Management of Patients with Relapsed and/or Refractory Multiple Myeloma

Elsevier CME Independent Conference Highlights of EBMT and EHA 2018

Dr Parameswaran Hari: Welcome to this CME Webcast on the conference highlights of the EBMT 2018 annual meeting and the 2018 Congress of the European Hematology Association on the management of patients with relapsed or refractory multiple myeloma.

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Faculty

I am Dr Parameswaran Hari, Professor of Hematology and the Chief of the Division of Hematology and Oncology at the Medical College of Wisconsin in Wisconsin, USA. I am joined today by Dr Noopur Raje, Professor of Medicine at Harvard Medical School and the Director of the Center for Multiple Myeloma at the Massachusetts General Hospital Cancer Center, as well as Dr Jesús San Miguel, Professor of Hematology and Medical Director of the Clinica Universidad de Navarra in Spain. Welcome to all of you.

Multiple Myeloma Background

Let's discuss multiple myeloma and specifically relapsed and refractory multiple myeloma in this CME session.

Myeloma, as you all know, is a plasma cell malignancy where malignant plasma cells accumulate in the bone marrow leading, eventually, to bone marrow failure and bone destruction, propensity for infection, renal dysfunction, etc.

"The second most common hematological malignancy" is how myeloma has been described, with approximately 30,000 new cases in the United States every year and approximately 12,000 deaths each year. New treatments have been improving outcomes of patients with myeloma for the past 1 to 2 decades. Five-year survival in multiple myeloma was approximately 35% in 2000, and is now about 53%, as estimated in 2010.

Most myeloma experts believe that median survival in myeloma patients has improved from about 3 to 4 years to more than 8 years in these past 2 decades. These successes have been attributed mainly to high-dose treatment and stem cell transplant in transplant-eligible patients, and the availability of numerous agents, such as immunomodulatory agents, otherwise known as IMiDs (examples are lenalidomide and

thalidomide), and proteasome inhibitors (such as bortezomib and carfilzomib), and a lot of improvements in supportive care that have happened over the past 2 decades.

Unmet Needs in RRMM

We still have unmet needs in multiple myeloma, especially in relapsed/refractory multiple myeloma. Relapse is almost inevitable in multiple myeloma, with most patients experiencing relapse after entering remissions. Prolonging the remission with effective, well-tolerated therapies is a huge unmet need.

Prognosis becomes particularly poor in myeloma patients who have received more than 2 lines of therapy and are then refractory to both proteasome inhibitors and IMiDs. Optimal combinations of novel proteasome inhibitors, IMiDs, and monoclonal antibodies have to be defined for these patients in particular.

Dosing regimens of current agents and new combinations are also an unmet need. Similarly, the role of autologous transplantation or donor transplantation (allogeneic stem cell transplantation) after relapse has to be clarified.

Finally, there is a plethora of immunotherapy agents that are in development for multiple myeloma.

Treatment Strategy for Newly Diagnosed Patients with Active Myeloma

We will discuss treatment strategies for relapsed/refractory myeloma in this session, but the treatment for newly diagnosed myeloma patients with active myeloma follows 2 specific pathways. It is primarily a strategy of high-dose systemic chemotherapy followed by stem cell transplant in patients who are considered transplant eligible, and this remains the standard of care for patients who are younger, fitter, and considered eligible for transplant.

For patients with multiple comorbidities or who cannot tolerate transplant, we depend on less aggressive systemic treatment and in both of these scenarios, whether they are transplant-eligible patients or -ineligible patients, maintenance is an important option. It becomes a particularly important option after a stem cell transplant and it has been shown in multiple studies to improve progression-free survival and overall survival.

Therapy for Previously Treated Multiple Myeloma

For patients who have previously treated multiple myeloma, in other words patients who have relapsed after therapy, the treatment regimens are numerous. This is a slide which summarizes some of the treatments that are in the National Comprehensive Cancer Network guidelines, otherwise known as the NCCN guidelines, in the United States.

These options may range from repeating the primary induction therapy if relapse happened more than 6 months after the initial therapy stopped, a combination of agents which are either doublets or triplets (one of the most popular triplets is bortezomib/lenalidomide/dexamethasone), and ranging from that all the way to novel triplets such as elotuzumab, lenalidomide, and dexamethasone or ixazomib, lenalidomide, and dexamethasone.

Choosing between these regimens is something that we will discuss, and the right side of the slide actually discusses a little bit about how we choose regimens based on the number of the relapse; in other words, a first relapse versus a later relapse, depending on the patient's exposure to previous agents and their refractoriness to previous agents.

So, in relapsed/refractory myeloma relapse, for example, we would end up using second-line, third-line agents, or clinical trials, whereas in first relapse, we could go for re-treatment or class switch and, depending on previous exposure, we can change the drugs within each class.

The option of treatment until a further relapse is now a well-established treatment paradigm in multiple myeloma, so for relapsed patients, we generally continue treatment until relapse or side effects dictate that treatment be stopped.

Discussion Outline

In this CME session, we will follow the following outline: initially we will discuss the role of proteasome inhibitors with the new data being presented by myself and Dr San Miguel. Dr Raje will then discuss the role of IMiDs, Dr San Miguel will discuss the role of monoclonal antibodies, and I will come back and discuss the role of allogeneic stem cell transplant with some of the data that have emerged at the EBMT meetings. Finally, we will discuss each of these sections in a moderated fashion.

Role of Proteasome Inhibitors

First of all, let's look at the new data presented on the role of proteasome inhibition at the EHA and EBMT meetings. I will present the subgroup analysis of this large randomized ENDEAVOR study and another subgroup analysis combining the results of the ASPIRE and ENDEAVOR studies, based on prior transplant status in relapsed patients.

After that, Dr San Miguel will present some other data relating to proteasome inhibition.

EHA-PF561: Subgroup Analysis of ENDEAVOR

The ENDEAVOR study is a large, phase 3, randomized study performed comparing 2 proteasome inhibitors: the novel proteasome inhibitor/second-generation proteasome inhibitor carfilzomib versus bortezomib, the first-generation proteasome inhibitor.

At the meetings, additional overall survival and safety data were presented from the study.

ENDEAVOR (Kd vs Vd): Study Design

Just as a reminder, this was a study of relapsed/refractory myeloma patients who had exposure to 1 to 3 prior therapies and had achieved at least a partial response after 1 of those prior therapies and had to have a performance status of 0 to 2.

These patients received carfilzomib at a dose of 56 mg/m^2 2 times a week for 3 weeks along with dexamethasone 20 mg on each day of the carfilzomib, and these were 28-day cycles given until progressive disease.

The control arm was bortezomib and dexamethasone, given in the conventional dosing fashion at 1.3 mg/m^2 2 times a week on Days 1, 4, 8, and 11 of 21-day cycles, again with dexamethasone 20 mg on the day of bortezomib and the day following bortezomib.

The primary endpoint of this study was progression-free survival, and the main data have already been published in *Lancet Oncology* by Dr Dimopoulos.

Results: OS in ENDEAVOR Follow-Up

At this meeting, we saw an overall survival advantage for the carfilzomib/dexamethasone (or the Kd56 arm, since carfilzomib was given at a 56 mg/m^2 dosing) with a median overall survival of 47.8 months versus 38.8 months in the bortezomib/dexamethasone arm. This led to a highly significant p-value and a hazard ratio of 0.76, indicating a 24% risk reduction in the risk of death.

These benefits in survival were observed in all patient subgroups analyzed, including elderly patients, patients with high-risk cytogenetics, and subgroups defined by prior treatment.

EBMT-B229/EHA-PS1309: ASPIRE and ENDEAVOR by Prior ASCT Status

Similarly, we had another abstract presented which combined the results of ASPIRE and ENDEAVOR and looked at prior transplant status and how that modified the benefit of the study treatment, including carfilzomib.

The objective of this abstract was to look at overall survival of patients who participated in the phase 3 ASPIRE study or the ENDEAVOR study, and define their responses and survival, based on prior transplant status.

ENDEAVOR (Kd vs Vd): Study Design

Again, the ENDEAVOR study is something that we just discussed, so I am not going to spend time on this. This was Kd56 versus Vd, or bortezomib/dexamethasone.

ASPIRE (KRd vs Rd): Study Design

The ASPIRE study was another large, multinational triplet versus doublet study in early relapse of myeloma. Patients with 1 to 3 prior therapies and relapsed disease were randomized between carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone.

Carfilzomib was given at a dose of 27 mg/m^2 for 12 cycles 3 times in each cycle 2 times a week for 3 weeks. Between Cycles 13 and 18, carfilzomib was given every other week and after Cycle 18, carfilzomib was discontinued and lenalidomide/dexamethasone continued.

The primary endpoint of this study was progression-free survival and 792 patients were randomized, and this study has also been published by Dr Stewart in the *New England Journal of Medicine* in 2015.

Results: ASPIRE by Prior ASCT Status

Coming to our data that were shown, based on prior transplant, it seems that the KRd arm had a significant median survival benefit with a median overall survival of 52.3 months in patients who had a prior transplant and were randomized to KRd versus 40.9 months for patients who had a prior transplant and were randomized to Rd.

This again led to a hazard ratio of 0.7 in favor of KRd, which meant a 30% decrease in the risk of death in patients who received KRd. So, this suggests that patients who were fitter, healthier, who had a prior transplant, were likely to derive even more benefit from KRd than Rd.

If we look at the patients who had 1 relapse or who were in their first relapse after transplant, the median overall survival was 57.2 months for KRd versus 38.6 months for Rd, again with a hazard ratio of 0.7 or a 30% risk reduction.

Now, coming to the patients who had no prior transplant, which presumably means patients with a less fit status or who were considered transplant ineligible or for whatever

reason did not receive a transplant at their initial induction, their median overall survival was actually no different between KRd and Rd at 39.8 months and 40.4 months, respectively.

The summary of this data is that the median overall survival in transplant recipients who have relapsed after transplant was improved by almost a year – 11.4 months' improvement with KRd versus Rd.

For patients who were in their first relapse after a failure of a transplant, the median overall survival with KRd improved by as much as 18.6 months, which is a phenomenal achievement for this group of patients.

Results: ENDEAVOR by Prior ASCT Status

Similarly, looking at the ENDEAVOR study, we see something entirely different. For patients who had a prior transplant and then had received Kd56 the median overall survival was 47.6 months, whereas with Vd, it was 41.1 months.

For patients who were in their first relapse after having had 1 transplant, the median overall survival was exactly the same for Kd56 at 47.6 months, whereas for Vd it was not reached; in fact, there was no significant difference, as you can see, the hazard ratios with the confidence intervals cross 1.

For patients who had no prior transplant, as you can see here in the right extreme, Kd56 had a median overall survival of 51.3 months, whereas Vd had a median overall survival of 36.8 months. In other words, the biggest benefit came to the patients who had no prior transplant. However, Kd56 was superior to Vd in all 3 groups. The biggest risk reduction seemed to happen in the patients who had no prior transplant and it was more evident in the no prior transplant groups as opposed to the ASPIRE study.

Safety: ASPIRE and ENDEAVOR

The safety data were also updated at these meetings and the extended analysis of the safety was consistent with previous reports, suggesting that carfilzomib was well tolerated, independent of prior transplant status.

We will now invite Dr San Miguel to discuss another study, the A.R.R.O.W. trial.

Dr Jesús San Miguel: Thank you very much indeed for the opportunity to discuss with you something that I think is really needed, which is to have information about the value of carfilzomib in a more convenient schedule – that would be the weekly dose.

EHA-S849: A.R.R.O.W. Trial – Carfilzomib Dosing

As you know, carfilzomib is a second-generation proteasome inhibitor that has high efficacy. The ENDEAVOR trial saw that Kd is superior to Vd in terms of progression-free survival, and now we saw also the benefit in overall survival, but a disadvantage is that it requires a twice-weekly infusion.

This study, the A.R.R.O.W. study, reports on the interim analysis of the phase 3 study in which once-weekly has been compared with twice-weekly carfilzomib plus dexamethasone in relapsed/refractory patients.

A.R.R.O.W.: Study Design

These patients should be refractory, should have received 2 to 3 prior lines of therapy, and they must have been exposed to proteasome inhibitors and IMiDs.

The patients received 28-day cycles of either carfilzomib at a once-weekly dose of 70 mg/m^2 with an infusion of 30 minutes on Days 1, 8, and 15 (20 mg on Day 1 of Cycle 1 as is standard of care), plus the dexamethasone 40 mg on Days 1, 8, and 15.

The control arm was the conventional twice-weekly schedule of carfilzomib at 27 mg/m^2 with a 10-minute infusion and the same dose of dexamethasone.

The primary endpoint was PFS, and the secondary endpoints were overall survival, overall response rate, safety, and PK studies.

A.R.R.O.W.: Results

Now let me share with you the results, but before that, I should emphasize that baseline characteristics were well balanced in both arms and the results indicate that the once-weekly schedule is superior in terms of PFS with a median of 11.2 months as compared to 7.6 months, and this was associated with a superior overall response rate, 62.9% versus 40.8% and the CR rate was 7% versus 1%. Both were highly significant.

Regarding toxicity, the incidence of Grade 3 adverse events was very similar in both arms. Grade 3 hypertension was equal in both arms as well, 5.9% versus 5.5% as well as cardiac failure, 2.9% versus 4.3%. This indicates that the once-weekly carfilzomib plus dexamethasone improved the progression-free survival and overall survival as compared with the twice-weekly, with a similar safety profile.

EHA-PF554: MUK FIVE STUDY: Carfilzomib Maintenance

Now let me move to another study that I think is intriguing and has addressed an important issue, which is the potential value of carfilzomib maintenance. This is a UK study,

it is a phase 2 trial in which patients were first randomized to receive either carfilzomib/cyclo/dex or bortezomib/cyclo/dex for a short period of time, and then, in the carfilzomib arm, the patients were randomized to maintenance with carfilzomib versus observation.

In the next slide, we can see the study design.

Phase 2 MUK FIVE (KCd vs VCd at First Relapse): Study Design

A total of 300 patients were included. They were relapsed/refractory patients at first relapse or with primary refractory disease. The randomization was 2 to 1; this means double the number of patients in the carfilzomib arm, 201 patients were included versus 99 patients in the bortezomib arm.

The dose of carfilzomib was 36 mg/m^2 on Days 1, 2, 8, 9, 15, and 16, and the dose of bortezomib was 1.3 mg/m^2 on Days 1, 4, 8, and 11. These were 21-day cycles for the bortezomib versus 28-day cycles in the case of carfilzomib.

The dose of cyclophosphamide was the same in both arms, 500 mg on Days 1, 8, and 15, and the dose of dexamethasone again was the same on Days 1, 8, 15, and 22 in the case of the carfilzomib arm, because the cycles in carfilzomib were 28-day cycles, 6 cycles versus the 21-day cycles, 8 cycles in the case of bortezomib, and for this reason, the dose of dexamethasone was only given on Days 1, 8, and 15.

The primary endpoint in this part of the study, the induction, was to have non-inferiority in terms of VGPR or better, and I can share with you the results because 40% in the carfilzomib arm as compared to 31.9% in the bortezomib arm achieved VGPR or better with an overall response rate of 84% versus 68%.

After this short induction, that was just either 6 or 8 cycles in total of 24 weeks, the patients in the carfilzomib arm were randomized to receive carfilzomib maintenance or no maintenance. The maintenance was for 18 cycles given in a schedule of 28 days each cycle at a dose of 36 mg/m^2 of carfilzomib given during the first 6 months on Days 1, 2, 15 and 16, while in the subsequent 12 months, carfilzomib was only given on Days 1 and 2.

A total of 141 patients were eligible for this second randomization; 69 in the carfilzomib arm and 62 in the maintenance non-carfilzomib arm. Both arms were well balanced for response. The response rate before entering into the maintenance phase was 58% and 54%, and also well balanced for the staging system and minimum residual disease.

MUK FIVE: Results

As you can see in the next slide, the primary endpoint, the progression-free survival from this second randomization, shows a significantly longer PFS for carfilzomib maintenance, 11.9 months, as compared with only 5.6 months in the observation arm. This is a hazard ratio of 0.59 with highly significant difference according to the p-value.

I should also mention that 44% of patients have completed the first 6 maintenance cycles, and 18% the total 18 cycles. On top of this, the incidence of adverse events during the maintenance phase was really low and predominantly Grade 1 and 2. Only 2% of patients suffered cardiac problems.

Overall, these results indicate that the carfilzomib dosage can be attenuated following induction in order to prolong the progression-free survival, and I think this is the first study in which carfilzomib has been tested as a sort of maintenance, following, in this case, a short induction phase.

Dr Hari: Dr San Miguel, thank you for that excellent discussion.

Discussion: Are These Results on Prolonged Proteasome Inhibitor Therapy Guideline-Changing?

As you suggested, the UK study is the first study that has shown the significance of prolonged proteasome inhibitor therapy, especially with carfilzomib, after achieving a response.

Is that something that is paradigm-changing in your opinion?

Dr San Miguel: I think so. In fact, we are aware that a prolonged treatment with bortezomib is associated with longer progression-free survival, longer disease control. For carfilzomib the data that we have are in the ENDEAVOR data (continuous treatment), but carfilzomib in the ASPIRE study was stopped and with these data, particularly with a weekly dose, with a weekly schedule, I think we can now improve our efficacy in terms of the use of proteasome inhibitors.

Dr Hari: I think that's very significant, especially with the A.R.R.O.W. study and the UK study suggesting a more tolerable fashion of giving carfilzomib to patients.

Dr San Miguel: And, in fact, I think the A.R.R.O.W. and the UK study are complementary in some ways, because one has tested the weekly schedule, the second one is investigating the possibility of maintenance, and in the possibility of maintenance, although during the first 6 cycles, it was given on Days 1 and 2, and 15 and 16; in the subsequent 12 cycles, it was given on Days 1 and 2 at a dose of 36 mg.

Why not use instead of that just 1 dose a week or even every other week, particularly if you have used KRd for 18 cycles, something like that, because in the UK trial only 6 cycles of KCd were used? I think probably this is too short an induction. Probably a longer induction and then follow it by maintenance with weekly, or instead of weekly every other week, would be very attractive.

Dr Hari: I completely agree. In fact, in the KRd study, there was 2-weekly for 12 cycles and then every other week for 6 more cycles and then it was stopped, so I do think the UK study was perhaps a little too short for the intense phase and having a weekly regimen would make it much more easy and attractive to patients and tolerable.

Dr San Miguel: Yes.

Dr Hari:

Discussion: Do You Consider Carfilzomib Standard of Care for Relapsed RRMM?

Now the second question is carfilzomib is not approved for first-line treatment at this point, although we are waiting for studies from various countries, including the US for KRd versus VRd as induction.

Now at this point, for first relapse or early relapse of multiple myeloma, would you consider this as standard of care now, a carfilzomib-based regimen?

Dr San Miguel: Yes, for sure, a carfilzomib-based regimen in patients who have been previously receiving lenalidomide, for instance, is going to be one of the most common combinations used.

Dr Hari: And in the US, we see that where lenalidomide became standard of care a little bit earlier than the rest of the world, a lot of patients now relapsing after transplant and having been on lenalidomide maintenance, we are more and more using carfilzomib, especially with other IMiD combinations.

Dr San Miguel: Yes, and if I am allowed just to add, considering the number of prior lines of therapy, the data that we have so far with ENDEAVOR indicate that the hazard ratio is better if you use in first relapse instead of in second or subsequent relapses. The hazard ratio moved from 0.45 to 0.6.

By contrast, in the ASPIRE that is a triplet, you have a similar hazard ratio, 0.69, in both patients treated as first relapse or patients treated as second or subsequent relapses. Then, I think, this also can help us in order to decide when to use a doublet or a triplet.

Probably, if I will use a doublet, I will go in early relapse and the triplet will be equally effective in later relapses.

Dr Hari: That's an important point to make, absolutely.

Discussion: How Do You Choose Between Carfilzomib Regimens?

And again, for practical considerations of carfilzomib usage, we now have several different combinations and several different regimens: we have 27 mg/m^2 as it was used before in the ASPIRE study with IMiD, lenalidomide; we have 36 mg/m^2 used in many other settings; and again, in the UK study, we have 56 mg as a doublet; and we have 70 mg as a once-weekly regimen.

How do you choose between these?

Dr San Miguel: Okay, I think, unfortunately, this has been a *caveat* of carfilzomib in practical terms, but most investigators started to realize that the higher the dose the higher the efficacy and if the patient is able to tolerate, I think everyone will try to maximize the efficacy by using higher doses of carfilzomib.

Another point about clinical practice is that in the patients with high-risk cytogenetics, the treatment combination, I think, is clearly superior to the doublet, because you combine a proteasome inhibitor and an IMiD. By contrast, in the elderly population, the doublet could be very attractive, and I imagine, in the future, that the once-weekly schedule in the elderly population will become very popular.

Dr Hari: Thank you so much, yes and that is something that I would also like to make the argument for; for high-risk patients and for people who are not responding to carfilzomib at lower doses, for example 27 mg/m^2, but tolerating it well, it well warrants an increase in dosage to a higher more tolerated dose.

Dr San Miguel: Definitely! Hari, this, I think, is a very, very important comment.

Dr Hari:

Discussion: Can You Discuss Novel Proteasome Inhibitors in Development?

And finally, Dr San Miguel, just let's talk about a couple of other novel proteasome inhibitors in development; for me oprozomib, which is an oral epoxy ketone second-generation proteasome inhibitor and marizomib come to mind. Anything else you would want to add on that, Dr San Miguel?

Dr San Miguel: I think the world of the proteasome inhibitors has just started again in several settings. Bortezomib was, after thalidomide, the first really valuable new anti-myeloma drug, but it was many years as part of induction, and has not been explored as the maintenance part, and I think the new oral proteasome inhibitors are going to have really a major role, particularly in the high-risk patients, but in all patients also during the maintenance phase.

Dr Hari: Excellent, so now let's move on to the role of immunomodulatory drugs and Dr Raje will now discuss the role of IMiDs.

Role of Immunomodulatory Drugs

Dr Noopur Raje: Today I will be discussing data presented at EHA 2018 on the role of immunomodulatory drugs for the treatment of relapsed/refractory multiple myeloma. I will essentially be talking about 2 specific clinical trials which were presented at this year's EHA. One of them was the OPTIMISMM trial with pomalidomide in combination with bortezomib, and the other one was a pomalidomide-containing regimen, the MM-014 trial.

EHA-S847: OPTIMISMM: Pomalidomide Regimen

We will begin first with the OPTIMISMM trial. This was a trial presented by Dr Paul Richardson at this year's EHA, and the objective of this phase 3 trial was to compare the safety and the efficacy of pomalidomide in combination with bortezomib and low-dose dexamethasone, and this was compared to bortezomib and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma who had been previously exposed to lenalidomide.

OPTIMISMM: Study Design

The trial design was a classic phase 3 randomized trial. This included close to 600 patients. The randomization was one-to-one and the patients included were relapsed/ refractory multiple myeloma patients. They had had prior 1 to 3 lines of treatment, and they all had to have been exposed to lenalidomide therapy, and this was important, so the majority of patients had seen lenalidomide, and they should have had at least 2 cycles of lenalidomide treatment prior to going on to the OPTIMISMM trial.

The trial comprised of the PVd arm, which was a 21-day cycle comprising pomalidomide given at a dose of 4 mg per day on Days 1 through 14. This was combined with bortezomib at a dose of 1.3 mg/m^2 on Days 1, 4, 8, and 11, the classic bortezomib schedule, and with dexamethasone at a dose of 20 mg, which was dose-adjusted for

patients above the age of 75. This was compared to the classic bortezomib/dexamethasone regimens of Days 1, 4, 8, and 11.

The primary endpoint on this study here was progression-free survival.

OPTIMISMM: Results

If you look at the data, the OPTIMISMM results data, there were 559 patients who were included, and we have efficacy data on 281 patients who received the combination of PVd versus 278 patients who received the combination of the doublet, which was bortezomib and dexamethasone. On an intention-to-treat analysis, the median PFS of this patient population was 11.2 months as opposed to the doublet of 7.10 months, and the overall response rate in the intent-to-treat patient population was 82% versus 50%, with more than 50% of patients achieving a VGPR or better on an intent-to-treat analysis in the triplet arm.

If you then look at patients who had just had 1 prior line of treatment, we had about 111 patients who got the triplet of PVd versus 115 who got bortezomib and dexamethasone, and we saw a near doubling of the progression-free survival, of 20.73 months in the triplet arm versus 11.63 in the bortezomib/dexamethasone arm, suggesting that PVd significantly improved progression-free survival versus Vd in patients who had had at least 2 cycles of LEN, suggesting that LEN-exposed patients had a very nice response rate as well as durable remissions in terms of a combination of bortezomib, pomalidomide, and dexamethasone.

Honing in now on the safety of the POM-based treatment, this was consistent with IMiD-based toxicities, and specifically pomalidomide-based toxicity. Most of the toxicity was neutropenia which was Grade 3 and 4, which was expected in patients on IMiDs, and infections were also slightly higher in the triplet combination as opposed to the doublet. Thrombocytopenia was equal between the PVd and Vd arms.

EHA-PS1292: MM-014 Trial: Pomalidomide Regimen

The next study I am going to highlight today was a study presented by Dr David Siegel. This was the MM-014 trial of the pomalidomide regimen. The objective of this trial was to present the efficacy and safety data for relapsed/refractory patients in this phase 2 setting which was this MM-014 trial who received pomalidomide, low-dose dexamethasone, and daratumumab, and all of these patients again had had prior exposure to lenalidomide,

so this was after lenalidomide-based treatment failure. In essence, this was a step ahead of the OPTIMISMM study, in that these patients were lenalidomide refractory.

MM-014: Study Design

The MM-014 study design: this was a classic phase 2 study design, which included relapsed/refractory multiple myeloma patients. They had to have had a LEN-based regimen in the immediate prior line and they had to have progressed on their last anti-myeloma therapy, therefore suggesting that they had to have progressed on a LEN-based regimen, so truly a study for LEN-refractory patients. These patients had to have an adequate performance status and the planned accrual on this patient study was 155.

There were 2 arms to this, 2 prior lines of treatment, which was Cohort A of 55 patients, where patients received just POM versus low-dose DEX, and the other arm was 1 to 2 prior lines of treatment. This was Cohort B of 100 patients, wherein patients received pomalidomide, low-dose dexamethasone along with the monoclonal antibody daratumumab targeting CD38.

The primary endpoint here was overall response rate by the modified IMWG criteria, and the follow-up for overall survival as well as progression-free survival was also noted in this study.

MM-014: Results

If you look at the data for this study, the overall response rate for all patients was about 71.7% on an intent-to-treat analysis. If you look at overall response rates in the LEN-refractory patients, which was essentially all patients here, it was 72.2%, and looking at clinical benefit rate in this patient population, it was 78.3%.

Most of the toxicities, again as expected with a pomalidomide-containing regimen, were Grade 3 and 4 hematologic toxicities, with neutropenia being the major toxicity noted in this regimen.

Discussion: The Role of IMiD Regimens in RRMM

Again, I think both of these studies have highlighted a very important feature for us, one being that if you have been exposed to lenalidomide as was noted in the OPTIMISMM study, you did respond to a combination of pomalidomide with bortezomib. This combination was, in fact, fairly well tolerated and those data, at least the OPTIMISMM data, suggested that in earlier lines of treatment, your median progression-free survival was significantly longer, almost double, close to 20 months, suggesting that early treatment with

pomalidomide could, in fact, afford a lot of benefit in patients in the relapsed/refractory space.

The second trial, which was the MM-014 trial, has again highlighted the fact that the addition of other drugs to pomalidomide in truly lenalidomide-refractory patients does afford an overall response rate in excess of 70%. It's an extremely well-tolerated regimen, and both of these are somewhat relevant to our practice in the United States, given that lenalidomide has become the default kind of maintenance regimen for all patients, so the majority of our patients, at the time of first relapse, are progressing on lenalidomide maintenance, therefore suggesting that both the MM-014 study as well as the OPTIMISMM study are very relevant in our clinical practice in the treatment of relapsed/refractory multiple myeloma.

In terms of IMiDs, I do think these are easy to combine with other drugs, and there are adequate data now to suggest that there are other combinations coming down the pike with these IMiD combinations, specifically with other proteasome inhibitors, such as carfilzomib, as well as also with other monoclonal antibodies, like the CD38 monoclonal antibodies, such as isatuximab, in the future.

Dr Hari: Let me invite Dr San Miguel again to talk about the role of monoclonal antibodies, specifically looking at this very exciting study, the ELOQUENT-3 study.

Role of Monoclonal Antibodies

Dr San Miguel: Okay, thank you very much again for the opportunity for discussing this, I think, very important study, in which elotuzumab, which is a monoclonal antibody that targets SLAMF7, has been, in this case, combined with a third-generation immunomodulatory drug.

EHA-LB2606: ELOQUENT-3 Study

As you know, elotuzumab did not show activity as a single agent, but in combination with lenalidomide, it was clearly synergistic, and the ELOQUENT phase 2 study saw that ELO plus LEN–DEX was significantly superior to the control arm, LEN–DEX, in terms of progression-free survival, and also now in overall survival.

We know that pomalidomide is an active immunomodulatory drug that is even efficient in patients who had failed lenalidomide, and has been approved for double refractory patients – patients refractory to proteasome inhibitor, bortezomib/lenalidomide.

This phase 2 trial decided to compare the efficacy and the safety of elotuzumab in combination with pomalidomide/dexamethasone to the standard of care, pomalidomide/dexamethasone, in relapsed/refractory myeloma patients.

ELOQUENT-3: Study Design

This ELOQUENT-3 trial is a phase 2 study that has included a total of 117 patients. The patients should have previously received more than 1 or 2 prior lines of therapy. They should have been refractory to the last line of therapy, refractory or relapsed and refractory to lenalidomide and proteasome inhibitor, and by the design of the study, prior pomalidomide was not permitted. This is because the control arm was pomalidomide/dexamethasone at the standard dose of 4 mg orally for 3 weeks on, 1 week off with dexamethasone 40 mg weekly. The cycles were given every 28 days.

The experimental arm was the same for pomalidomide and dexamethasone but included elotuzumab as the experimental drug, in this case at a dose of 10 mg/kg i.v. weekly on Cycle 1 and 2 and then, after Cycle 3, elotuzumab was given at a double dose, 20 mg/kg every 4 weeks.

The primary endpoint was progression-free survival and the secondary endpoint was response and overall survival.

ELOQUENT-3: Results

The median age of the population included in this study was 67 years. The median number of prior lines of therapy was 3, ranging from between 2 and 8. Eighty-seven percent of the patients were refractory to lenalidomide, 80% of the patients were refractory to bortezomib, and, what is really impressive, are the results that have been obtained because the experimental arm, ELO/POM/DEX saw a 46% reduction in risk of progression or death as compared to the control arm, pomalidomide and dexamethasone, with a median PFS of 10.3 versus 4.7 months and a hazard ratio of 0.54. The overall response rate was 53% versus 26%, with VGPR of 20% versus 9%, in the experimental and the control arm, respectively, and although the overall survival data are immature, there is already a trend for a benefit in the ELO arm.

The safety profile is consistent with previous reports on elotuzumab and pomalidomide. Only 5% of the patients had infusion reactions. Most of them were Grade 1 or 2. Neutropenia Grade 3 was lower, as well as anemia in the ELO arm; 13% versus 27% for neutropenia, 10% versus 20% for anemia Grade 3, and, in fact, the rate of discontinuations due to adverse events was lower again in the elotuzumab arm, 18% versus 24%, and this was observed despite longer exposure in the experimental arm. Forty percent of the patients

remained on treatment versus 20% in the control arm, pomalidomide and dexamethasone, and I think these results confirm the synergies between this monoclonal antibody and the IMiDs.

Thank you very much.

Dr Hari: So Jesús, let's discuss the role of monoclonal antibodies now.

Discussion: Role of Monoclonal Antibodies in RRMM

This is a very surprising, or, in fact, positive surprise in terms of the synergy between elotuzumab and pomalidomide, and in some ways, even more exciting than the combination of elotuzumab and lenalidomide. Would you say so?

Dr San Miguel: Yes, definitely, and the difference in the curves, if you have looked at the shape of the curves, they separate very soon from the beginning, and it is very consistent, the benefit along all the curves.

And if we keep in mind the data on ELO plus LEN/DEX, in which now with 5 years' follow-up it maintained the difference in the PFS and the overall survival benefit, I think this speaks about the value of this type of combination.

Dr Hari: Yes, it's very exciting data, and, as you mentioned, there are some patients who seem to maintain that benefit for a very, very long period, suggesting this is true immunotherapy here.

Dr San Miguel: Yes, definitely. In fact, I had one US colleague tell me that this combination has been tested in his case in patients who are penta-refractory, with high success.

Dr Hari: That is very exciting news for patients.

Discussion: Patient Selection for Combination Therapy With Elotuzumab Versus Daratumumab

Now, coming to the whole topic of monoclonal antibody-containing regimens, we have 2 monoclonal antibodies at this point: daratumumab, which is a directly effective drug, and elotuzumab, which has no independent activity but significant combinatorial activity, especially with IMiDs.

Would you distinguish in which patients you would go with daratumumab, and in which patients you would go with elotuzumab, in combination?

Dr San Miguel: I think if you need a rapid tumor-debulking reduction I would probably go for the anti-CD38 monoclonal antibodies. By contrast, if you are in a situation in which the patient is having either a non-aggressive relapse or you have a situation that a patient has a slowly progressive disease, in these types of patients probably elotuzumab can be a very attractive drug to be tested.

Dr Hari: That's exactly how we also thought about it in the US here. One of the other situations is patients on maintenance with lenalidomide, for example, and slowly biochemically progressing.

Dr San Miguel: Yes, these types of patients. This will be, in fact, Hari, this will be a very attractive trial design, to have a group of patients under lenalidomide maintenance in which you have a biochemical relapse, and as soon as you have a biochemical relapse, just to add elotuzumab and to see how the disease behaves. A type of randomized study like this will be really exciting.

Dr Hari: Very exciting, and it adds many more months or perhaps years to patients' lives, without using up another drug, for example.

Dr San Miguel: Yes.

Dr Hari: Thank you so much, Jesús.

Dr San Miguel: Also, I think it's important to keep in mind that in this study, elotuzumab was used after the first 2 cycles every 4 weeks, which, I think, is also convenient for the patient.

Dr Hari: Yes, that's an important point to mention.

Dr San Miguel: Yes, and the other point that I think should be added in this topic discussion about monoclonal antibodies is the new era that has been opened with the BCMA antibodies, both the bispecific and the conjugated. I think these are very good news for patients.

Dr Hari: Exactly.

Role of Allogeneic Stem Cell Transplantation

Now we go to the final couple of abstracts here. Now we are going to talk about a technique that's rarely used in multiple myeloma and perhaps may be on its way out with new immunotherapy happening. But let's discuss the role of allogeneic stem cell transplantation, or donor transplants, in multiple myeloma.

EBMT- OS4-2: Haploidentical Transplantation – EBMIT/CIBMTR Report

The first of the studies that I would like to discuss is the role of haploidentical transplantation which is a situation in which we use a donor that is only half matched to the recipient, typically a sibling that's half matched or a parent or a child of the donor. Myeloma patients being elderly, this most often happens to be either a sibling or a child of the patient.

This is a combined EBMT/CIBMTR report with a retrospective analysis of outcomes after haploidentical allogeneic stem cell transplantation. The thing to note about haploidentical transplantation is that a new technique of doing haploidentical transplantation with post-transplantation cyclophosphamide as prophylaxis for GvHD was developed over the past decade at several centers all over the world, predominantly at the Hopkins' transplant program. This has been applied all across the world in many diseases, and this is the first report that comes out looking at a large number of patients using the post-transplant cyclophosphamide technique in multiple myeloma.

Study Design and Patient Characteristics

Patients who received a haploidentical transplantation between 2008 and 2016 at an EBMT or a CIBMTR center were included, and this included 96 patients with predominantly multiply relapsed myeloma. As you can see, the vast majority of patients, 82%, had a time from diagnosis to allogeneic transplant of more than 2 years. These patients were treated with either myeloablative or reduced intensity conditioning, and the majority of the patients, actually 80%, received reduced intensity conditioning with or without total body radiation, which means they had a very low dose of radiation.

Again, we are depending on an allogeneic immune system to do the work of disease control in these patients, and these are multiply relapsed/refractory patients in an advanced myeloma setting.

Haploidentical Transplantation: Results

For me, the most important finding was that non-relapse mortality was reduced to 26%. Typically, myeloma patients don't tolerate allogeneic transplants, especially after many relapses. They don't tolerate allogeneic transplant very well and relapse remains a huge risk. Overall survival in multiply refractive patients with allogeneic transplants is very dismal, usually in the 20–30% range, and here, with haploidentical transplantation, we did show that although there was a high incidence of relapse at 56%, overall survival at 2 years was 48%.

The incidence of chronic graft-versus-host disease was 45%, but predominantly limited chronic graft-versus-host disease as we see with the post-transplant cyclophosphamide approach.

Median follow-up of these patients was about 2 years, so this is still early data and some of the findings that showed up in the univariate analysis were that the role of ATG-based transplants is perhaps going away. We saw that there was inferior overall survival when ATG, or anti-thymocyte globulin, was used.

I would just suggest that this abstract is more an exploratory or hypothesis-generating dataset, not really something that changes practice.

EBMT-B213: Allogeneic HSCT: Number of Prior Therapy Lines

Secondly, there was an abstract presented by the German group which again evaluated the outcomes of patients who received allo transplant for myeloma and looked at transplant characteristics and prior therapies that predicted benefit.

Study Design and Patient Characteristics

Here, there were 88 patients with myeloma transplanted over a very long period, almost 17 years between 1999 and 2016, and the significant finding from this, again, is that allo transplant was used after relapse in the majority of patients. Sixty-six percent had an allo transplant after relapse, but a third of the patients had up-front tandem auto-allo transplants, which again translates to a very small number, less than 30 patients in this dataset, and 73% had cytogenetic abnormalities. Only 26% were considered high-risk, but one could argue that after relapse almost everyone who needs an allo transplant is high-risk.

Allogeneic HSCT: Results

Median overall survival from the transplant was 30.5 months, and at 5.6 years of follow-up, about 37% of the patients were still alive. Again, this was a median PFS very limited at 12.3 months and non-relapse mortality here again was about 30% at 3 years.

The big finding is that overall survival was significantly reduced for patients who had received more than 2 lines of therapy prior to stem cell transplant, which tells us one thing; allo transplant is rarely used in myeloma, very few patients are eligible, very few patients are young enough to get it, but if you are considering it for a patient, try to do it a little earlier, for diseases such as plasma cell leukemia, where there is a significant role still for allogeneic transplant or for patients who have an early relapse after an autologous transplant and who are still young to receive an allo transplant, this would still have a role.

However, if you leave it until the end in somebody who is eligible, you are actually going to face a higher risk of non-relapse mortality and a very short progression-free survival, which then translates to a lack of clinical benefit for the patient.

Discussion: Role of Allogeneic SCT in RRMM

Finally, let's discuss a little bit about allo transplant, although I think new immunotherapies might change the whole paradigm in a very short time. What do you think about that, Jesús?

Dr San Miguel: Okay. We consider the allogeneic transplant in early phases of the disease, not in late phases of the disease, and the reason is because, in the past, we did it in many patients with refractory disease after 4 or 5 lines of therapy and it was, I would say, almost a disaster. And now, if I have in front of me a patient who has received an optimized induction treatment with a proteasome inhibitor plus an IMiD: autologous transplant.

If the patient relapses within the first year, particularly if a patient has high-risk cytogenetics, for this patient, I would consider the possibility of an allogeneic transplant, provided that I am able just to re-induce almost a complete response before the allogeneic transplant.

In other words, the allogeneic transplant in this patient is going to be like immunotherapy in early relapse.

Dr Hari: That's almost exactly how we use it in the United States too, and in the US, there is a little bit more use of allo transplant in the last couple of years, since some of the insurance providers, especially our big insurance provider, Medicare, has opened it up for patients with relapsed myeloma and patients with very high-risk myeloma.

Discussion: Role of Haploidentical Transplant in RRMM

And the role of haploidentical transplantation is important in this setting because patients with myeloma, being elderly, most of them don't have matched sibling donors and we have shown in many other diseases that haploidentical transplantation has become an effective technique for patients without donors, and we now can offer donors for patients. But I wouldn't call it when you use it, especially in multi-relapse myeloma, a curative option. It may be a platform on which you can build something else. Would you say so?

Dr San Miguel: Yes, definitely. I think it's an attractive approach as a platform.

Dr Hari: Dr Raje, could you comment on emerging therapies for multiple myeloma, especially with the CAR T-cell data that are coming out?

Discussion: CAR T-Cell Therapy

Dr Raje: I am going to highlight the CAR T-cell approaches. These data were presented by us at EHA in 2018 as well as at ASCO earlier this year. This was a phase 1

study of an anti-BCMA CAR T-cell strategy. The antigen used here was BCMA, also known as B-cell maturation antigen, and what has been noted in the myeloma world, at least, is the fact that this BCMA seems to be a potentially good target for all kinds of approaches, including conjugated monoclonal antibodies as well as BiTEs, and now these data with the anti-BCMA CAR T-cell.

The BB2121 product is a product using 41BB as co-stimulatory domain of this CAR T-cell approach. Data were presented on close to 43 patients at this year's EHA and the response rates in this patient population were in excess of 90% if they had a dose of more than 50 million CAR T-cells.

What was also quite remarkable with this cellular therapy approach was the fact that the toxicity noted or the toxicity signal from this cellular therapy was quite low. CRS, any grade, was seen in about 60%, but really significant CRS was seen in less than 20% or 30% of patients and the other complication which is commonly noted with cellular therapies being neurotoxicity, or significant neurotoxicity, was seen only in 1 patient, suggesting that these are very safe treatments.

What was also quite remarkable was the fact that this was a very heavily pretreated patient population with a median of about 7 lines of prior therapy with an overall response rate of about 90% and with a remission duration or a progression-free survival of close to 11.8 months.

When looking at patients who had achieved an MRD-negative state, those patients actually had a median progression-free survival of 17.8 months, so this is the longest follow-up of cellular therapy in multiple myeloma, and at least the initial data suggest promise with manageable toxicity in this very heavily pretreated relapse/refractory patient population.

Along with cellular therapies, there are other approaches targeting BCMA. These include strategies such as conjugated antibodies as well as BiTEs, so I think there is a lot of promise with immune strategies targeting BCMA as an antigen in multiple myeloma.

Discussion: Impact of the Presented Data on Clinical Practice

Dr Hari: Dr San Miguel, based on the data that we've presented, we have presented data on novel proteasome inhibition combinations, novel schedules, such as giving carfilzomib, IMiD combinations, monoclonal antibody with elotuzumab and CAR T-cells, how do you see these data impacting clinical practice in the next 1 to 2 years, and how do you feel the field is moving?

Dr San Miguel: Okay, in multiple myeloma, I think we have a dilemma in this disease in that sometimes we are very optimistic talking about we are going to cure, and at the same time we are a bit conservative. Yes, not facing the intensive treatments as are needed and everybody is trying to get rid of autogolous transplant, to get rid of the allogeneic transplant, and to get rid of chemotherapy. Chemotherapy, high dose, is effective in the context of several biological statuses of the disease. Then, I think, we need still to use all the potential tools that we have if we really want to cure a substantial proportion of myeloma patients.

Dr Hari: I totally agree. I think it's too premature to see a future without stem cell transplant, especially autologous transplant should remain the standard unless we find a therapy that actually is superior to it. We may have to test CAR T-cells in this setting, we may have to test other things in this setting, but it's not happening right now and I think it would be premature to say that it is gone because of the new treatments that are coming.

Discussion: Choosing the Optimal Treatment Regimen for Patients with Multiple Myeloma

Finally, when you select an optimal treatment regimen for a patient, I would like to emphasize that this is something that you would think about for the whole course of the patient's life, not just for the next 3 months, for example. You would lay out a strategy for fighting myeloma for the life of the patient and not just something that will give them a quick response. How do you see this?

Dr San Miguel: As you know, I have two topics that have driven part of, probably, the last 20 years in my career, and one is early treatment intervention within the smoldering setting and the other is minimal residual disease.

When you have residual cells in leukemia, let's talk about CML or acute leukemia, you know that the patients are going to relapse very early, and I think, in myeloma, we need to make strategies that are able to eradicate the disease, to eradicate the minimal residual disease, because the only exception will be the small subgroup of patients who have a very strong immune system, probably preceded by an MGUS situation, but in the rest of the patients, if you have residual cells, you know that the disease is going to progress very early on.

The second is to treat the disease as soon as possible, and this applies not only to early detection for the smoldering, but also at the time of biochemical relapse. Usually, we wait until the patient has clinical relapse, and again, unless there is a reason based on the immune system, in other contexts, I would prefer to treat the disease when they are having just a biochemical relapse. But this is a philosophy.

Dr Hari: No, that is actually very important when somebody with this kind of eminence in the field and specifically in the management of people with residual disease says this.

Again, this brings us to the point; high or deep responses translate to everything for these patients. Deep responses translate to a longer time for remission, to overall survival, and also improved quality of life for patients.

Dr San Miguel: Definitely!

Key Messages

Dr Hari: Finally, these are some of our key messages from the discussion today. We have shown with these data that novel combination regimens and novel schedules have created a bigger impact on patient outcomes in relapsed/refractory myeloma.

We just showed the data with Kd56 and KRd demonstrating high response rates, overall survival benefit, and, specifically, the KRd triplet was associated with a significant overall survival benefit of almost 18 months in patients who were in their first relapse after 1 transplant.

We also showed that pomalidomide-based treatments have shown promise in patients who have received prior lenalidomide. We showed the combination of elotuzumab with pomalidomide as an option for patients who are in their second relapse or beyond, and we showed a variety of immune strategies including CAR T-cells and the role and timing of allo transplants for selected patients, which will also need further clarification and work.

On behalf of myself, Dr Jesús San Miguel, and Dr Noopur Raje, we thank you for joining us.

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