



PART II: INTERNATIONAL HEMATOLOGIC ONCOLOGY TUMOR BOARD

Practical Perspectives on Current Challenging Cases of Multiple Myeloma

Friday, December 9, 2011

DR LOVE:

Good evening, everyone. I'm Neil Love from Research To Practice, and welcome to International Tumor Board. Those of you who were here this afternoon for Part I with NHL and CLL, welcome back. We're honored and excited to be able to spend the evening listening to our distinguished faculty — from the far side of the podium, Dr Carol Huff, Dr David Siegel, Dr Morie Gertz, who co-chaired this crazy event with me, Dr Michele Cavo, Dr Pieter Sonneveld and Dr Nikhil Munshi.

Now in continuing education we're always focused on the doc in practice, particularly the oncologist who's trying to keep up with so many different tumors where there's just an explosion of information — everything from hepatocellular cancer to T-cell lymphoma, breast cancer. We actually just got back from the San Antonio — well, we didn't get back — we went from the San Antonio Breast Cancer Symposium, where we did a meeting Wednesday night very similar to this in breast cancer. It's just amazing how these people are able to keep up.

And what we're going to do today is talk about 6 cases from practice. As you know from this afternoon, we went to 4 different countries: India, Canada, United States and France. And here are the 6 cases we're going to be talking about. For each case, first you'll hear the medical oncologist who took care of the patient talk a little bit about the patient. Then you'll see some of the imaging and pathology, and then we'll look at some of the answers you gave to the polling question using the PDA. And then we'll ask the faculty to review a little bit about the science and what we know about this situation. And then we're going to chat.

These are the 4 medical oncologists who really coordinated the effort with this program. We're really grateful to them. Now, this is the team in Sandusky, Ohio. That's our US group. This is the Canadian group out of Ontario, the France group from Nice and finally Bangalore, India. And actually Dr Munshi was saying one of these — Dr Shah — was his fellow, that he just realized. And I actually interviewed all of these people through Skype™ but we had production crews, and here's all the crew that was down in India with the physicians there.

You have a PDA, and hopefully you've taken the survey. But we want you to ask questions. We actually tried something this afternoon that we've done in some of our audio programs. Morie did this, where we just get a list of questions and cases from docs, and we just fire through them as fast as we can. We're going to try to do that 2 or 3 times tonight. We've got some great questions and cases today, so see if you can stump the group a little bit with some tough questions.

Now if you find this program useful, which hopefully you will, please tell your colleagues to watch it when we post it online as a video web program. And I'll send you out an email when it's ready to go, so other people will be able to enjoy what happened here tonight.

I think with that, we should — Did you want to say something, Morie?

I think with that we're going to begin with our first case, and I'll ask Dr Cavo if he can come to the far podium there. Michele, here's the situation and the patient that we're going to talk about. We're just going to pick select areas to chat about these cases. We're not going to go through every piece of it.

Dr Cavo, this is a 42-year-old math teacher — actually had a history of myocardial infarction in the past, but was actually doing well — and, bottom line, came in with anemia, was diagnosed with IgG myeloma, has sheets of plasma cell in the marrow and actually has a normal skeletal survey. The patient got RVD and actually was put on zoledronic acid and now is being scheduled for a transplant.

Here's the team discussing this case and the questions they want the faculty to address.

DR GUPTA: I induced him with RVD and I think I gave him 3 or 4 cycles, and he was in a very good partial response. He's now being worked up for an autotransplant.

DR LOVE: Any questions you'd like to see the faculty address about his case?

DR GUPTA: Transplant or not to transplant? "Wait for it to relapse or right up front?" is one. Would they use a different regimen? Subcutaneous bortezomib, is that usual now or not? Because with RVD, my major challenge in this case was that he was not able to hold the piece of chalk while writing on the blackboard. I would like to see the actual thoughts of the faculty about what they think about this.

DR PRABHUDESAI: As you can see, it was like an open and shut case of myeloma for us. It was an aspirate and a biopsy, which was packed with plasma cells. We had many mature forms as well, with nucleoli.

Diagnosis-wise, it really was not a problem for us.

DR LOVE: Here are the related questions we asked. And actually, even before we start talking about these cases, I'm going to turn to my co-chair, Dr Gertz, and ask him to comment on this question. When you see a fellow who comes onto your service and hasn't seen myeloma since 5 or 10 years ago, how do you describe kind of what it's like to take care of patients today compared to, say, 10 years ago?

DR GERTZ: It's pretty typical that back before 1999 when all we had was melphalan/prednisone and autotransplant, for nontransplant-eligible patients it was still 24 to 30 months — no change from when I started in 1980. With the introduction of novel agents and refinements in supportive care to make the risk of auto stem cell transplant reduced — we've published that since 1995 — median survival is 7, 8 years. And everyone on the panel has patients now who are surviving over 10 years. It's tripled.

Let's talk about this specific case. And we go to the next question? Can we go to the next polling question? Basically we asked people, what kind of induction treatment would you likely use for a patient like this? The most common answer, Dr Cavo, is RVD — probably not a big surprise — but I'll be curious to see what the faculty has to say about it.

Finally, what about transplant in a patient like this? It looks like the majority of the audience would be thinking more about moving forward rather than not. I'll ask Dr Cavo to review just a couple of issues related to this case. Please send us in some questions, and we'll see what the group thinks.

DR CAVO: These are my disclosures.

Over the past decades, the novel agents thalidomide/bortezomib and lenalidomide have shifted the treatment paradigm for transplant-eligible myeloma patients. These new drugs have been extensively used as part of induction before transplant and, more recently, are also investigated as post-transplant consolidation and maintenance therapy.

Over the next few minutes, I will provide a brief overview of the major goals and the results of novel agent-based induction regimens and will address the issue of the optimal timing of autotransplant in the novel agent era.

The major goal of novel agent-based induction therapy is to enhance the rate of a response up to the CR and/or VGPR or better level. Achievement of high-quality responses to novel agent-based induction therapy is an early predictor for extended progression-free survival after autologous stem cell transplantation.

Basically, the novel agent-based induction regimens can be divided into 4 major groups: bortezomib based and IMiD based. Both bortezomib and IMiDs can be successfully combined with all the cytotoxic drugs, such as cyclophosphamide or doxorubicin. In addition, bortezomib and IMiDs combine well with one another so that a fourth group of newer induction therapy based on the combination of bortezomib with thalidomide or lenalidomide can be recognized.

In 2005 our group first provided demonstration of the superior activity of thalidomide/dexamethasone over VAD as induction therapy for autologous stem cell transplantation, a finding which was subsequently confirmed by other groups. Based on the results of these trials, thalidomide/dexamethasone has been the first novel agent-based induction therapy used in daily clinical practice before transplant.

This slide summarized the results of several recent large Phase III clinical trials aimed at evaluating the role of thalidomide or bortezomib as part of induction therapy before transplant. In 2 of these trials, in comparison with VAD thalidomide/dexamethasone combined with either doxorubicin or cyclophosphamide effected significantly higher rates of CR and/or at least a VGPR both before and after autologous stem cell transplantation. In 2 additional trials in comparison with VAD, bortezomib/dexamethasone or the same regimen with added doxorubicin was associated with an increased rate of high-quality responses before and after autologous stem cell transplantation, again which translated into extended progression-free survival and overall survival in one of these trials.

In 3 additional trials, the combination of bortezomib with thalidomide and dexamethasone, VTD, was independently investigated by 3 groups. And VTD was superior to thalidomide/dexamethasone or bortezomib/dexamethasone in terms of increased rate of CR, ranging between 15% and 35%, and at least a VGPR up to the maximum value of 62% after 3 21-day cycles.

Autologous stem cell transplantation further enhanced the rate of high-quality responses, a finding which highlights the important concept that high-dose melphalan and the novel agents are complementary.

An alternative possibility to combine bortezomib with an IMiD is to replace thalidomide with the lenalidomide. Differently from VTD, RVD has not been plagued by Phase III clinical trials, it having been explored so far in Phase I/II or Phase II clinical trials enrolling quite limited numbers of patients. And although cross-trial comparison is inadequate, the rate of CR or at least a VGPR after 4 cycles was not superior to that previously reported with VTD. And in a third study, high-quality response rates were almost comparable to that seen with VTD.

In 2 of these studies, the rate of Grade 3/4 neurological toxicity seen with RVD was between 6% and 12%, while in a third trial no case of Grade 3/4 neurological toxicity was seen with RVD.

Thalidomide- and bortezomib-induced neurological toxicity are the major concerns associated with the use of these novel agents as part of induction therapy before autologous stem cell transplantation. However, this slide shows that after a short-term exposure to any of these 2 novel agents, 90% to 95% of patients were able to receive the entire treatment program, comprising 3 to 6 cycles of induction therapy.

Moving to the conclusions, regarding induction therapy, a triplet bortezomib-based regimen is likely to effect the highest rate of high-quality responses and should be actually considered as standard of care. Three to 6 cycles of induction therapy represent a reasonable balance between efficacy and toxicity. Thalidomide- and bortezomib-induced neurological toxicity is a major concern. However, neurological toxicity is likely to be significantly reduced by use of sub-Q bortezomib.

What about autotransplant outside the clinical trials comparing early versus late transplant? The preferred approach should continue to use transplant up front. In fact, a burning question, which continues to be brought up by the efficacy of novel agents given in a continuous fashion is the optimal timing of transplant. Several trials aimed at retrospectively analyzing early versus late transplant provided conflicting results, but none of these trials were conclusive since none of them was randomized and there was a major bias, which was represented by the choice of early or late transplant based upon patients' preference or physicians' discretion.

Therefore, the better way to address this issue is to perform well-designed prospective randomized clinical trials. Such a trial is currently running in Europe. This slide summarized the design of EMN-02 clinical study. As you can see, after an induction therapy and stem cell collection, patients are randomized to a nonhigh-dose therapy program comprising VMP with subsequent transplant at the time of relapse or are randomized to high-dose melphalan and a single or a double autologous stem cell transplantation. Patients in both arms do receive a second randomization to consolidation versus no consolidation.

A similar trial is currently running and is headed by IFM and Dana-Farber with a consortium of US centers. The design of this study is very similar to the European trial. The only difference is that RVD is the induction and the consolidation therapy for patients randomized to the nonhigh-dose arm of the trial.

This is my last slide. Thank you for your attention.

DR LOVE:

You can have a seat, Dr Cavo. I was thinking about this thing about the progress in this field, and maybe this is a measure of the progress. Last April, we did a closed video/audio recording to talk about myeloma. We had 19 investigators and 19 oncologists in practice, and actually Carol Ann, David, Morie and Nikhil were there. We talked about myeloma about 17 hours over 2 days.

When we first started thinking about this, I was like, “How can we talk about multiple myeloma for 17 hours?” We had stuff we didn’t even get to. I think that might be a measure of the amount of information. David, let’s start out with this issue of the pretransplant induction.

We actually, if you remember, we had a physician, Elizabeth Simmons from California, who had emailed us and said, “I keep hearing about all your investigators talking about RVD, but do we really need to use 3 agents? Couldn’t we use 2 and maybe use the other one on maintenance?” That sparked a lot of discussion.

What’s your take, Dave, in terms of the long-term impact of 2 versus 3 therapy?

DR SIEGEL:

I think the myeloma community, in general, has moved to 3-drug combinations or beyond that. I don’t know that we put that topic to sleep entirely, but the fact that we can now give bortezomib with substantially less toxicity certainly makes the inertia somewhat less to get to that point. There’s clearly evidence that greater depth of response pretransplant leads to greater depth of response post-transplant, and this is associated with better outcomes. I think now that we can more comfortably administer bortezomib with less fear of toxicity — that that’s an easier step to take.

DR LOVE:

Morie, do you buy into that?

DR GERTZ:

No. We haven’t bought into triplet therapy. I think what Michele showed quite well is that the depth of the response is clearly far superior. My patients that I see don’t know the difference whether their M protein is on 85% or 95%. It’s down. What we’re lacking, really, is the overall survival data because really, for me, what’s relevant is that they receive a doublet induction containing a novel agent, what the role of the third unused agent in salvage will be and whether that will turn into a survival advantage. All of these things are based on depth of response and relapse-free survival. Those are the best endpoints, actually, that we can strive for at this time, and we haven’t seen the overall survival data that says triplet beats doublet, so I don’t feel compelled or obligated to induce with that off study.

DR LOVE:

Let’s get a little bit into this issue of transplant immediately or not. Nikhil, of course Michele referred to the trial that’s coming out of Dana-Farber looking at that. What are your thoughts about this? What evidence has come out? There was an Italian trial recently reported for the first time looking at this with novel agents. What do we know right now about immediate versus delayed transplant?

DR MUNSHI:

I think that the data currently exists that shows — and there are 2 studies, one is a SWOG study, which is an old study, and a very old French study — that early versus late transplant has provided similar overall survival outcome. However, these are 2 studies which were done not when thalidomide was available and other newer agents were available. Now that we can really get a good depth of response — and that’s why I disagree a little bit with my esteemed colleague, Dr Gertz, that getting a depth of response up front is quite critical in then getting benefit from the transplant.

With that in mind, I think early transplant would provide substantial benefit because you can use the initial depth of response in eventually getting even further cytoreduction with transplant. What’s coming up is this molecular CR, and if we get molecular CR — in one of the studies from Italy, patients have not relapsed. It’s a short study. It’s a new study. But within the limits of the time frame, they have done better. I think we need to get a maximum cytoreduction up front, conserve it with transplant and then we’ll talk more about the maintenance. But that’s what is going to get us the best outcome.

DR LOVE:

Let’s bring in another issue, and that is risk status and assessing risk status. We didn’t ask Michele to talk about that, but I want to ask Pieter, what are the factors that you consider that put a patient at high risk? And, I mean, a simple question: How does that change your approach to a younger patient like this who’s transplant eligible?

DR SONNEVELD:

Well, of course, we know the well-known clinical risk factors like high ISS stage. But more recently, I think the FISH data, that convinces that there are certain high-risk groups that can be identified using cytogenetics or FISH, and the poor prognosis of those patients in some cases can be overcome by using, for example, proteasome inhibitors like bortezomib. And this is especially true for 4;14 translocation — maybe the 17p in some trials. So, for these patients, we know for sure that we should treat them with a triple combination induction, including bortezomib or another proteasome inhibitor maybe.

The point is that, in fact, you would like to use that in all patients because also the good-risk patients might benefit from such a combination. Up to now, we don't have the best regimen available for poor-risk patients that you would not apply in good-risk patients.

DR LOVE: That was a subject of some controversy, Nikhil.

DR MUNSHI: I think I actually sort of disagree. And I agree with Dr Sonneveld that we have not cured yet, or maybe we are curing, but it's a very small proportion of low-risk patients. The concept that we're going to do something different for high risk, we are not there yet. We have not cured low risk. Why do we want to do something less for them and more for high risk? I think our current strategy has to be to do best for all. We figure out that this treatment is going to be enough for low risk, and then we move on to doing something different for high risk.

DR LOVE: Carol, another regimen we hear a lot about from, particular investigators, is CyBorD. Can you talk about your approach to induction in a transplant situation and how it varies, if at all, with the higher-risk situation?

DR HUFF: My approach, actually, in using a 3-drug combination is to use CyBorD as the 3-drug combination — my preference in treating patients. I agree with Dr Sonneveld. In what we do know of the 4;14 translocation, certainly the bortezomib is an important agent in that situation, perhaps less so with the 17p deletion patients. But certainly the higher-risk patients are probably the ones that, although we may be doing a little bit better for, we have not benefited the high-risk patients as much as we have benefited the lower-risk patients at this point in time.

And I personally prefer the CyBorD regimen because I think it's well tolerated, yet nice responses. I'm not convinced that you need to add in lenalidomide at this point in time, but I don't think we know whether you do or you don't.

DR LOVE: I think we can go on to the next case. Pieter, if you can come to the podium over there, this is from the United States, Sandusky, Ohio.

A 62-year-old woman presents with progressive fatigue, is anemic and on bone marrow biopsy has 80% plasma cells. She has an M spike of 0.2 and a normal skeletal survey. She actually goes through RVD, stem cell transplant, lenalidomide maintenance and actually, interestingly, zoledronic acid. We'll get into that a little bit later. And here's the patient's oncologist and his team talking about the patient.

DR LOBINS: In this patient, one of the problems I'm going to have with her is she had an M spike at initial presentation of only 0.2, and her light chains were not very abnormal either. After her first treatment of induction with RVD, her M spike completely went away. Now that she's had her induction and her transplant and is now on maintenance lenalidomide, I have a question on how to exactly follow this patient because clearly they're an oligosecretor.

When you look at cellularity, cellularity is greater than 90%. Normal marrow cellularity should be at 60%. The 40% that isn't cells is generally fat. And as you see in here, there are really not fat vacuoles. When you get up close on this, it's a sea of relatively monotonous round cells. They have a flame-like configuration to them. Just dead center, 6 o'clock, there are a few round, very dense cells, which are smaller. Those are erythroids. Everybody else in there looks like a monoclonal population.

These cells, when you get them into a smear and even in the peripheral blood, have this configuration. The cell almost dead center has that flame appearance — that's a plasma cell. This is a circulating plasma cell. This slide even has more of these very bizarre-looking plasma cells. You have one at about 3 o'clock, which has a little flame appearance to it. These are more rounded, but when you look at the nuclei, the NC ratio is extremely high and they have angulated nuclei. So this is really diagnostic of a plasma cell leukemia.

DR LOVE: In terms of maintenance lenalidomide, did you bring up the potential issue of increased risk of second cancers?

DR LOBINS: I did bring up theoretical increased risk of second cancers. I would like to see more data to understand exactly how much of a risk it is to the patient because that's their first question: How much of an increased risk of second cancers is there? I have a hard time answering that question.

DR LOVE: Before we get into this question we posed to the audience, Morie, how would you answer his question about how to follow the patient?

DR GERTZ: He mentioned that the free light chain level was somewhat elevated, and it's a question of how elevated it was. I think most of these patients can be followed — most, not all — with quantitative IgD immunoglobulin as well as the free light chain level. No 24-hour urine was done. I was wondering

about whether the 24-hour urine might show a measurable monoclonal protein. But patients who are truly nonsecretory really, in practice, end up getting lots of bone marrows for surveillance because you have no other way to monitor their status.

DR LOVE:

Dr Sonneveld, here's an interesting question we posed to the audience, which is, what would you do about maintenance in a patient like this? Can you go back to that? Yes. Interestingly, it looks like 70% of the audience would use some form of lenalidomide maintenance, but it's interesting in terms of duration. There's a spectrum of answers. We'll see what you all have to say about it.

And then the next question we asked was, would you administer a bisphosphonate to this patient who actually doesn't have bone disease? And two thirds of the audience says yes.

Pieter, we asked you to really focus on this issue of maintenance, particularly from the point of view of efficacy. And Morie will get more into the issue of side effects, but particularly second cancers.

DR SONNEVELD:

Maintenance — “Je maintiendrai,” en Français it means “I will maintain.” And this is an interesting question. The answers are also interesting because post-transplant maintenance has not been approved, at least not in Europe, so we are talking about an experimental treatment for a large part.

These are my disclosures.

What is the concept of maintenance therapy? In the upper part of the slide you see a patient that has gone through transplant then gets no further treatment. He has a treatment-free interval which is usually of good quality if the patient has responded well. This lasts a certain time until he progresses. Then second-line treatment needs to be started.

If we would apply maintenance, of course the patient will not have a treatment-free interval, but maintenance could improve progression-free survival, especially if the maintenance period is longer than the treatment-free interval in the upper case. Maintenance could even improve overall survival if the maintenance period is much, much longer than the treatment-free interval.

Of course, effective options should be available for the treatment of relapsing patients. Thalidomide has been used for maintenance treatment after high-dose melphalan and autologous transplant in many trials. Here are listed 7 trials that all observed a significant improvement of progression-free survival with maintenance with thalidomide. However, in 3 of the trials, no overall survival at all was observed. And in the 3 other trials, there was some survival improvement but only after a long time, as was the case in the Barlogie trial, or it disappeared after longer follow-up.

It was especially notable that in patients that had a relapse after thalidomide exposure, they had reduced overall survival. This was especially true in patients with poor-risk cytogenetics, as has been demonstrated by the MRC trial for Morgan et al. For this reason, thalidomide has not been used any longer for maintenance — also because it's usually not well tolerated by patients who use thalidomide for a prolonged time.

Lenalidomide has been investigated in 2 large trials after autologous transplant. The upper case shows the French IFM trial, where patients received lenalidomide consolidation for 2 months and then were randomized to receive either lenalidomide or placebo. As you can see here with the follow-up of almost 3 years, as shown at last ASH, there was a progression-free survival, 42 months in patients receiving thalidomide as compared to 24 months in patients on placebo. This is a significant advantage for lenalidomide maintenance. However, there was no overall survival advantage.

In the lower case, you see the CALGB trial from the US. Patients did not have consolidation. They were randomized for lenalidomide and placebo. At a short follow-up in the French trial, there was already a progression-free survival advantage in favor of lenalidomide maintenance. These trials were updated at the myeloma workshop in Paris last May, and here you can see with a slightly longer follow-up that progression-free survival in the French trial with lenalidomide was 41 months as compared to 24 months. In the US trial, it was 48 months against 30 months. Overall survival at 5 years in the French trial was still not different. In the CALGB trial, I will show you the curves in a minute.

Here you see the progression-free survival according to response, preconsolidation, in the French trial. And here it's shown that both in patients that have only a PR or stable disease, there is a benefit of lenalidomide, as well as in the patients that have VGPR or better. However, a more recent analysis that I'm not showing here shows that especially patients with less than CR benefit from the lenalidomide maintenance.

The question arises whether patients with poor-risk cytogenetics also benefit from this maintenance treatment. As you can see here, patients with the 4;14 translocation on lenalidomide have 27 months progression-free survival as compared to 15 months in the placebo-treated patients.

Patients with a 17p deletion also have a benefit, 29 months as compared to 14 months. However, if we look to patients with or without these abnormalities, you can see that there's still a progression-free survival advantage in favor of patients without the cytogenetic abnormalities. So the conclusion is, lenalidomide is not able to fully overcome the negative prognostic impact of these cytogenetic abnormalities.

Here we can see the curves of the CALGB trial. On the left, the time to progression as presented at the workshop in May this year. A significant advantage for time to progression, 48 months compared to 13 months. There is also an overall survival benefit in favor of maintenance, and this is in spite of crossover of patients from the standard arm to the lenalidomide arm when they were progressive. This survival analysis, I think, needs longer follow-up before we know for sure that indeed there will be a survival benefit in this trial.

Dr Cavo has already shown this slide. I'm not going to discuss it except that in the European trial, we will use maintenance lenalidomide in both arms until relapse, based on the promising data from the trials that I showed you.

There's 1 or 2 other trials that didn't use lenalidomide. They used bortezomib for maintenance — like the Dutch-German trial compared bortezomib and lenalidomide maintenance for 2 years. I am not going into detail at this meeting, but here you see progression-free survival from the last high-dose melphalan and autologous transplant, showing a small but consistent benefit for bortezomib maintenance over thalidomide maintenance in these patients. And up until now, there is a small but significant survival advantage for the bortezomib arm.

Recently, the International Myeloma Working Group made a consensus statement on the use of maintenance, where they conclude that maintenance may improve progression-free survival but so far not overall survival in the far majority of the trials. Thalidomide should not be used for maintenance because of intolerance and unfavorable effects. Lenalidomide has not yet been approved but is an effective maintenance in 3 clinical trials. The safety profile remains a point of concern, especially the second primary tumors. Long-term survival advantage needs to be demonstrated.

Here I will briefly touch upon the second primary cancers with lenalidomide. The French trials, in the upper part of the left table, show that with len there is a 5.5% incidence of second primary cancers as compared with 1% in the placebo arm. And remarkably in the French trial, there were a number of cases of B-cell malignancies, including cases of Hodgkin's lymphoma that occurred beyond 20 months after start of treatment. Also in CALGB, there's an increase of second primary cancers, especially AML/MDS, and some invasive solid tumors.

I will briefly touch upon the nontransplant trial, the MM-015, where MPR plus lenalidomide maintenance was compared with MPR alone plus placebo or MP. In this trial, there was a clear progression-free survival advantage for patients receiving MPR plus len maintenance as compared with the other arms. I am sure you have seen these data before.

However, if we look in this trial to the second primary malignancies compared with the risk of myeloma progression, it is evidenced that the risk of undergoing disease progression is much higher in all patients — namely, patients receiving lenalidomide or patients not receiving lenalidomide.

Based on this, in my last slide I would like to conclude that maintenance treatment is effective and it adds to improvement of progression-free survival but as yet not overall survival. Lenalidomide and bortezomib seem to be more effective than thalidomide. The efficacy of these drugs across high-risk groups may differ. There is a rationale for investigating maintenance post-transplant therapy, even beyond the trials that I showed you, and the risk of second primary malignancies seems acceptable and it is outweighed by the progression-free survival benefits.

And here I would like to stop.

DR LOVE:

Thanks. You can have a seat. Nikhil, agree or disagree: Lenalidomide maintenance has no effect on survival. Is that true or not?

DR MUNSHI:

No. I think I agree with the point that the benefit outweighs the risk of second malignancy. The last slide — that is Palumbo's data — clearly shows there are patients dying from second malignancy, or are they dying from myeloma? The answer, clearly, from that data is that they are still predominantly almost exclusively dying from myeloma. So we need to focus on myeloma, keeping a very close eye on second malignancy.

DR LOVE:

Didn't the CALGB study show an overall survival benefit? I mean, I don't know if it really matters, but didn't they show that?

- DR MUNSHI:** In answer to your question, the CALGB study clearly shows an overall survival benefit. 0.018 was the *p*-value, and it has sustained now over a period of 6 months. They presented in Paris. They presented it subsequently more recently, and if anything, the difference is increasing. I think that we have one clear overall survival benefit. I don't know what else we are looking for.
- DR LOVE:** Dave, you saw the heterogeneity in the audience about duration of maintenance. First of all, is lenalidomide maintenance, in your view, standard post-transplant right now? And what about duration?
- DR SIEGEL:** I would venture that I'm one of the few up here who does not use maintenance lenalidomide. None of these trials were actually designed to answer this question. The question is an overall survival one, and while there is a very marginal overall survival advantage for the patients on the CALGB trial, the trial did not guarantee a crossover to lenalidomide. The French trial, a minority of patients cross over to get lenalidomide, but the actual mandatory crossover that happened may actually dilute the ability of the control arm of that trial to actually compete with the experimental arm because patients are now on low-dose lenalidomide. They're not being salvaged with full-dose lenalidomide. So the question of, is there something magical about the post-transplant period in which low-dose lenalidomide actually contributes in the long term, I don't think it's been answered at all.
- DR LOVE:** Michele, what's your view on this?
- DR MUNSHI:** No, I do not. I think biologically, if we see how lenalidomide works at a low dose, there are multiple mechanisms of action — one of the most obvious ones is the immunological effect, which at a higher dose is suppressed. At a lower dose you see more immunological effect. We and many others are looking at vaccination approaches, and lenalidomide might be serving that purpose.
- DR LOVE:** Michele, what are your thoughts about lenalidomide maintenance? David is correct. We've surveyed many investigators, and many more do use it. What's your thought about it?
- DR CAVO:** I think that surely lenalidomide is the ideal agent to be used as maintenance. The data in favor of progression-free survival benefit are very robust. My personal opinion is that we need to be cautious and we need a longer follow-up in order to show the clear survival advantage. At this time, there is a borderline survival benefit for lenalidomide-treated patients in 1 of the 2 trials and, unfortunately, I guess that in the other trial, a survival advantage will never be demonstrated. This is my personal opinion.
- DR LOVE:** Morie, we were in here earlier this afternoon arguing about rituximab maintenance — and a little bit of an analogy in terms of relatively nontoxic, certainly compared to chemotherapy, long-term treatment. It seems to be able to delay disease. Quality of life is another question that comes in here. How do you see this whole argument?
- DR GERTZ:** Right now I think that we also exercise caution. We're not routinely using lenalidomide maintenance post-transplant. The thing I find most disturbing is, I look at these 2 studies that have 600, 800 patients, and in both arms the relapse-free survival and the overall survival is superior in the American study versus the French study, and I don't know what's going on about such heterogeneous results. It just makes me suspect when I see very marginal survival benefits when the populations at large are showing such very different progression-free and overall survivals.
- DR LOVE:** Carol?
- DR HUFF:** I would agree. We actually also do not routinely use maintenance lenalidomide post-transplant. I really am waiting for survival data that clearly demonstrates a difference. Something that hasn't been mentioned here, but this is at an enormous cost that we will be incurring if everyone is on maintenance therapy. We need to be sure that it really is beneficial.
- DR LOVE:** David?
- DR SIEGEL:** I would say longer-term follow-up is not going to solve the problem with these trials. These trials weren't designed to answer that question. If we follow the CALGB trial and the curves separate even further, this is still not going to answer the question. These trials weren't designed to guarantee a crossover and ultimately answer this question. These trials aren't the answer to the problem that we have.
- DR LOVE:** Nikhil?
- DR MUNSHI:** I think we need to look at what the trials represent rather than dissecting it too much. It shows the curves separate. The French results have I don't know how many zeros in their curve in progression-free survival. The curves are separating by 50 degrees, and that's a result. We know that in myeloma now, with all the very good treatment, we have to wait a long time for getting overall survival benefit.

Two versus one transplant, we had to wait for 5 years before the curves separated. We have to go with what we have today. We have one clear — whether that is a 10-mg dose or a 25-mg dose — overall survival benefit. Now we are looking for a second one. I don't know when we will end. When we get the second one, we might ask for a third one. I think we have to go with what we have. Patients are dying from myeloma, not from second malignancy or other. We build on this. We do need longer follow-up and longer studies, but treat with what we have.

DR LOVE: For what duration?

DR MUNSHI: Duration is not very clear. I think that question is totally open. Currently, I think 2 years is the deadline that the French group used. After 2 years, they discontinued them. I think within 2 years, we will have a little better clarity on whether 2 years or until progression.

DR LOVE: Pieter?

DR SONNEVELD: I would like to comment on the overall survival issue. I think there are very few trials of any kind for myeloma at this time that show an overall survival advantage anyway. This is partly because so many patients get all the different agents at some time during their treatment.

DR LOVE: This came up Wednesday night in San Diego at San Antonio in breast cancer, the same thing. Bevacizumab, no survival benefit, but then there's all the downstream things. Michele?

DR CAVO: Another important issue to be taken into consideration is the quality of life. Although lenalidomide is devoid of neurological toxicity, none of these trials has provided a careful analysis of the quality of life of these patients. So overall survival and quality of life are 2 major issues and probably we still need more time.

DR LOVE: Let's go through a few of these questions real fast in a lightning round, so to speak. Morie, you can take this one:

Seventy-year-old woman with free light chains, 10% plasma cells in the marrow, negative skeletal survey, severe gastroparesis requiring J tube for feeding, biopsy amyloidosis. She's on melphalan/RD with excellent normalization of the light chains but no improvement in her stomach. Weekly admissions to the hospital for dehydration.

No matter what clinical complication you tell Morie, he goes, "Oh, yes, yes. I've seen 50 of these." Any other suggestions?

DR GERTZ: I have seen that.

DR LOVE: I know.

DR GERTZ: Quite frankly, people who develop gastroparesis from GI amyloid frequently end up on home total parenteral nutrition, even when you get a spectacular hematologic response. Reversing gut amyloid, whether it's pseudo obstructions, steatorrhea or gastroparesis repeated vomiting, these patients do not do well with enteral management and you don't take the amyloid out of the gut. That patient likely needs an evaluation for continuous home CPN.

DR LOVE: Dr Cavo, in your opinion, what is the maximum number of cycles to give in a pretransplant induction when len is used, without affecting mobilization?

DR CAVO: With the len? Probably no more than 4. After 4 cycles, the risk of an impaired stem cell collection is high, especially in older myeloma patients.

DR LOVE: Carol, if we decide not to treat smoldering myeloma, do we need PET to be sure in terms of bone or soft tissue lesions?

DR HUFF: No.

DR LOVE: Would you like to elaborate on that?

DR HUFF: I mean, the data for determining smoldering versus active myeloma is not based on PET scan criteria. And I don't think we need that at this point in time.

DR LOVE: Morie?

DR GERTZ: It's the one place I actually do use the PET scan. I use it very sparingly, but if I'm seeing someone with an IGG of 5,500 with a normal hemoglobin and normal kidney function with a normal bone survey, I get a little skittish. I don't want to say, "Come back in 3 months" and then at 6 weeks have them call and say, "I can't get out of bed because my back hurts so bad." I like the reassurance, and it does change my treatment. If the PET scan lights up with that big M spike, then I'm glad I got it. In the patient with smoldering myeloma with 1,100 IGG and 12% plasma cells, I'm not particularly excited about it, but the really big smolderers, I get it. No evidence.

- DR LOVE:** Pieter, what's the optimal therapy for a 50-year-old with acute renal failure, says creatinine 500 micro-moles per liter, and light chain only myeloma, 2 vertebral fractures?
- DR SONNEVELD:** We will treat such a patient with bortezomib/dexamethasone induction regimen for 3 or 4 cycles or maybe even longer, if he continues to improve on the regimen.
- DR LOVE:** So, Morie, can you come to the podium and we'll talk about our next case? Again, clinical in terms of complications and real-life problems: The patient is a 64-year-old man with a history of chronic depression and anxiety and presents with bone pain. He's found to have IgG lambda monoclonal gamopathy, bone marrow 10 to 15% plasma cells, diffuse lytic bone disease, has deletion 13, gets RD using 40 milligrams of D and develops severe exacerbation of psychiatric problems. The oncologist was telling me he had to go to anger management and had very, very serious problems with psychiatric symptomatology.
- So everything was stopped. They restarted the lenalidomide, and then the patient developed a rash. They tried stopping the lenalidomide and started back. The rash came again. Biopsy showed that it was vasculitic. And here is the team talking about the patient.
- DR MURPHY:** I was using the weekly dexamethasone, 40 milligrams once a week with the lenalidomide, and he was having a very difficult time emotionally. In fact, he had to go into anger management it got so bad for him. And it's hard for me to know what he was like prior to his diagnosis, but I think the steroids did have a lot to do with it. So, really, we stopped the lenalidomide/dex early because of his difficulty with the high-dose dexamethasone. So, really, the question I have is: Does he need to do that much dexamethasone? Would he be okay with less or none?
- DR ZIEBER:** This is a patient who was seen for a bone survey for multiple myeloma. The initial image on the right shows what was thought to be a permeative lesion within the distal humerus. There's a slightly magnified image on the left side of the screen showing what appears to be a slightly permeative lesion within the marrow cavity of the distal right humerus. There's also mild scalloping of the inner cortical margin as well, which would be compatible with a myelomatous lesion.
- Additional lesions were thought to be in the right femur. There's some artifact from a tissue fold over this area, but the area was still thought to show slightly greater permeative appearance within the marrow cavity and a small amount of endosteal scalloping compatible with myeloma.
- The radiographs of the skull were more definitive. What we see here is what we call "punched out" lesions. They have nice, well-defined margins with no sclerotic border compatible with myeloma.
- DR CRABTREE:** In this patient, we got a bone marrow biopsy. When you get up close on this, we have essentially normal marrow elements. Because you look, there's a mix of cells — there's big cells, small cells, pink cells. There's some, actually, orange cells in there. So you question, are there some plasma cells in here? Well, there may be.
- This is actually an immunohistochemical stain for plasma cells, CD138. Any time I have a patient with a suspicion of myeloma or I see a number of plasma cells that doesn't register in at the normal 1% or 2%, I'll do a CD138 stain. This is very nice for taking plasma cells out because all the brown blotched areas here are plasma cells. This patient had 10%, 15% plasma cells in their marrow.
- This is a lambda stain, which shows that they are monoclonal for lambda. Again, the brown are the positive cells. A concurrent kappa stain was done and the marrow was essentially negative.
- DR MURPHY:** Our thought was, do we want to keep him on the lenalidomide, maybe keep him on a maintenance dose, just 10 milligrams rather than 25, which may be reasonable to control the disease. And without the dexamethasone, not too many side effects.
- But literally, he developed this very unusual rash fairly quick. I wasn't sure it was the lenalidomide, so we stopped it, and it did go away. And we said, let's just try it again. And within a week or two, it came right back.
- DR LOVE:** So, Morie, we asked the audience here: What would you likely have done at the time that he presented with the exacerbated psychiatric symptoms on the RD? It looks like the most common answer was to keep the RD going but reduce the dose of the D. But whenever you see that kind of heterogeneity, it means maybe we don't all know exactly what to do.
- Before we go to the next one, what would you have done, Morie?
- DR GERTZ:** In this type of a situation, I would have halved the dose of dexamethasone. If the half dose of dexamethasone wouldn't have worked, I would have given him 12 milligrams. If that wouldn't have

worked, I would have switched him over to oral prednisone 7 days every 4 weeks, much better tolerated. If I still couldn't get away with that, I would have used IV methylprednisolone.

DR LOVE:

Hmm. Interesting. The other question we asked is related to this question we wanted Morie to talk about in terms of maintenance len and risk of second cancer. We were curious what you would say to a patient in terms of what the risk is, if any. And it looks like it's kind of a split between there is or is not, Morie, and you can talk a little bit about it.

And finally, just to lead into some of the comments you're going to make about pomalidomide, I was kind of curious how much information is out there right now. Looks like a lot of people haven't heard enough about it to decide. So maybe we ought to repeat this after your talk. So, Morie, can you address these issues?

DR GERTZ:

Right. I'll start first with the pathologist's bone marrow examination. I must admit, in our practice, routinely we don't require flow for the diagnosis nor do we require immunohistochemistry. We think it's a lot easier, though, to look at the right stained aspirate than the H&E biopsy to distinguish plasma cells. And if we get a count of an appropriate number of obvious plasma cells by right stain on the aspirate, we don't think more sophisticated diagnostic tests are required.

My disclosures.

What about those individuals who said, "Let's not use steroids"? It was just too toxic. This patient is going to end up with a psychiatric hospitalization or they're cleaning the kitchen at 3:00 AM or their blood pressure's up or their glucose is 400. You know all of the problems with the steroids. How about just cutting them out?

And I think that's not a wise idea, because steroids are still a critically important treatment for the management of multiple myeloma. And I'll cite 2 studies. First of all, in a retrospective study of 35 patients who received contemporaneous dexamethasone compared to 72 patients who received VAD — so this is prenovel agent, where single-agent dexamethasone was still ethical — the response rate just getting dex — and that's in the old days of 1 through 4, 9 through 12, 17 through 20 — was 63%, almost as good as VAD.

And in the ECOG study that first looked at thalidomide/dexamethasone versus single-agent dexamethasone, the response rate to single-agent dexamethasone alone was 41%. So cutting out corticosteroids on that basis is not a good idea.

We did a study at Mayo looking just at lenalidomide and then adding dexamethasone in after the fact. After cycle 1, adding 10 milligrams, after cycle 2, 20 milligrams, up to 40 milligrams until we achieved a response. And it turned out that was an inferior way to go. On-demand dexamethasone, adding it in was inferior to just starting at a higher dose and tapering it.

The same thing can be said when you look at the bortezomib data. When Sundar Jagannath used bortezomib as a single agent and added dexamethasone in, the response rate in a substantial number of patients, 18% in SUMMIT and 33% in CREST, had an upgrade. So just not using dexamethasone or a corticosteroid is generally not serving your patient.

So what we really need to do is start to manage the toxicity. What we don't know is: Is 20 milligrams as good as 40? Is 10 milligrams as good as 20? We have to make compromises based on that patient's toxicity. And I am very comfortable reducing the dose. But dexamethasone is not the easiest steroid. There's no question that prednisone, prednisolone and methylprednisolone have a much shorter half life and are much better tolerated by patients. So if you can't work with dex, you change your corticosteroid.

I want to talk a little bit about the IMiD toxicities, skin, fatigue, the DVT. What do you do when your kidneys are bad and the second primary cancers? And I'll finish with pomalidomide.

This is a typical rash that you see with lenalidomide. Most of them are nonvasculitic, but in my experience cutaneous reactions to lenalidomide are the number 3 side effect after leukopenia and thrombocytopenia so that finding a skin problem was not some kind of minimal trivial. It's very common in day-to-day practice, and we have to figure out a way to manage it because the agent itself is so very effective.

So there are a number of consensus recommendations that have been published regarding how to manage nonhematologic adverse events in patients who are receiving len/dex. This was published for relapsed/refractory myeloma.

For the rash, antihistamine treatments are recommended for these patients. If the rash persists, however, you can get away with low-dose prednisone. If they're taking len 21 days out of 28, you can give them prednisone, 10, 15, 20 milligrams a day. That's not going to cause a big problem 3 weeks out of 4. And I would generally add that.

The rash usually is self-limiting, but I've seen it also recur with rechallenge. Those patients can be controlled with steroids. In a very small number do you have to finally abandon it, saying, "We can't manage it. The rash is too toxic for our patient"?

Fatigue related to lenalidomide is also a major issue. Obviously you have to worry about, is it because their hemoglobin's 9? Is it related to depression, corticosteroids and the other things? But dose reduction is commonly required for severe fatigue. If you're at 25 of lenalidomide, fatigue can sometimes actually drive — if no other hematologic abnormality, reductions to 15, I think that's legitimate.

And just reminding you that dexamethasone does predispose to infections. In the old days, when we gave it 1, 4, 9, 12, 17, 20, PCP pneumonia was a big deal. I still use routine antibiotic prophylaxis for the first 4 months after starting treatment. I think there are no data. We've used fluoroquinolone antibiotics. We've also used sulfamethoxazole trimethoprim. There's not much evidence justification for vaccinations. We do it, but we're unclear that it really helps. I think the most important thing regarding infection in patients with myeloma induction is prophylaxis for herpes zoster, which is really a devastating problem that we encounter.

What about how do we prophylax against deep vein thrombosis? These are cumulative data based on a retrospective analysis in nearly 100,000 patients, of which 13,000 were in trials, and then 85,000 were in FDA surveillance, reported by pharmacies. And the VT incidence with aspirin is running between 3 and 5%. It clearly is higher when you're using either a doxorubicin-based regimen or a steroid-based regimen. Thalidomide alone, for example, doesn't increase VT at all. It's when you added the dexamethasone that it became a problem. Clearly, the higher the dose of steroid, the higher the risk of VTE and the lower the steroid dose weekly, the lower the risk.

Basically it's all over the place. I don't use warfarin, because I can't get the INR controlled in these patients, because they're taking pulse dexamethasone. They're taking fluoroquinolone antibiotics. I can't stand chasing the INR. I've also had, at least in the United States, problems with reimbursement with low molecular weight heparin. Some of the insurance companies require you have to show up in the office to get it, the treatment, which is a problem on Saturday and Sunday. So my patients are getting aspirin and I'll anticoagulate those patients that get a DVT.

There are obviously a lot of factors that actually drive the decision about who should be getting prophylaxis. Most of the patients that I see have a relatively low risk, and I feel comfortable with aspirin. Obviously if they've had a prior history of a deep vein thrombosis or they're highly sedentary or they're immobilized because they had an orthopedic procedure from their lytic disease, I'll give those patients low molecular weight heparin for the first month or so.

This is the consensus guideline that was published in *Blood Reviews* by Palumbo and colleagues from the International Myeloma Working Group, where they actually risk stratified. And if the patient had 1 or less risk factor, they gave aspirin. If it was greater than 2, they gave low molecular weight heparin for 4 to 6 months. And again, those risk factors are age, sedentary, history of prior DVT, significant cardiovascular disease. In my experience, I don't modify those changes based on the platelet count.

What about your patient that presents with myeloma-cast nephropathy and you're considering use of lenalidomide? This was published last year in the *European Journal of Hematology*. And basically, if your creatinine clearance or EGFR is greater than 50, you're fine to use full-dose lenalidomide. I think the recommendations are reasonable. Most of it's really based on myelosuppression. If you use too high a dose, you can fix that with the second cycle if you run a little high. But if you're 30 to 50 and your creatinine clearance 10, and even patients who are on dialysis can get 15 milligrams 3 times a week. After dialysis, 15 milligrams every other day for nondialysis dependent, but Grade IV or V chronic renal failure.

Second primary cancers. It was briefly summarized already by Pieter, but in the French trial there were 10 versus 2 hematologic cancers and 6 versus 1 nonhematologic cancers. But the trial was stopped by the federal authorities. And that's going to make the relapse-free and overall survival a problematic endpoint to assess, because everybody got taken off maintenance lenalidomide.

In the CALGB-led trial, CTN, there was, of interest, 1 Hodgkin's and 1 ALL out of the 231 patients. And in my entire career, I have never seen Hodgkin's disease or ALL in a myeloma patient. So that's a

little bit disturbing. That's not your typical prostate cancer or melanoma in an elderly myeloma patient. They had 5 AMLs in the len group, which is 2.1%, and 1 MDS in the placebo group, which is 0.4%. And there were 1 MDS patients at the time of diagnosis when they were randomized.

And when we look at the toxicity between the 2 groups, you can see there's a substantially greater number of patients in whom we have to stop lenalidomide therapy due to toxicity, 33% of which was nonhematologic adverse events. There's your second malignancy numbers: total, 18 versus 4.

But having said that with these second cancers, you have to ask yourself: What do I tell my patient? Here's what I tell my patients: "Is there a risk of second cancers? There really may be, and you really need to think about it. And I'm going to tell you that the odds of dying of a second cancer are one fifteenth the odds of dying of multiple myeloma. Multiple myeloma is the problem immediately, not the question of a secondary cancer, and you need to think about that when you make the decision as to whether this is an issue."

In addition, when patients live longer and are followed longer, they clearly have a higher risk of developing secondary cancers, because there are more years at risk. So when you do the analysis, you actually have to do it when you're using the cancers as a secondary event. And when they did that in the CALGB trial, there really wasn't very much difference at all.

The incidence of secondary malignancies after 6 years' follow-up of continuous lenalidomide was published this year at ASCO by the group at Cornell. They looked at their patients who were treated with clorithromycin, lenalidomide and dexamethasone in newly diagnosed nontransplanted patients. There were no cases of secondary MDS, hematologic. There were 6 skin cancers, 2 colon, a prostate, a pancreas and a melanoma. But when they looked at the SEER database for comparably matched age controls, there was a very similar incidence.

This was also referred to by Pieter Sonneveld. And this is the MPRR maintenance trial and, again, in the MPR plus R, there were 12 second primary malignancies, 9 in the MPR group and 4 in the MP group. And I'll take you down to the bottom. You can see AML, 2; MDS to acute AML, 1 and MDS, 2 but no Hodgkin's, no ALL. And in the MVRR, 3.5%; MDR, 2.6%; MP, 1.1%. So there may be a difference. There may be a difference of a percent or 2, but when you do standardized incidence ratios over time you can see that although it might be a bit higher, these are still very, very small numbers that we're contending with.

And this also was shown by Pieter. So in green means problems with multiple myeloma. And purple means problems with your secondary malignancy. And I would show this to a patient and I'd say, "That purple line is not what you really need to be worrying about."

In a meta-analysis that was published this year in almost 2,500 myeloma patients with 9 trials, there were 30 second primary malignancies — that's two thirds of a percent — 6 with melphalan/lenalidomide, 7 stem cell transplant lenalidomide and 17 that didn't ever receive lenalidomide. The risk of a malignancy death at 6 years was 4% and, at 6 years, 40% died of multiple myeloma.

So, just trying to conclude, lenalidomide plus dexamethasone treatment and the risk of second primary malignancies, I'll bring you to the bottom. Len/dex, 471 patient years, 5 second primary malignancies; placebo/dex, 222 patient years, 2 second primary malignancies, an incidence rate of 0.24. And these were studies of salvage len/dex versus dex for relapsed disease.

Relapsed/refractory multiple myeloma: Again, if you look at the incidence per 100 person years, you see it rises with age — the older you get, the higher the risk of malignancy. It also makes a difference how long you receive treatment, but if you look at those numbers compared to the SEER data for age 60 to 85, it's pretty close. The differences are very, very marginal.

I'll finish up by telling you a little bit about pomalidomide. Look closely at the chemical structure on the right, because it looks awfully close to thalidomide and lenalidomide, very little difference between these 2 drugs. Yet on the left, you're using a drug at 100 to 200 milligrams a day. In the middle, you're using 15 to 25 milligrams a day, and on the right, you're using 1 to 4 milligrams a day as a reflection of the higher potency of this agent.

There have been 4 studies in relapsed/refractory multiple myeloma. The important thing is that in the beginning it was prior therapies. But then pomalidomide was used for lenalidomide-refractory patients, 32% response rate with len refractory. With len- and bortezomib-refractory patients, a 26% overall response rate. And in a second study at a different dosing schedule with len and bortezomib, relapsed/refractory patients had a 26% response rate. So my opinion is that pomalidomide has legs, and I think it'll be an important addition to the therapeutic armamentarium for myeloma.

This is just a summary. For pomalidomide, pomalidomide therapy at 4 milligrams is efficacious. It's tolerable, and it's effective no matter what their disease status is, how many drugs they've failed and what their cytogenetics are. It's also effective in patients who fail bortezomib. The toxicity profile is actually pretty easy. We use aspirin for our patients. Myelosuppression is pretty typical for an IMiD, and it wasn't associated with peripheral neuropathy.

Thank you.

DR LOVE: Thanks, Morie. I'm going to ask Dave to come to the podium, and we'll present the next case in a second. But maybe just to provide a little bit of perspective, it's kind of difficult for oncologists in practice to hear about new drugs. But, Carol Ann, when you listen to stories about patients who receive pomalidomide and, for that matter, carfilzomib in relapsed disease and seemed to have useful responses when they're resistant to the more conventional agents, you kind of wonder whether this — even though it's not available — referral to a trial for these patients should be almost standard in people who want optimal care. What are your thoughts about this?

DR HUFF: Absolutely. I mean, I think even when bortezomib initially came out, it was an agent that, for patients who were refractory to all other therapies — and I think that pomalidomide and carfilzomib offer options for our patients when other agents aren't working. So yes, I think referral to open trials — there's the expanded access program for carfilzomib at this point in time for patients who aren't eligible for trials. So there are plenty of mechanisms available at the moment.

DR LOVE: So just a couple more quick questions before we get to Dave. Pieter, there's a question about bendamustine. Carol mentioned before in terms of alkylating agents, CyBorD. What about bendamustine in myeloma?

DR SONNEVELD: Bendamustine is quite an old drug already from Eastern Germany at the time. That has been approved by EMA in Europe for use in multiple myeloma. We see responses. It has not been widely used so far, but trials are ongoing for combinations of bendamustine with proteasome inhibitors and other agents.

DR LOVE: So we want to move into, I think, one of the more interesting areas that's evolving right now in myeloma, which is related to the question of neuropathy and particularly related to administration of bortezomib. So Dave, here's the next case we're going to talk about: A 65-year-old man presents — this is from Canada — with weight loss, fatigue, is found to have an M spike, positive cells in the marrow, deletion 13, widespread lytic disease. He actually gets treated with a variety of agents, develops peripheral neuropathy related to bortezomib and yet seems to be responding in the long term to bortezomib very well. And here's the physician, as well as the supporting people talking about the case and the questions they have about it:

DR SEHDEV: This was a 65-year-old gentleman, very active in municipal politics. He responded well on treatment with bortezomib-based therapy. We actually used, initially, bortezomib twice weekly, a regimen that's popular at Princess Margaret Hospital in Toronto called CyBorD. And he had a very good response, but he had very aggressive disease and rapidly relapses within a short timeframe, not a candidate for second transplantation. What is the optimal management there? He did well on bortezomib. After stopping, he relapsed again. He was on bortezomib recently indefinitely afterward. He developed neuropathy. We cut him back to once weekly and subsequently had to lower his dose slightly, and he did well for a long time, with a dramatic remission afterward. If we use bortezomib, what regimen would the faculty recommend? Would they start off, for example, with a once-weekly regimen in this kind of patient? Would they use twice weekly initially and cut back to once a week thereafter? The dose of dexamethasone, should it be on a 4-day-on 4-day-off regimen in the beginning or once weekly? What would optimal prophylactic medication include in terms of prophylaxis for shingles or infectious complications? Should there be consideration of DVT prophylaxis on regimens like that?

DR CARVALHO: This is a bone scan, which was done before he presented to the oncologist, and it shows multiple areas of increased uptake in the ribs, in the thoracic spine and the lumbar spine, which certainly raised the possibility of malignant neoplastic disease metastasis or myeloma or lymphoma. Here is an MRI done. In the lumbar spine, we see multiple areas of abnormal signal on this T2-weighted sequence. There's also lots of height of some of the vertebrae in the thoracic-lumbar junction. These appear to be consistent with diffuse bone marrow infiltration with myeloma. Metastasis could also cause a similar appearance.

DR RUIJS: This patient had a bone marrow aspirate and biopsy. I'm showing you just images of the bone marrow aspirate here, and it's fairly easy to see that this is almost a single population of cells with eccentric nuclei along with perinuclear panel staining. So these are all plasma cells. And the next thing, which is a slightly higher power, just to demonstrate that a lot of these plasma cells are — there's some fairly

mature-looking, smaller, and then there are larger cells, and some you can see in pale blue nucleolus that's in there. Those are more immature plasma cells.

DR LOVE: Any questions for the faculty?

DR SEHDEV: Subcutaneous bortezomib is very exciting for us. I think in British Columbia, one of our largest lymphoma centers in Canada, I understand they have adopted that as a fairly routine intervention. We think of it as a new idea. We haven't yet implemented it. It's not routinely approved by our current guidelines, but I would like the faculty's opinion on the role of subcutaneous bortezomib and maybe a discussion of the advantages and the adequacy of the current evidence to support that at this point in time.

DR LOVE: So Dave, we asked the audience what they might do in a patient like this, who's responding to bortezomib but having problems with peripheral neuropathy. And it looks like the vast majority would try sub-Q. I'm really interested to see the next one, because we asked the audience: In how many patients have you used sub-Q? And it looks like about a third of the audience has. Two-thirds have not. And, finally, a topic that you're going to touch on, also: Do you have patients right now that you think could benefit from carfilzomib? And about half the audience said, "Yes." And we'll ask you all the same questions.

So Dave, can you review this?

DR SIEGEL: I think this case is illustrative of one of the most daunting problems that we have, and that is that bortezomib, perhaps arguably the most active drug that we have, is very limited in certain patients because of the peripheral neuropathy. So I'm going to talk about that.

Here are my disclosures.

So peripheral neuropathy, as you all know, is a significant problem in multiple myeloma. This is a very complicated issue. It's not exclusively related to the drugs. There is a significant incidence of clinically relevant peripheral neuropathy in newly diagnosed patients before they ever see treatment, 20% of patients. And if we look with more sensitive tools, 70% of patients will have evidence of peripheral neuropathy at diagnosis.

In the overwhelming majority of these patients, this does not significantly impair them. There are a number of treatment-associated factors that predispose patients to peripheral neuropathy. And overall, more than 50% of our patients using the drugs that we use today will ultimately develop significant peripheral neuropathy. This is problematic not only because of the impact on the patient's quality of life but also because it forces dose attenuations as in the case that we just heard. That will ultimately compromise the efficacy of treatment.

And it is not only bortezomib that causes peripheral neuropathy. Thalidomide obviously has become a significantly less important drug in the United States but worldwide still a critically important drug. Vincristine and cisplatin have become much more specialty drugs, given in very specific circumstances, not widely used for the treatment of multiple myeloma any longer. And again, this can be a life-changing kind of complication of therapy.

So what are the risk factors that patients have for peripheral neuropathy? What should we be thinking about as the patient comes to us and we're making decisions about therapy? Well, there are biological issues intrinsic to the patient. Obviously, patients with greater age not only are at higher risk for developing peripheral neuropathy, they become much more compromised in terms of their ability to function at a high level much more quickly when they do develop peripheral neuropathy.

Other comorbidities: Diabetes would be one of the very obvious ones that can impact on the likelihood of developing peripheral neuropathy. And then peripheral neuropathy is a very common problem in the age group that is predisposed to developing peripheral neuropathy.

And then there are the treatment-related issues, the duration of therapy, the only reasons that we have questions as to how long patients should be on therapy, we heard a whole series of questions about how long should patients be placed on maintenance therapy. All these things have to do with the cost. The cost is sometimes a dollar cost, but it's also a cost in terms of the toxicities that the patients will develop.

Dose intensity: Well, again illustrated by this case, as we are forced to attenuate doses, we lose activity and the intensity of therapy will certainly correlate with the likelihood of developing clinically significant peripheral neuropathy, and not only the intensity but ultimately the duration of therapy.

So how can we affect the likelihood of developing peripheral neuropathy? Obviously we change the dose. We can play with the dose of the drug. That will impact. We can adjust the schedule of the dose. That will impact on the likelihood. And we can change the mode of administration. All 3 of these were touched on, and they all significantly change both efficacy and toxicities.

So Morie had touched on the CREST trial. This is 1 of the 2 trials that ultimately led to the accelerated approval of bortezomib for use in patients with multiple myeloma, but this trial randomized patients to get 1 mg/m² of bortezomib on the 1, 4, 8, 11 schedule that is the most familiar one versus 1.3 mg/m². Now this is a relatively small trial, obviously, but as you can see from the data in front of you, the depth of response, certainly not significantly compromised by the lower dose of bortezomib, although the overall response rate, the patients achieving PRs or better, was slightly lower in the patients receiving lower-dose bortezomib.

However, the likelihood of requiring dose attenuation, something that significantly impacts on the outcome, was significantly improved in the patients getting the lower dose. Nonetheless, progression-free survival was better in patients getting higher-dose bortezomib. So we know that the dose makes some difference, but we also know that the drug is an effective drug even at attenuated doses.

So what's the other way that we can impact? We can change the schedule. And we've heard on a number of occasions, trials that have used once-weekly dosing of bortezomib versus the twice-weekly dosing that we are more familiar. And 2 of these trials, the CyBorD trial in the upper half of this figure shows the differences in the overall response. And you can see these are not significantly different. However, the likelihood of developing peripheral neuropathy of any grade, but the likelihood of developing peripheral neuropathy of high grade was significantly reduced in patients getting the once-weekly bortezomib schedule.

And in the VMPT study in the lower figure, very, very similar outcomes, that patients getting once-weekly bortezomib had very similar response rates to those getting twice-weekly, and a dramatic improvement, particularly, in the likelihood of developing high-grade peripheral neuropathy. So now we can decrease the dose, we can attenuate the schedule, as well, without dramatically compromising the quality of response, and significantly impacting on the likelihood of developing peripheral neuropathy.

The mode of administration, perhaps the most exciting, at least in my opinion the most exciting, is illustrated in this, I think, seminally important study by the IFM, the French Intergroup, in which patients were randomized to get subcutaneous bortezomib versus intravenous bortezomib. And it is remarkable how close the outcomes are in these 2 patient populations. So the depth of response is identical, the overall response rate is identical, the time to progression is virtually identical, slightly better in the subcutaneous group, the 1-year survival, the likelihood of being continued response was not changed by the administration of subcutaneous bortezomib. However, as you can see, the incidence of neuropathy was reduced, and the incidence of high-grade peripheral neuropathy was reduced by more than 50%.

So if we look at the pharmacokinetics, the area under the curve is virtually the same. There is a significant — the C_{max} is significantly higher in the patients getting intravenous bortezomib, but the area under the curves was basically identical. So you can see here, the pharmacokinetics/pharmacodynamics are really identical with subcutaneous and intravenous bortezomib with the exception of the differences in the C_{max}.

So the conclusion — and I'll just say it easily — is that subcutaneous bortezomib seems to be equally efficacious with significantly lower toxicities, particularly the one toxicity that seems to limit our ability to administer bortezomib long-term. So we should all be strongly considering subcutaneous bortezomib rather than intravenous bortezomib, and perhaps not just in the situation where we're responding to peripheral neuropathy but also in an effort to prevent peripheral neuropathy.

DR LOVE:

Could I maybe just — before you go on to the next thing, take a breath for a second before you get onto carfilzomib and just quickly ask the faculty this burning question that the doc in the video asked, and I think everybody is curious about, is: Are you using sub-Q bortezomib?

Nikhil?

DR MUNSHI:

We haven't totally switched over to sub-Q. We still use predominantly IV. I'm waiting for some more data on sub-Q and also ease of administration. There are some local issues in the sense of how and where to do it. So our staff is getting ready to do it. But I think the data from Dr Moreau's study, which is well randomized, clearly shows that they're equal in efficacy, and we are beginning to incorporate but not switched yet.

DR LOVE: Now what about within, say, triple regimens, for example, RVD?

DR MUNSHI: So currently the RVD is by IV. And I think we probably would need to do studies, a smaller study, to show that it is efficacious, equivalent to what IV administration is, because in RVD we are trying to combine the synergism between the IV dose with lenalidomide. Would sub-Q provide the same? Probably yes, but I think we need to show that.

DR LOVE: Dave, what are you doing in your own practice right now in terms of sub-Q?

DR SIEGEL: We have entirely switched over to sub-Q.

DR LOVE: Carol?

DR HUFF: By and large, we have switched over to sub-Q.

DR LOVE: Morie?

DR GERTZ: All nonstudy patients, sub-Q.

DR LOVE: Michele?

DR CAVO: I cannot use because it is not yet approved.

DR LOVE: Pieter?

DR SONNEVELD: In the intensive induction setting we are still using IV, because we follow the patients closely and we want to see what happens, so once patients who come in, there's no benefit for the sub-Q. In the more chronic use of bortezomib we are about to introduce it, awaiting approval, as well Michele says.

DR LOVE: Okay. Maybe we can just talk for a minute about new developments in proteasome inhibition, and particularly carfilzomib.

DR SIEGEL: So this is perhaps the teaser in this, is if you look at cell culture systems for dendrite growth, bortezomib significantly inhibits dendrite growth and an equimolar concentration of carfilzomib does not. So it may, in fact, not be an on-target effect of proteasome inhibition that causes neurotoxicity in patients with multiple myeloma. So second generation proteasome inhibitors, all of you have seen this picture.

There are 3 catalytic sites in the proteasome, the beta-1, beta-2 and beta-5 subunits with slightly different proteolytic activities. There is a series of proteasome inhibitors in clinical trials. This is not a complete list. It is the list that I know something about.

Most of them attack the same catalytic site, which is the beta-5 or chymotryptic-like site. There is 1 proteasome inhibitor, the Nereus compound, MPI-0052, that actually attacks all 3 catalytic sites.

The pharmacokinetic qualities of these drugs are distinctly different and, hence, the toxicity profiles will be different.

So here is a timeline looking at the proteasome inhibitors that I listed previously. Obviously, bortezomib is there at the top. It is one of the seminal drugs that we have developed in the treatment of patients with multiple myeloma. The other proteasome inhibitors and where they are in their clinical development is shown below.

Carfilzomib as monotherapy, there's actually been several clinical trials. This is the accelerated approval trial, the one that is currently under submission to the FDA. It was originally designed, the 003-A0 trial, patients with progressive myeloma receiving a dose of 20 mg/m². Once we became comfortable with that schedule, an expanded cohort of, quote unquote, unmet-need patients, meaning patients more heavily pretreated, were enrolled on a trial that was 27 mg/m² trial actually, 20 into 27.

So 266 patients enrolled in this trial. The median of 4 lines of therapy, so this is an extremely heavily pretreated patient population, and we'll quickly show you some of the data.

Here is the overall response rate, 24%. The overwhelming majority of these patients were bortezomib refractory. The response rate in the bortezomib-refractory patients was slightly lower, still a robust response rate. The clinical benefit rate, including those with minimal responses, was 34%. You can see the progression-free survival and overall survival numbers for the drug, again quite robust.

So the overall duration of response was 8.3 months. The toxicities, as you can see in comparison to some of the other molecules, this is probably slightly less myelosuppressive. And most importantly, in the context of this discussion, an extremely low incidence of high-grade peripheral neuropathy in these 266 patients who were treated.

The experience with carfilzomib has now been extended to combination therapy, so carfilzomib/len/dex in the relapse setting, highly active. This was a trial that was led by Rubin Niesvizky at New York Hospital. It has also been tried in the up-front setting, pioneered by Andrzej Jakubowiak at University of Michigan, now in Chicago. Again, any extremely active compound. You can see that virtually 100% of patients respond, and the depth of response in patients treated with 8 cycles of therapy, 67%, two thirds of the patients, achieved near CRs or better. So this combination is extremely active.

So this is just a list of some of the abstracts that are relevant to that.

DR LOVE: Thanks, Dave. I'm actually going to ask Nikhil to come to the podium and we'll go to the next case. I mentioned this summit workshop we had in April on myeloma. And right before that, there was a really fascinating article published in the *New England Journal* by Nikhil's colleague at Dana-Farber, Ken Anderson, as well as Antonio Palumbo. It was a review article, the first time *New England Journal* had done one on myeloma, I think, in about 10 years. But the thing that caught our attention was something that Dr Palumbo had been talking about for about a year, which is the question of in the management of the elderly, preemptive dose reduction. And I hadn't seen that before in the literature, and we talked a lot about that.

We asked Nikhil to talk about the issue of the older patient, and it was prompted by this interesting case from India, if we can bring up the next case. This is a 74-year-old woman who, interestingly, presented with fever, weight loss, lymphadenopathy and had an FNA and was thought to have tuberculosis, was actually treated for tuberculosis for several months, didn't get better and had an excisional biopsy and, interestingly — I'd never heard of this — actually had a plasmacytoma in the lymph nodes but on workup clearly had myeloma as well as other adenopathy. And here's the treatment team talking about this interesting patient:

DR SHAH: This lady presented to the physician with this lymphadenopathy and some weight loss, low-grade fever, and the commonest differential for these things would be tuberculosis. This was called tuberculosis and treated her for 3 months. Of course, didn't get better and at that time we were called in, where we did an excisional lymph node biopsy. Thank God for the pathologist who really thought that this is not like a typical lymphoma. Then further workup was requested, immunohistochemistry was done, and it seems like this was extranodal plasmacytomas, limited to the lymph nodes only. It's the first time I saw such a case where, on the PET-CT also, there were only lymph nodes, no bone lesions, no other lesions. Then we underwent more workup. We did the bone marrow biopsy and immunofixation and of course, turned out to be multiple myeloma.

DR MALLARAJAPATNA: This is an actual PET-CT fused image, which is showing highly metabolically active nodes in the prevascular region, part of the anterior mediastinum and some smaller nodes that are also positive on the FDG-PET in the right prevascular region, as well as right axilla.

DR PRABHUDESAI: You don't very often see plasmacytomas involving the lymph nodes and causing a generalized lymphadenopathy.

From a pathology point of the differentials, which would have to be entertained, would be a lymphoplasmacytic lymphoma or a plasmablastic lymphoma. But morphologically, this was really a very classic plasmacytoma. It had very mature-looking plasma cells, which had replaced the entire lymph node. The pathologist suggested to Dr Shah that he investigate for the myeloma and, lo and behold, showed up plasma cells in the bone marrow aspirate.

DR SHAH: I would really like to know from the faculty, how common is such a presentation and would you treat such a case differently compared to another routine type of myeloma?

DR LOVE: Any other questions for the faculty?

DR SHAH: Yes. In the elderly, what kind of cases would you treat with RVD? In general, len/dex or thal/dex is a more common approach that we use.

DR LOVE: So, Morie, have you seen 50 of these?

DR GERTZ: No. That's tough. There's no question about it. I don't know what the natural history is relative to your standard myeloma.

DR LOVE: Interestingly, half the audience has seen a case like this. I think that's really interesting. And kind of relevant to what you're going to talk about, Nikhil, is this question of preemptive dose reduction. We asked the audience: In a situation like this with a 74-year-old woman, would you just go ahead and use standard dose, or would you dose reduce? About a quarter of the audience would use standard dose, but if she were 80 — it's always tricky, what's the line between dose reduction — but most people

would use standard dose in a 74-year-old woman. So, Nikhil, maybe you can talk a little bit about older patients.

DR MUNSHI:

So these are my disclosures.

So first the question about unusual presentation, I'll just briefly touch that issue. Soft tissue plasmacytoma is one of the more uncommon ways of presenting myeloma. And it may involve one of many organs. One example here is a very classic case of just liver-only plasmacytomas on biopsy, confirmed, but you could have lymph node leptomeningeal disease, pulmonary pleural effusion. These are usually more aggressive disease. They are associated with symptomatology, night sweats, fever, typical B symptoms.

If you do their cytogenetics, most of the time they are quite aggressive disease, high-risk disease cytogenetics. And the therapy also needs to be aggressive. These are one of the situations where I would prefer to use a 3-drug regimen. And if a younger patient, even more aggressive treatment. And their survival ends up being, most of the time, much shorter.

There are a few other ways, unusual presenting features, a high LDH disease, various manifestations of forms — immunoglobulin Y is different myeloma, which may or may not be different than the traditional myeloma. But one of the most important points for this particular patient and, in general, half of the myeloma patients are more than 70 year old. The fact is that we should consider while deciding on the treatment, and one of the most important issues is comorbidity. These are old patients. They have diabetes. They have hypertension. They have renal problems associated with each of these problems, cardiac issues, neuropathy. We need to keep that in mind in deciding how well patients would take the treatment.

The second issue is their decreased functional capacity and the frailty. And if one is in geriatrics, one would know what frailty means, but when we see an older patient we know this patient is frail. Performance status is low, and other attributes of the day-to-day life are quite affected, including gait, physical activity, et cetera. And we need to keep that in mind.

Another issue is polypharmacy. Patients are taking a lot of medicines. In one of our studies, they were taking 13 medicines on median. So we need to look at interactions and what else might be happening.

And, most importantly, all this translates into their decreased capacity for tolerating any toxicity. So we need to keep this in mind in deciding what to do. So this is an agent to be used — is best on availability of the MP-based regimens, which means we can use those. Not by itself, but as I would show in combination, keeping the toxicity in mind.

The second issue is we can change the doses and schedule that we can use in this patient, either reduction based on patient-specific factors, also alternate routes of administration, as we saw, sub-Q or, if available, oral agents. And then alternate schedules, weekly, and also to keep in mind transportation needs of the patient.

The goal, however, still remains to get the maximal cytoreduction that we can get in this patient. And one point I want to highlight, although it doesn't belong here in this slide, is that we do not have to use an MP-based regimen. As we will briefly touch, we could use all those regimens which were described by my colleague in older patients, also with similar results.

So first we can look at, quickly, the MP-based regimen. MP is not used alone. It is used now with some of the novel agents, either MPT with thalidomide, or with bortezomib, MPV regimen, and MPR and/or MPR-R regimen. And the results are summarized in this table, which shows that responses are superior when we use a novel agent with MP compared to MP alone. CR rate, for example, with MPT is between 2 and 16%, 30% for MPV and close to 20% for MPR-R combination. And if you look at the survival outcome, PFS was superior in all 5 patients with MPT and 4 of the 5 patients for overall survival. And similarly, benefits were observed with MPV and MPR, also.

If we take the global view of all the 1,600-plus patients treated on the MPT study for meta-analysis, clearly there is superior PFS and OS with MPT. And similarly, if we look at MPR-R in older patients, which is an older-patient study, there's a significant benefit for PFS, so a number of zeros. And if you look at a patient group, 65 to 75 — so gender within the old group, we see even more greater reduction with MPR-R regimen, suggesting that novel agents need to be combined if MP is being used.

However, the toxicity also would be increased, so, for example, see the neutropenia was higher, infection risks were similar but you would have blood count problems. DVT, as expected, if we add the lenalidomide, incidence would be higher.

I won't touch the issue of second malignancy, I think we have discussed quite well earlier on today. And if you use MPR it may require dose reduction, which may affect overall outcome. So that needs to be balanced.

And for VMP regimen, number of modifications have been made to treat the older patient population, to see if the fourth drug helps. Look at alternate schedules. Look at including maintenance with VT or VP and then changing combinations to replace melphalan with more immunomodulatory-agent type of regimens. An MPT plus VT regimen, maintenance with bortezomib and thalidomide has been evaluated. And as you see here, VMPT had a superior outcome compared to VMP for both progression-free survival and time to next treatment.

If you look at how the VMP schedule affects the outcome, there are 3 different studies, the old, we start to use this twice-weekly bortezomib, while the next 2 studies have used either once weekly or a short period of twice weekly followed by a once-weekly regimen. And if you look at results of these studies, you could clearly see that by reducing the frequency of bortezomib to once weekly, the overall response rate and CR rates, more or less similar. PFS and OS are also similar.

But if you look at now the toxicity, the neuropathy is significantly reduced, both all grades and Grade III. Discontinuation due to neuropathy is down, and discontinuation due to other AEs are also decreased. So just by changing the regimen, the scheduling, we might be able to affect the toxicity, but not efficacy. And this is what we need to do for the older patient population.

Now, replacing the melphalan with some other alternative regimen, including immunomodulatory agents, there's a more recent study, CTD, which includes thalidomide or cMP. You can see an increase in overall response rate with the CTD regimen. And comparing what happens when using RVD and Dr Shah, who presented the case, did mention that they more often use RD with cis and RVD.

What are the results of using a lenalidomide-based regimen without melphalan in older patients? We can look at these data that Dr Rajkumar published last year, where lenalidomide with high-dose dex was used with lenalidomide with low-dose dex, and in patients who are more than 65, the older patient population, the low-dose dex was quite significantly superior compared to high-dose dex. And when cycles were given beyond 4, the overall response rate for that regimen was 91%.

Toxicity, of course, is also improved with the low-dose dex regimen, as Dr Gertz quite elegantly described the benefits of using dex and, also, reducing the dose. And those principles apply more specifically for older patient populations because they do not tolerate dex very well.

And now if we compare the MP-based regimens, MP backbone versus novel agents — and they're all not described here — from CR with GPR and PR, you can see that, in general, the novel agent without MP may have higher response rates compared to the MP backbone-based regimen. And if you look at the VR, which was a specific question from this case, it provides 100% response rates. In this particular study by Dr Richardson, 15 of the 64 patients had age about 70, and their response rate was similar to the younger patients. So VRD is a good regimen for older patients also, except the tolerability may be affected, so we need to consider alternative VRD regimens. There are a few of them already in investigation, what we are calling VRD-lite, either by changing the bortezomib dose, changing the lenalidomide and our scheduling.

So if we look at dose adjustment, this was what was published in the *New England*, that we could have dose levels based on patient characteristics with age and, also, their performance status and their comorbidities. And we could have dose levels from 1, minus 1 to minus 2 to decrease the dose. However, in patients who are tolerating the dose, I would prefer to start with dose level 0 and then decrease the dose, unless patients have extremes of any of the factors that I mentioned and I'm going to review.

So this is just general guidelines of what dosages we could use in older patient populations and/or with a number of comorbidities. So we know that novel agent combinations are superior to MP or old conventional chemotherapy, that maintenance with bortezomib or lenalidomide may have some significance in overall PFS. However, we need longer follow-up and larger studies specifically in older patients to see if maintenance therapy makes a difference and how big a difference it makes.

We need to optimize the treatment duration in all patients to treatment 'til progression and/or stop at a certain point. And dose, I just mentioned, should be done based on age and comorbidities. So the recommendation when you have an old patient is to assess patients' biological age, not just the numeric age, comorbidities, frailty and other disabilities. And this will depend on the degree of functional impairment patients may have. We select the most appropriate regimen and adapt the

dose, if required, based on the above factors. And then we need to optimize the supportive care with bisphosphonates, antibiotics, including anti-infective agents, cotrimoxazole or something similar, to prevent infection while getting dexamethasone, antivirals if the patient is taking a bortezomib-based regimen, importantly anticoagulation, as it was mentioned that old age increases the risk, and then pain control and growth factors if and when needed.

Thank you very much.

DR LOVE: Thanks, Nikhil, you can have a seat. And, Carol, you can go to the podium. And let's take a few quick questions, though, before we go to our last case.

Pieter, what about the octogenarian, 80, 85-year-old, still without very many comorbidities? How do you approach selection of therapy, duration of therapy in these patients?

DR SONNEVELD: Well, in general, we follow now the recommendations as was shown by Dr Munshi and published in *New England Journal*. But I think what was mentioned, that the biological age of the patient is, of course, very important. And — but if he is still quite fit, we treat him at the “slow-go” schedule, so to say.

DR LOVE: So a couple of other questions from the audience: Michele, is tandem transplant dead?

DR CAVO: Transplant ineligible?

DR LOVE: Tandem transplant.

DR CAVO: Oh. It is an open issue. It is an open issue. And I think that in the novel agent era it should be addressed in the context of randomized clinical trials. This is the reason why in the EMN-05, patients randomized to high-dose therapy will receive a single or a double autologous stem cell transplantation.

DR LOVE: Dave, allogeneic indications?

DR SIEGEL: We actually do a fair number of allo transplants. In the up-front setting, we will encourage patients with high-risk disease to do allo transplants. There's obviously very little data to support that. We tend not to do mini allo transplants. We tend to do near ablative transplants in that patient population. And certainly there continues to be a role for a salvage allo transplant, as well.

DR LOVE: Morie, a lot of questions about management of the patient presenting with acute renal failure, and I'll throw in, also, there are a couple about bone management with renal failure. Morie?

DR GERTZ: Sure. I think the main thing is that if you've got acute renal failure, bortezomib is mandatory because there are two key issues. One, you've got to get the light chain circulating, causing the cast nephropathy down quickly, so you need rapidly acting agents. And it's very helpful, because no dose modification is required for bortezomib in renal failure, a thing that's tremendous.

Where I think there's still controversy is what's the role of total plasma exchange in the patient who presents with cast nephropathy? There's only 1 trial that showed no benefit. But there are others who feel that if the light chain level is really, really high, there is some benefit. Now there's a new technique, high cutoff dialysis, that's being studied, where patients get a membrane done that has a pore size that removes light chain, that removes the albumin, as well, and that's being explored to rapidly reduce the light chain while chemotherapy is becoming effective.

DR LOVE: So, Nikhil, Carol is going to talk about bone-targeted therapy, but in terms of patients with chronic renal failure, what's your preference in terms of bone-targeted therapy, reduced-dose bisphosphonates? Would you ever use denosumab?

DR MUNSHI: So I think we do not have much data yet with denosumab, of its benefit in myeloma. So one would prefer to use zoledronic acid with a reduced dose if that is physically within the renal function range that patient may have.

DR LOVE: Okay. Let's go to the last case. And, Carol, this is a patient from Nice, a 64-year-old woman presents with widespread lytic bone disease, a lot of pain, found to have kappa Bence-Jones protein, basically has myeloma. And the thing that was interesting about her — and I didn't realize this — actually, cement injections were first done in France. So she twice had cement injections during the course of her treatment, once in the femur and the other, interestingly, in the sternum, which I thought was really interesting. And we asked the docs to talk a little bit about this patient.

DR MOUNIER: This is a good way to treat the pain, and this is a good way to spare the marrow. If we use radiation therapy, we can damage the marrow and then not go to other second- or third-line treatment due to cytopenia. We do the kyphoplasty with the cementoplasty, and we preserve the marrow.

- DR LOVE:** What happened when she had the cement injection in the sternum?
- DR MOUNIER:** She had pain in the sternum. We do the radio. We do the CT scan, and we can see that there is a destruction of the bone of the sternum. In this case, the radiologist agreed to inject the cement into the necrosis, into the gap in the bone. The injection was done in the afternoon, and on the second day, the day after the injection, she said, "Okay. I think I feel better and we can decrease the drugs." And 2 or 3 days after that, she has no more pain in the sternum and we can stop the drugs, the analgesic drugs.
- DR VIAU:** This is the CT we had done in June 2009. At the initial diagnosis when the patient had pain in the knee, in the left knee, we discovered something like an osteolytic lesion on the medial femoral condyle, so after a first good response of the treatment we are suspicious of a relapse and we found this lesion in the sternum. This FDG-PET we made showed FDG uptake, so this was an osteolytic lesion actually. This is the treatment we made for this second osteolytic lesion in the sternum, which was again the cementoplasty for the sternum. We have a good response but secondary to the chemotherapy and, of course, the cementoplasty and the pain. There was local pain.
- DR BENCHETRIT:** This is a surgical sample from the osteolytic lesion of the patient. And there is no normal tissue anymore because it has been destroyed and replaced by a diffuse perforation, which consists in sheets of the plasma cell. We recognize them because of their eccentric and dark stained nuclei. Immunohistochemistry shows that tumor cells expressed CD138, which is a plasma cell marker. There is also kappa light chain section, and this confirms the monoclonality of the tumor, and so we can assess it is a plasma cell neoplasm.
- DR LOVE:** So before what Carol's going to talk about, bone-targeted treatment, but I wanted to get some thoughts from the panel in terms of local treatment in the bone. And as I suspected, Dave, a lot of people here would have preferred radiation therapy. We had a big discussion about radiation therapy in myeloma in our workshop that we were talking about, Dave. Can you comment about your philosophy about local therapy for bone?
- DR SIEGEL:** Well, the overwhelming majority of lytic disease in myeloma is not caused by plasmacytomata. So for those patients, radiation is not going to help them. So I think one of the big mistakes that we see are patients that get radiation because of pain and not because of plasmacytoma. I would actually have said C, the delay, wait for therapy, see if it affects the patient. But I use very, very little radiation.
- DR LOVE:** What about vertebroplasty, Michele? To what extent are you using it? Have you ever had a patient have an injection in something like the sternum?
- DR CAVO:** Yes. Certainly not in this case. I agree that probably radiation was the best choice. What I would like to say, that in a certain percentage of patients with severe, with pain, especially with the novel agents and they are very speedy action, most of these patients do improve symptoms. And my practice is to reserve vertebroplasty only to those patients in which there is a risk of neurological damage or in whom pain persists after therapy.
- DR LOVE:** Let's go to the last interactive question, which touches on what Carol is going to be talking about. We've been watching the MRC data evolve since ASCO 2010, a fascinating data set that we're going to chat just briefly about. But one of the key issues that's come out of that is how is the two-year duration that we've had for so long really still appropriate. And you can see that a substantial, maybe a minority of the audience, is now using more than 2 years.
- Just before Carol reviews it, Nikhil, how are you approaching duration right now?
- DR MUNSHI:** No. I think the guidelines and what we follow is that we do give for 2 years. And then if patient is in a good remission, then decrease the frequency but continue the bisphosphonate.
- DR LOVE:** And how long have you been doing that? Did the MRC change what you do at all?
- DR MUNSHI:** Yes. So I think we were treating patients before MRC for a long period of time with the reduced frequency. So MRC just substantiated what we were practicing, more or less, as far as the length is concerned.
- DR LOVE:** So, Carol, can you review this, please?
- DR HUFF:** Sure. Okay. Thank you all for sticking with us 'til the end. So what I'm going to talk about now is bone-directed treatment of myeloma, and particularly focusing on bisphosphonates in 2011.
- These are my disclosures.

If we talk about the management of bone disease in myeloma, bisphosphonates, which is what we'll spend the bulk of our time talking about, really are a mainstay of the therapy for managing bone disease for patients with myeloma. As we talked a little bit about, radiation can be used, but I think most of us, myself included, tend to not use radiation unless there is imminent neurologic compromise that is about to occur or if there's pain that's persistent beyond initial induction or salvage therapy for patients.

Surgical procedures such as kyphoplasty, vertebroplasty and even cement injections have been used. And most importantly, direct antimyeloma therapy for the management of bone disease.

The first data for this came out in the mid 1990s and, again, I'm sure you're all familiar with it, but I'd just like to refresh everyone's memory. This is the data published by Jim Berenson in '96 and updated in 1998, where patients with myeloma, Stage III Durie-Salmon myeloma and at least 1 lytic bone lesion were enrolled in the trial and randomized to either receive pamidronate once every 4 weeks or placebo. And at 9 months, there was an improvement or a reduction in the risk of skeletal-related events that deepened with 21 months of therapy. And patients were treated on a monthly basis and followed through this, but there was not follow-up beyond 21 months of therapy from this study.

Then came out the data that were published in early 2000 by Lee Rosen and colleagues looking at zoledronic acid versus pamidronate. And this was a noninferiority study looking at patients with either breast cancer or myeloma and at least 1 lytic bone lesion. So, to date, all of the studies had been in patients who had documented bone lesions. And what this trial found was that zoledronic acid and pamidronate were equally efficacious as far as the incidence of skeletal-related events. And so both agents are available and there was largely an adoption of zoledronic acid, in part based on the decreased time of infusion, and they thought that it might be a more potent agent.

So what is the optimal duration of bisphosphonate therapy? And I should say some of the questions to answer are: What is the optimal duration of therapy? Who should get bisphosphonates at this point in time? If so, which bisphosphonate might they get, and what is the frequency of administration?

And the true answer to what is the optimal duration is actually not known, because we do not have trials that study the question of limited duration versus ongoing therapy. And in the beginning, everyone began these agents monthly indefinitely for the rest of patients' lives until the recognition of the development of osteonecrosis of the jaw in the early 2003 period, at which point in time the guidelines or the recommendations were modified to give this monthly for a 2-year period of time. And you can see listed here several of the published recommendations for doing so: ASCO guidelines, the Mayo Clinic guidelines and European Myeloma Network, to give this monthly for 2 years and then reevaluate at that point in time.

And, again, a lot of this was based on the time to when skeletal-related events occurred and the observation of the development of osteonecrosis of the jaw. Osteonecrosis is an issue that the exact frequency isn't known but is probably somewhere in about the 5% incidence or less for patients getting bisphosphonates. And there are certain risk factors that we all recognize for this — that is, invasive dental procedures being the greatest risk factor, but patients who have poor oral hygiene, longer duration of myeloma therapy. And we try to mitigate this risk by dealing with dental issues up front, if you can. I mean, there are patients who come in with hypercalcemia and you need to treat them with a bisphosphonate and don't have time to deal with dental issues, but to monitor their dental status closely and avoid invasive procedures if at all possible.

But there's no real consensus as to what to do with bisphosphonates in the event that osteonecrosis develops. And you really need to tailor that to the individual patient based on the severity of their bone disease and what you believe their risk of skeletal-related events is.

But along came the MRC IX trial, which was, as Dr Love just mentioned, first presented in 2010. And this trial looked at the role of zoledronic acid versus clodronate in patients with newly diagnosed myeloma. And in this trial, this was independent of whether patients had evidence of bone disease based on skeletal lesions.

And there were 2,000 patients enrolled in this trial, half of whom were randomized to zoledronic acid and half of whom were randomized to clodronate. And they were treated until progression. So there was no finite duration of bisphosphonate therapy. And within each of these arms, they could either get intensive treatment or nonintensive treatment, based on what the treating physician thought their risk or what their ability to tolerate therapy was. And this was thalidomide-based therapy, so it does not include lenalidomide- or bortezomib-based regimens.

And the primary endpoints for the trial were looking at progression-free survival, overall survival and response rates and secondary endpoints looking at skeletal-related events and time to first skeletal-related event. And what this trial showed was that, in fact, patients who received zoledronic acid had an improvement in overall survival compared to patients who received the clodronate, with a 50-month median overall survival for those receiving zoledronic acid versus 441/2 months for those receiving clodronate, so a 16% improvement in overall survival and a 12% improvement in progression-free survival for those getting zoledronic acid versus clodronate. And this persisted even when you adjusted for the time to the first skeletal-related event. So this is really the first evidence that suggested that there was a potential survival benefit for patients receiving zoledronic acid regardless of whether they had bone disease present or not.

The median duration of bisphosphonate therapy was about a year for patients on this study but extended upwards of 2 years for some patients and even beyond that, because they were treated to time to progression. But there was a higher incidence of osteonecrosis for those getting zoledronic acid, about 4% versus less than 1% for those getting clodronate, which is a less potent bisphosphonate.

There was no difference in overall response rate for patients getting zoledronic acid versus those getting clodronate, suggesting that it wasn't a difference in response that led to this observed difference in overall survival.

What's interesting is that, in fact, the zoledronic acid decreased the skeletal-related events relatively early in the process, so the curves began to separate by 6 months with a 25% reduction in the skeletal-related events for those getting zoledronic acid versus those getting clodronate.

And this difference in skeletal-related events was cumulative over subsequent years of therapy. And you can see here, illustrated in the orange bars, the incidence of skeletal-related events for those receiving zoledronic acid versus the green, those with clodronate. And you can see that over time, the difference expands between those getting zoledronic acid, or the benefit improves.

What's interesting is that the benefit in reduction of skeletal-related events was present for those who had bone lesions, which you can see on the right-hand panel of your slide, as well as those who did not have bone disease at present. But you can see that there was a much greater incidence of skeletal-related events in those who had bone disease at baseline. So, a 34% incidence of skeletal-related events for those receiving zoledronic acid with bone disease at baseline versus 43% for clodronate and 9% versus 17% for those who did not have skeletal-related disease at baseline.

Interestingly enough, the survival benefit that was seen in this study was limited to the patients who actually had bone disease at present. So those who did not have bone disease at baseline did not show a difference in overall survival with the receipt of zoledronic acid.

So, from this trial, we can conclude that zoledronic acid significantly improves both overall survival and progression-free survival for the patient population as a whole, as compared to clodronate, and that the overall survival benefit becomes present early, suggesting a reason to treat patients early on with zoledronic acid as opposed to waiting.

The skeletal-related event improvement was seen within the first year, again supporting the early initiation of zoledronic acid, and there was a significant reduction in skeletal-related events during each of the first 3 years that patients were on study, again trying to get to the question of how long we might treat patients.

I will just briefly mention why these might work. And there's a lot of literature out there on the potential antitumor effects of bisphosphonates, not just in myeloma, but in other diseases. And there appears perhaps to be direct antitumor effects of the aminobisphosphonates, impacting tumor cell invasion, tumor cell proliferation and increasing tumor cell apoptosis, as well as some indirect effects on osteoclasts and tumor angiogenesis.

And excitingly, there are multiple agents in myeloma that are being studied at this point in time, which are summarized here or depicted here, that interfere with signaling pathways that are important. These include DKK1 inhibitors, as well as those that interfere with rank ligand, BAFF inhibitors, and multiple exciting agents that are undergoing investigation at this point in time, which will hopefully be forthcoming, which may, in fact, help explain some of the mechanisms of action of these agents.

So who should get bisphosphonates? Well, prior to 2010, the data that we had available suggested that there was benefit for patients with lytic bone lesions, but we didn't have data to suggest what to do for patients without bone disease. I think with the MRC IX trial, we can say that all patients with myeloma benefit from the addition of zoledronic acid. Even if they didn't have bone disease, they had a reduc-

tion in skeletal-related events for patients without bone disease and an overall survival benefit for the population as a whole.

It's unclear if pamidronate offers a similar benefit, because it hasn't actually been studied. And several consensus panels are now recommending the treatment of all patients with symptomatic myeloma, and I think many of us are doing that in clinical practice.

What's the optimal duration of bisphosphonate therapy? It's not clear. Initially we did it indefinitely, then scaled back to 2 years based on the appearance of osteonecrosis, and now with the MRC IX data, several groups have now made their recommendations open ended, including the UK, as well as the NCCN guidelines for 2012.

So what frequency should they be given? Most of the data are looking at monthly, but, again, in an endeavor to reduce toxicity, efforts are ongoing to look at whether you could give these less frequently. And these are data that was presented last year at ASH by Noopur Raje, looking at the Z-MARK trial, trying to decide whether you could dose bisphosphonates based on bone turnover markers, in particular looking at urinary N telopeptide levels. And if they were elevated greater than 50, depicted at the top, patients received zoledronic acid once every 4 weeks. But if they had low bone turnover markers, an N telopeptide less than 50, then they were treated once every 3 months and followed for a change in their N telopeptide levels, skeletal-related events or progression, at which point in time they then crossed over to the every 4-week dosing.

The early data suggest that there is a low incidence of skeletal-related events in both arms and time will tell whether this will be perhaps a way to tailor our therapy for our patients with myeloma and perhaps reduce the frequency of dosing.

So, in summary, I think we have data now to support the use of bisphosphonates for all patients with active myeloma, that the MRC IX trial shows us a benefit as far as overall survival and reduction in skeletal-related events and an improvement in progression-free survival for patients getting zoledronic acid. And in 2011, the data would support monthly dosing with close attention to risk and prevention of osteonecrosis.

Thank you. I just have mentioned here several abstracts on bone-related markers and bisphosphonates.

DR LOVE: Thanks, Carol. Just a couple of practical questions. So this fascinating issue, Morie, of using bisphosphonates in people without bone disease. Do you ever do it?

DR GERTZ: Yes. The MRC data suggest that there's a survival benefit. So, even though I don't really understand it, it's very difficult to argue with the data, and so I think it's justified.

DR LOVE: And what are you doing about duration?

DR GERTZ: Our group, by consensus, is still using it for 2 years, but we're not certain that that's right. And I have some degree of discomfort here because of the MRC data.

DR LOVE: So final question to Nikhil, and please, turn in your CME forms. Let us know what you like, what we could have done better. Nikhil, what about the issue of novel agents and their effect on bone? And are these kinds of studies actually maybe relevant in the era of novel therapy?

DR MUNSHI: So bortezomib, for example, has clear osteoblastic activity. And there are a few other newer bone-directed agents, as Carol described, important also in improving the bone function. However, I think the role for bisphosphonates is still going to be that its primary target is osteoclasts, which is what causes more bone destruction, and that's probably the most powerful agent we have so far to cover that angle. Bortezomib, for example, will help with bone healing and they both can synergize with each other. So I think bisphosphonates still remain a very important agent for managing the bones and preventing the bone problem.

DR LOVE: So I'd like to thank our faculty, thank Morie, my co-chair, thank the physicians who presented these cases, and thank you for coming tonight. Have a great evening.