That’s my take home message, but I will listen to you since you argued this point.

Sagar Lonial, MD

Well, I don’t know that the two goals are necessarily at odds with each other. I think that ultimately we do want control of the disease. I look at it from the standpoint of combining agents together that are not additive. I think when you combine steroid with an alkylator, that’s additive. And so, if all you have is different combinations of alkylators, then there is no benefit, and we’ve shown that multiple times, to putting them together at one time versus giving them sequentially over time.

I think when you have drugs like bortezomib and lenalidomide, that I think are synergistic when you put them together, you have drugs like melphalan and bortezomib or cyclophosphamide and lenalidomide. Those drugs, when you put them together, are not additive, they’re synergistic together. And if you sequence them you lose that synergy. You don’t get the depth of response. You don’t necessarily get the ability to perhaps supersede the development of immediate resistant clones, and a lot of that’s theoretical data.

So, do I think that we should go for the cure? I think in the context of appropriately designed clinical trials, yes, I think depth of response is important. In the induction setting, we’re now not just looking at immunofixation negative complete remission (CR). We’re now looking at immunophenotype complete remission as defined by the Spanish, or even molecular completed remission. Those are things we couldn’t even do ten years ago, even five years ago.

So, I think in order to try and drive the level of residual disease lower and lower, these are the kinds of measures we have to do, and I will strive to do that when it’s appropriate in the right clinical setting.

Sundar Jagannath, MD

I just actually, as you were speaking, it suddenly occurred to me, one of the most important observations that I came to know, coming to this meeting, was the fact that there are two groups of clinicians who have made the note. W. Michael Kuehl, MD, presented, I think, the Veteran’s data, the Army data, where the serum is stored for people who are on active duty for years together and

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when some of them develop myeloma, they now went back and started checking two years, four years, six years, eight years ago, what the serum was stored, where there was any evidence of myeloma. And to their surprise, every patient who had myeloma, over 80% of them or 90% of them, I'm told, they were able to detect that they actually had the protein six years and eight years ago. So, this is a completely new concept for me because we used to say, there were patients who were monoclonal gammopathy of unknown significance (MGUS), a small group who went on to develop myeloma and, actually, we used to say from Arkansas, when we were there, we used to say, "Those patients may not achieve complete remission and they would live very long, and gene array, those who looked like MGUS or those who looked like smoldering myeloma, their outcome is much better. But, now we come to know almost every myeloma patient actually was MGUS years before, so they all had a phase of MGUS and a phase of smoldering myeloma.

And this is where myeloma is different from other cancers. Leukemia, either you're in complete remission or you die from cancer. If you go to non-Hodgkin lymphoma, either you're in complete remission or you die from your cancer. So, in those diseases, you have to aim for complete remission is equivalent to cure and therefore, in myeloma, complete remission is not equivalent to cure. Patients could have achieved complete remission, could have had the high-risk genetic features you said, t(4;14), you know, t(14;16), and then they would relapse and they could die shortly. And another patient who does not have this high-risk feature and does not achieve complete remission has still the paraprotein or maybe even not very good partial remission that you're aiming for, and that patient may come and see you ten years from now. And that is very important and unique to multiple myeloma, and that should be kept in mind.

But, having said that, it may come to pass that we may understand precisely how MGUS and smoldering myeloma happen and we may find the right drugs and suddenly all these plasma cell clones could be eliminated. And, in that case, you know, we can say we can cure the cancer. But, at this time, patients with myeloma have to understand that complete remission, and if you're not in complete remission, very good partial remission, you're not going to do well, is not a correct statement. Yet, the clinical investigators, when they are developing new drugs, they have to have clear-cut goals what their protocol is; are they making progress? So, we are looking at this information, but, as a patient, I would rather be alive at ten years, even if I have some protein in my blood, so I'm not in complete remission. That's not my goal. My quality of life is good and I'm playing golf and I'm alive ten years, I'm more than happy than achieving this complete remission today and I'm dead in three years.

Anne Quinn Young, MPH

Dr. Lonial, do you share the same perspective on achieving a CR?

Sagar Lonial, MD

You know, I think the way I would think about it is that the first goal is to get to a CR and then the second goal is to try and maintain that CR. And that's where I think the risk stratification comes in. I think that you can get high-risk and low-risk patients into CR. Low risk they probably will stay in CR for a longer time unmaintained, whereas high risk probably won't, and those patients I think do need aggressive maintenance therapy.

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I think the other analogy to make, if you want to refer to another disease as a paradigm, is not just the acute leukemia but chronic leukemia, CLL. We know that the best regimen for CLL in patients who can tolerate it is the combination of FCR plus, (fludarabine, Cytosan[®], and rituximab). You would never consider giving them each of those drugs individually and sequentially. You put them together because you get a great overall response. And, in CLL, patients that achieve a molecular remission stay in remission longer than patients who don't.

Now, is that a surrogate for disease biology? Maybe. But depth of remission, even in a disease like CLL that you can't cure does eventually correlate with good outcomes. And I think we just have the difference in myeloma is that we need to understand how cytogenetics and risk plays into what you do once people get to a CR.

Upfront and Induction Therapy

Candidates for Transplant

Anne Quinn Young, MPH

The one area we really haven't discussed is stem cell transplant. What are the data presented here telling us about the role and timing of stem cell transplant?

Sundar Jagannath, MD

That's an excellent question. That is evolving in the field. That is good news because as we get more and more drugs which are more effective and you don't have to give melphalan in high dose in order to accomplish the goal, so much the better. Right now, why we give high-dose melphalan, because we have shown that high-dose melphalan consistently from 1990s onward increased the depth of response and, therefore, the patients have durable response without any maintenance therapy and their life expectancy is improved, so we have improved the quality of life of the patient and life expectancy. So, high-dose therapy has played an important role from 1990s onward.

Now, we learn that with these newer drugs, we are able to get more and more patients into so-called complete remission and very good partial remission. Dr. Sagar Lonial seems to be partial to, you know, so that is always good. But the question comes down to me is that when you take these novel agents like bortezomib and dexamethasone or bortezomib, thalidomide, dexamethasone, and you bring the cancer down as low as possible, then you follow it up with the high-dose therapy and stem cell transplant. Again, the investigators who believe in transplant and doing it early and consistently, they showed that more of the patients have actually very good partial remission and, complete remission, and they have a very good outcome.

So transplant still delivers what it's supposed to do, bring patients' disease under control and give a period of time of unmaintained remission. So, I think it consistently still does what it did in 1990, it's still doing it now. But the only philosophical difference that is coming in is that if we give lenalidomide and low-dose dexamethasone and the patients are alive at three years, not disease free, alive at three years, because the disease-free survival is still one year, about 26 months we would say, 26 months, 27 months, something like that. So the cancer is coming back and they need more therapy. So, the patients who are going through transplant are not going through transplant simply because they are looking at three year outcome is so good, why don't I delay the transplant. If the cancer comes back, I can have it later on. And there was a study, one study from Jean-Paul Fermand, MD, saying that early versus late transplant was no different. Some people use that as a reason to delay transplantation.

My personal bias, if you are going to use high-dose therapy and stem cell transplant, if you have collected stem cells, etc, and that is a goal for you. I think doing it as immediate induction with one of these wonderful combinations Dr. Sagar Lonial talked about either VTD or bortezomib, thalidomide, dexamethasone, or bortezomib, dexamethasone, whatever he chooses to offer them, followed up with a transplantation and perhaps a short period of maintenance therapy will give the maximum bang for the buck at this time.

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If you are not totally interested in transplant at all, you have an option not to go through transplantation, sure. Or, if you are someone you want to have the stem cell collected and not go through it, you can consider that, but I would not necessarily say if you really are someone who likes transplantation to offer you long durable remission. It is better to give transplant upfront rather than in a relapse situation. That's my recommendation.

Sagar Lonial, MD

Yes, I think we're never going to be able to understand whether transplant adds to an already achieved complete remission, unless we start to, at least from time to time, ask the question of how durable are these remissions without a transplant. And, so, given the data from Dr. Fermand, that says early versus delayed or equivalent, we have been collecting cells on everybody and I think this is really the key piece here is that patients are referred to the transplant centers within the first four cycles of their induction therapy to have the discussion about transplant and have stem cells mobilized. But we are offering patients who achieve a complete remission with induction the opportunity to collect and store those cells and then transplant them later on down the road.

I think that does not mean that you can stop therapy after four cycles. Patients do have to continue with ongoing therapy and then maintenance therapy. And I agree, you don't want to transplant people in the context of florid relapse, but if you're watching them every month and you start to see the protein recur, then that's a point where you don't necessarily have to reinduce them and can take them to immediate transplant. But I think the young patients should have cells collected early on and the same discussion that Dr. Jagannath mentioned I think is an important one to have with them.

Sundar Jagannath, MD

But when you say that one thing has to be, if you don't want transplant upfront but at the first sign of relapse you're going to go for transplant, then the transplant should be done, not again a newer drug, you know, salvage now with bortezomib or something like that.

Sagar Lonial, MD

Agreed.

Sundar Jagannath, MD

Because once you have multiple relapses, then high-dose melphalan will not give you much time. At that time, exactly what you don't like about transplant is to go through high-dose therapy and its possible side effects and the remission lasts less than a year. Then that would not be a good outcome at all. Whereas, if you have the same transplantation upfront, the median duration of remission now is pushed on to five years and seven years, so it makes a big difference.

Novel Agents for Relapsed/Refractory Disease

Anne Quinn Young, MPH

Switching gears to relapsed/refractory disease. There are a number of abstracts presented here, either oral presentations or posters, looking at some novel agents by themselves or in combination with agents like lenalidomide and bortezomib. Can you talk to us a little bit about some of these novel drugs, carfilzomib, panobinostat, elotuzumab, vorinostat, perifosine, and the list goes on and on.

Sundar Jagannath, MD

That is the best and optimistic view. I mean, that is the excitement in the field why we have all these meetings and everybody comes to attend the myeloma meeting just to learn something about the next drug in the pipeline, you know, why we are all interested in how to put together an alphabet soup bortezomib, thalidomide, dexamethasone, bortezomib, lenalidomide, dexamethasone, or something like that. The most important information for patients is that what are the new drugs which are going to be there in the next couple of years, so in case the currently effective drug wouldn't work for me, what can I expect? That's very important for the patients. And that's what is most important for physicians like me to come to this meeting to look at what else is coming on.

So, let's see what else is coming on and I would have my colleague here to chip in too. So carfilzomib is a new proteasome inhibitor and it has been shown to be effective, and that is what is very exciting, that we have a new proteasome inhibitor which in phase I clinical trial has shown activity, and now it is going through phase II clinical trial.

Now, in the phase II clinical trial, it is being tried in patients who have already failed all drugs including bortezomib, including lenalidomide, including thalidomide, including transplant, whom we feel like at this time they really need a new drug and we are trying to see whether carfilzomib will fulfill that particular role in that group of patients.

Then we are also doing a study where we are doing carfilzomib before the patients have had an opportunity to have bortezomib at this time to see whether if they got carfilzomib instead of bortezomib, whether they would do better.

One thing that is coming out of this information is carfilzomib is effective. Carfilzomib is beneficial to the patients who have already failed bortezomib, so that is very encouraging. And carfilzomib is quite active but the number of patients accrued is small so I cannot really say at this time it is going to be better than bortezomib or not yet, but the early results are encouraging that perhaps it could be. But the most important excitement for physicians in this area, at least for me, was that there was no peripheral neuropathy or painful peripheral neuropathy encountered among the patients between all these clinical trials treated so far. So, we really can look forward to a new drug, proteasome inhibitor, which is active. If it's at least as active as bortezomib and yet does not cause painful peripheral neuropathy, to me, that is an advancement, so that's number one. And, if it would do a little better, then so be it. That'll be even better for us.

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Now the second thing we talk about is a number of monoclonal antibodies are in clinical trials at this time. For instance, in lymphoma we know now that using CHOP chemotherapy, which is a four-drug combination: Cytoxan[®], Adriamycin, vincristine, prednisone, which has been around from the '70s, as soon as a new monoclonal antibody called Rituxan[®] (rituximab) was added, then all these patients did very well. And the monoclonal antibodies typically do not have much of a side effect to speak of, so that's why we really wanted to have a monoclonal antibody for myeloma. So, there are several monoclonal antibodies in clinical trials; one of them is elotuzumab and you may want to say a few words about that.

Sagar Lonial, MD

So, elotuzumab is a CS-1 antibody which is a protein on the surface of most plasma cells that has been tested in single agent phase I trials and there are two trials that are reported on at this meeting. One combining with bortezomib, again based on preclinical data from the Dana-Farber Cancer Institute, suggesting that a proteasome inhibitor in combination with elotuzumab resulted in synergistic myeloma cell death and they've seen some very encouraging responses in that early phase I trial.

There was also a second phase I trial presented combining elotuzumab with lenalidomide and low-dose dexamethasone, also which shows very encouraging data. And the concept of combining an IMiD like lenalidomide with an antibody that is mediated by natural killer (NK) cell activity is very, very interesting and exciting because not only are you getting the antimyeloma effects of lenalidomide, but you're also getting the immune-enhancing effects of lenalidomide, which may make the antibody better. And so we're very excited about this combination and there are a number of patients that will be reported on at American Society of Clinical Oncology (ASCO) as well.

Sundar Jagannath, MD

There is also another antibody agonist CD138. This is, you know, when a patient with myeloma is diagnosed after the bone marrow biopsy, is seen by the pathologist, when they want to count the number of plasma cells in the bone marrow, they use the antibody agonist CD138. So now they have attached this monoclonal antibody CD138 with a poison and they are doing this clinical trial. Do you want to comment on that?

Sagar Lonial, MD

Yes, I think, you know, one of the reasons why antibody-based therapy in myeloma has probably not been as effective as it has in lymphoma and other diseases, is that you may not have a normal effector immune system in patients with myeloma. And so the CD138 antibody in this trial that you're referring to has chemotherapy attached to it. And so it, in a way, gets around that idea of requiring immune activation for the antibody to be effective. It essentially delivers its own target once it hits 138. And this is an antibody again that's in very early phase I development but I think we're all optimistic that it will have some activity.

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Anne Quinn Young, MPH

There seems to be some excitement around the histone deacetylase inhibitor (HDAC) inhibitors as well. Can you comment on those?

Sundar Jagannath, MD

Yes. HDAC inhibitors, there are several of them which are in clinical trials. One is called LBH.

Sagar Lonial, MD

589, panobinostat (LBH 589).

Sundar Jagannath, MD

Panobinostat LBH. And this is now in a clinical trial in combination with bortezomib and this was presented by Orhan Sezer, MD, from Germany, and there was another in clinical trial in which we are involved, in which it is combined with lenalidomide. The preclinical data, that means in the lab, the two together seemingly, works very well. Now that is what has spawned these clinical trials. One of them, as I told you, with panobinostat in combination with bortezomib and in combination with lenalidomide. And another one is vorinostat. Vorinostat is a drug which is already approved for another indication for the treatment of another type of blood cancer, and that one in combination with bortezomib is going through a phase III clinical trial. This is a large international trial to see whether combining with bortezomib is superior than using bortezomib alone. So, that's a large ongoing trial. What would you think about these trials?

Sagar Lonial, MD

Yes. I think that the laboratory data suggests that blockade of both proteasome function with bortezomib and aggresome function which occurs through the HDAC inhibitors is a very synergistic method by which you can kill plasma cells. I can tell you that a project that we've had in the lab that's been supported by the MMRF is a combination of tipifarnib with bortezomib that also seems to do almost the same thing and in the laboratory is very potent and, actually, in clinical experience has been very potent as well. So, I'm actually very optimistic that the HDAC bortezomib or the HDAC lenalidomide combinations will be very positive. We've all treated patients in some of these trials and have seen some very encouraging responses. Obviously, we need a larger patient population, both in bortezomib sensitive and resistant, to really get a handle for what this can do, but I've been really struck by at least by limited experiences with these combinations. And there is a third HDAC that's been studied in Australia by H. Miles Prince, MD, MDRACNA, FRACP, FRCPA, and his group, romidepsin, that's also been combined with bortezomib, and I think they've actually seen responses as well in patients with bortezomib-resistant disease.

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Anne Quinn Young, MPH

So, we talked about a second-generation proteasome inhibitor. Are there others, and are there other upcoming IMiDs as well?

Sundar Jagannath, MD

Yes. I think there is a new IMiD compound called pomalidomide. This drug has been shown to be effective in a phase II clinical trial. The results were presented both in the American Society of Hematology (ASH) Annual Meeting as well as in this meeting from the Mayo Clinic investigators. Martha Lacy, MD, presented the data.

What was exciting is that they had a number of patients who had been already previously treated with thalidomide or lenalidomide and then subsequently, when the patients' disease came back, when they treated them with pomalidomide, they showed good response, almost to the tune of 60% of the patients responded to this drug, which is very, very amazing to me. So this is really promising that we have a new proteasome inhibitor, carfilzomib, marching along the pipeline, and we have a new immunomodulatory molecule marching along the line, and I would anticipate both these drugs will eventually get approved. So, if patients are wondering what would happen two years from now or three years from now, we could honestly say they'll be at least one proteasome inhibitor new drug and one immunomodulatory molecule in the pipeline is likely to be approved by that time, should your cancer come back, and you could expect that that would be able to control your cancer back. That's the real excitement about it in addition to the number of combinations with these drugs which are also marching through the pipeline.

The other combinations with bortezomib, you know, I would like to say bortezomib is a good platform drug. That means you can use this drug in combination with many other drugs so it really synergizes or works well with them in an additive fashion. And one of the combinations which has shown to probably have a synergy is when bortezomib is combined with a heat shock protein drug.

Sagar Lonial, MD

Tanespimycin.

Sundar Jagannath, MD

So, would you want to comment? What I heard Paul Richardson, MD, and the Dana-Farber Cancer Institute information was there were two advantages. One is it may have increased activity but number two is neuropathy may be down.

Sagar Lonial, MD

Yes. I think there were a couple of things that were anticipated in the phase I trial. The first is that, again, the laboratory suggested that a resistance mechanism for bortezomib is activation of the stress response and heat shock proteins. And by using a heat shock protein inhibitor like tanespimycin, you may block that stress response and induce apoptosis in myeloma cells.

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I think that in the phase I experience that that was borne out. We did see very – I certainly, personally, took care of a couple of bortezomib-resistant patients that responded to the combination of tanespimycin with bortezomib.

I think the second unexpected finding was that the incidence of Grade 3/Grade 4 peripheral neuropathy was actually lower in that trial and there were about 58 patients I think that were treated on that study, so it was a reasonably sized trial. And that actually, it turns out, may be again as a result of the HSP blockade where stress to the nerve may be part of the response that results in peripheral neuropathy. So that was an unexpected finding.

The Akt inhibitor perifosine is a drug that we've worked with in the laboratory as well and has been looked at in combination with both lenalidomide and dexamethasone. That was reported at this meeting by Andrzej Jakubowiak, MD, PhD, and was also reported on at ASH and at this meeting as well combined with bortezomib. Again, with the idea that bortezomib activates Akt signaling and if you use an Akt inhibitor like perifosine you may be able to block that.

Now the response rates in that trial were somewhat modest but what I think was most striking about the follow-up on that trial, as Paul Richardson, MD, has presented, is that in the cohort of patients with bortezomib-refractory disease, their median time-to-progression on perifosine, bortezomib, and dexamethasone was six months. And you would not have expected that, given that bortezomib is part of that combination, if there weren't some activity for the triplet together. So, that I think is interesting and is being tested in a randomized phase III trial; bortezomib, dexamethasone versus bortezomib, perifosine, and dexamethasone.

Sundar Jagannath, MD

Would you comment on something which I thought was interesting, understanding of the peripheral neuropathy from bortezomib and its potential effect on the ganglion? Do you want to say anything about that? Will it mean in the future we will have less peripheral neuropathy giving weekly bortezomib versus twice weekly?

Sagar Lonial, MD

Yes. I think there is some animal, and now clinical data as well, suggesting that a by product of proteasome inhibition is the accumulation of these granules or vacuoles within the dorsal root ganglion that contribute to the development of peripheral neuropathy. In preclinical models there is suggestion that the addition of an HDAC inhibitor may mitigate that to a certain extent. Again, there are data suggesting that HSP90 inhibitors may mitigate that to a certain extent.

I think, in my mind, the best way to prevent peripheral neuropathy outside of those approaches is to never let it develop. And that means very prudent attention to patients when they come in for each dose of bortezomib, whether it's day four or day eight or day eleven, the nurses should be asking patients about their neuropathy to decide whether or not that dose is delivered on that day. And, if so, then making dose modifications or perhaps going to weekly schedule as indicated by the Italian and the Spanish studies that may lessen the incidence of severe peripheral neuropathy.

Symptom Management Strategies

Anne Quinn Young, MPH

So, on that theme, there was a symposium this morning, as well as some abstracts, focused on symptom management, bone disease, bisphosphonates, balloon kyphoplasty, as well as strategies to manage toxicities. Could you talk a little bit about some of the data presented here on those topics?

Sundar Jagannath, MD

Well, I had the pleasure of presenting the data on prevention of thrombosis or deep vein thrombosis and pulmonary embolism. There has been a study looking at large population of veterans; we are talking about four million veterans who were looked at. And it was clear that as they were transplanted getting older there was an increased incidence of blood clots in their legs, deep vein thrombosis, especially the patients who had to be admitted to the Veteran's Affairs (VA) system at least once, they had a higher incidence of deep vein thrombosis.

But then there were a subgroup of patients who had developed multiple myeloma or MGUS or monoclonal gammopathy of unknown significance. They found that their incidence of deep vein thrombosis was much higher than the regular population of veterans who did not have that particular condition. So, it is clear that the patients with multiple myeloma have a greater tendency to develop blood clots anyway.

This was never really a problem when we were using melphalan, prednisone, for instance, in the elderly patient population. The incidence of deep vein thrombosis was running around 2% to 3%, so when it happened you treated them but you didn't worry about prophylaxis, etc, because the incidence was so low. You know, 2 or 3 patients out of 100 is going to develop this complication, you're not going to treat all 100 patients with anything to prevent blood clots.

But once we started using immunomodulatory molecules like thalidomide and lenalidomide in combination with the dexamethasone or other drugs, then suddenly the incidence of deep vein thrombosis increased. So now we went from 2% to 3% suddenly to about 10% with lenalidomide or thalidomide and dexamethasone. And then if you combine it with the Adriamycin or any other drug or they had a catheter or they had a pacemaker, then it could go up to 25% to 30%. So, under those circumstances, one out of four patients may develop blood clots and it could be serious with blood clots going to the lung, etc, then we actually have to start using medication to prevent the blood clots.

So there has been a guideline which has been already published by having the expert and the field get together and the first author was Antonio Palumbo, MD. Where we said that if the patient is going to get thalidomide or lenalidomide by itself, they really don't need a prophylaxis because, again, it's very, very low. But if you're going to give thalidomide and lenalidomide with the dexamethasone, and if the dexamethasone is only once a week, then in the majority of patients you can get by, by giving an aspirin a day. It could be 81 milligrams of aspirin, the Italian's use two

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of those pills, and then in the ECOG trial they used three 25 milligram pills, one just regular adult aspirin. So you can use the aspirin and mitigate it.

But if the patient has other mitigating circumstances, if they are hospitalized, you know, if they had a hip fracture and they had to go through hip surgery or something like that, or had a rod put in and they are not really mobile very much, or they are overweight, they have diabetes, they had previous history of blood clots even before this particular thing happened, a couple of years ago, before they were diagnosed with myeloma, they had a blood clot and they were on blood thinner for a year and then they stopped it or something like that. Under those circumstances, they really have to be on a real blood thinner. It could be an oral pill, which we call as warfarin or Coumadin[®], and the dose has to be adjusted. Or if it is difficult for the patient to adjust, you know, they are just getting this drug and so many things are happening in the patient at this time, then they could be on a low molecular weight heparin, there are two drugs available at this time. Both of them are easily administered, self-administered by the patient at home. That could be used.

So this is now known to the physician so, certainly, once we knew how to use lenalidomide and dexamethasone in combination, along with these blood thinners, now the incidence of this complication has gone down quite a bit. Wouldn't you say the incidence has gone down?

Sagar Lonial, MD

Yes. I think just paying attention to the problem has probably dropped the numbers. Being more aggressive in terms of making sure patients get appropriate prophylaxis has really made a big difference.

Sundar Jagannath, MD

Because these drugs are life-saving drugs. Yes, every drug has a side effect, so this one has a greater chance for a blood clot. But nowadays we can mitigate or prevent the occurrence of blood clot and still the patient can benefit from a life-saving drug. So, I think, you know, we could not say, "Oh, it may cause a blood clot so I'm not going to take this drug." These are really life-saving drugs. It's just a matter of how to use them. Now that we know it and we know how to use it very well, I think this is good.

Sagar Lonial, MD

Yes. And, actually, I think that point is a good one because there have been a couple of analyses now that have shown even if you develop a blood clot, your survival is not significantly affected. And we've actually done a small analysis of it in our own center of 150 patients that received lenalidomide and dexamethasone and a very small percentage actually developed thrombosis. I think it was 4% developed deep vein thrombosis, and those 4% actually were on therapy longer than everybody else who didn't get a clot. So, there is no reason to say that you shouldn't be on these drugs or that you can't or that you can't gain benefit, even if you have a history of clotting.

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Sundar Jagannath, MD

Let us look at the bone disease and what new information is out there. I would say that the use of bisphosphonate, pamidronate or Aredia[®] and zoledronic acid or Zometa[®]. The guidelines that have been put out by various bodies, including ASCO guidelines out there published in *Journal of Clinical Oncology* (JCO). I think the guidelines are still valid. You treat the patients monthly for a minimum of a year or so. If the patient is already in complete remission or in very good partial remission, has gone through transplant, there is very little disease, then you can hold off and give less frequently, and at the end of two years you can make a decision whether you want to continue or you can stop the drug completely. That's the way it is left out.

If the patient has osteoporosis or other mitigating circumstances, or the disease is still active, then you can continue bisphosphonates in these patients.

If you have discontinued the bisphosphonate, if the cancer came back, when the cancer came back, you can also reinitiate the bisphosphonate back.

So, I think those guidelines are very valid and so nothing new came out of this meeting. But what is new about it is a new way to mitigate bone disease, the use of bortezomib more effectively and in combination, and some new targets of DKK1 RANK ligand, etc. Do you want to say something about the new excitement?

Sagar Lonial, MD

Yes. I mean, I think we may have alternative ways to augment bone regrowth. I think what we can do currently is prevent further destruction of the bone by inhibiting osteoclast. What we don't have is a drug so far that has been actively proven to benefit is drugs that will actually regrow bone and that's where we hope the new drugs like RANK ligand inhibitor, or Wnt signaling pathway drugs, I think, will be very encouraging. And, in addition to bortezomib, drugs like panobinostat, actually, it turns out may recreate that lattice on which bone grows.

So I think a number of our novel agents, you're right, are not just targeting the plasma cell, but may be reinvigorating the normal bone homeostasis to allow us to strengthen bone, not just prevent loss.

Sundar Jagannath, MD

Where are you using kyphoplasty at this time and how aggressively are you using kyphoplasty?

Sagar Lonial, MD

For us, the first step is when patients present with back pain, is obviously to image the spine with a magnetic resonance imaging (MRI). And then we have our interventional radiologists or orthopedic surgeons look at that film and see the patient to make a decision about whether they think their intervention can benefit. And I think one of the problems is that if the fracture's very old, sometimes

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there may not be enough. If the bone is really quite thin and has been significantly compressed, you may not get normal height back as, you know, we would hope with kyphoplasty.

I think the third issue is that patients may have other causes for back pain besides compression fractures. As, you know, the population ages, we know we all get those kinds of things and I think it's really incumbent on the operator of the maneuver to identify whether they think that bone pain can be made better by the introduction of the balloon, or the cement, or whether it's just a chronic kind of a back pain.

Sundar Jagannath, MD

So, if I rephrase it, if the patient has very acute pain in one or two vertebra, then I think it is amenable for kyphoplasty because it gives instantaneous pain relief. And since the bone cement is injected, whether they get their height back or not, at least it may prevent further collapse while they start on treatment so they can avoid these narcotics and feeling dizzy while you are trying to treat them with frontline therapy.

Sagar Lonial, MD

Right.

Sundar Jagannath, MD

And I think this kyphoplasty maneuver has reduced the use of local radiation therapy, which was another well tested treatment option which has been given in the past, because radiation therapy doesn't mitigate the pain right away. Chemotherapy and radiation therapy work the same way in terms of how they kill the cancer through apoptosis, whereas the kyphoplasty gives instantaneous pain relief if it is very well localized. I think that's the advantage of kyphoplasty.

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Closing Remarks

Anne Quinn Young, MPH

Thank you for listening today. I would especially like to thank our speakers, Dr. Jagannath and Dr. Lonial, for providing such a helpful overview of the treatment options for multiple myeloma covered during IMW this year.

The MMRF is the world's number one private funder of myeloma research and we are focused on urgently and aggressively funding research to bring new treatments to patients. We are also the leader in educational programming for the myeloma community. We offer live, online, and print programs for you and your healthcare providers. You can always check our website, www.themmr.org, or www.multiplemyeloma.org, to find the latest information on multiple myeloma and its treatments, as well as information on upcoming programs including our annual webcast from the ASCO annual meeting and the ASH annual meeting. You can also find information on many of the clinical trials discussed here today.

Your feedback and comments are also very important to us as we plan for future webcasts and other types of educational programming. So, I would encourage all of you to take a few minutes to complete the evaluation form at the end of the webcast. Your feedback helps us to plan both the format of our educational programs as well as future topics.

Again, thank you for listening and have a wonderful day.

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