Proteasome Inhibitors

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Welcome to *Managing Myeloma*. My name is Jacob Laubach. I am an Assistant Professor at Harvard Medical School and Clinical Director of the Multiple Myeloma Program at the Dana-Farber Cancer Institute, and I am live at the 58th American Society of Hematology Annual Meeting. Today, I will be reviewing four abstracts that have been presented at this meeting on the use of proteasome inhibitors for patients with multiple myeloma, including two abstracts that involved patients with newly diagnosed myeloma and two abstracts focusing on patients with relapsed disease.

So, the first study is a post hoc analysis of the phase 3 TOURMALINE-MM1 trial in relapsed and refractory multiple myeloma. The TOURMALINE-MM1 study was a randomized phase 3 trial comparing lenalidomide and dexamethasone versus ixazomib plus lenalidomide and dexamethasone in patients with relapsed multiple myeloma. The study showed a significant progression-free survival (PFS) benefit for individuals receiving the three-drug regimen with minimal added toxicity associated with the inclusion of ixazomib in combination with lenalidomide and dexamethasone. This study was the basis for the FDA approval of ixazomib and lenalidomide and dexamethasone in the treatment of patients with relapsed disease who had received one to three prior lines of therapy. In terms of this post hoc analysis, it analyzed the long-term outcomes for patients based on PFS according to their best response, as well as time to best response. This study demonstrated that those patients who had improved depth of response associated with treatment had long-term benefit in terms of progression-free survival, an expected finding. Notably, it was also shown that patients who had longer time to best response also had benefit in terms of progression-free survival, suggesting that a slow gradual response to therapy may be beneficial. What do these results mean in terms of clinical practice? It means that if you are managing a patient with relapsed disease and treating an individual with the combination of ixazomib, lenalidomide, and dexamethasone and you see a response that in your view is slow or taking hold slowly, do not give up, maintain therapy on this patient with the three-drug combination, provided there is no evidence of progression or evidence of intolerance to therapy, and continue therapy. This study also showed that prolonged exposure to this regimen did not lead to added toxicity. So, it demonstrates that this is a regimen that overall is well tolerated, and if continued to the point of maximum benefit in terms of response rate, typically translates into benefit in terms of duration of progression-free survival.

The next abstract that we will be considering pertains to a phase 2 study of the all-oral combination of ixazomib plus cyclophosphamide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma. This study included individuals who had received one to three prior lines of myeloma therapy, who received, as mentioned, the three-drug all-oral combination of ixazomib with ixazomib at 4 mg, days 1, 8, and 15 of a 28-day cycle, oral cyclophosphamide at 300 mg/m^2 given on the same days, 1, 8, and 15 of the 20-day cycle, along with dexamethasone at either 40 mg or 20 mg based on age, same days, days 1, 8, and 15 of the 28-day cycle. In terms of efficacy, the overall response rate in this study was approximately 50% and that included 16% of

patients who achieved at least a very good partial response or better. Interestingly, it was noted that responses in terms of overall response were better for patients over the age of 65 than those under the age of 65. At the time of this analysis, median progression-free survival has not been reached, but it was also noted that progression-free survival at time of analysis was more favorable for individuals over the age of 65 than those under the age of 65. In terms of safety data, common adverse events in this study included diarrhea, nausea, respiratory infections, as well as hematologic side effects including thrombocytopenia, anemia, and neutropenia. Grade 3 or higher adverse events occurred in roughly 60% of the patients, and adverse events led to dose reductions in 36% of patients and discontinuation of therapy in 14% of patients. One treatment-related death occurred on the study, related to cerebral hemorrhage that was secondary to thrombocytopenia. The question then comes up, how does this all-oral regimen compare to a regimen like ixazomib, lenalidomide, and dexamethasone as in the TOURMALINE study? The first response to that is just a word of caution, it is very difficult to make cross-trial comparisons. It is also important to note that a significant percentage of the patients in this trial had received lenalidomide as maintenance following their initial cycle of therapy and may have been refractory to lenalidomide at the time of enrollment in the study, suggesting it may have been a more heavily pretreated group of patients. So, it is difficult to make cross-trial comparisons. I will say that this space of course as we all know is getting more and more crowded. There are now five randomized phase 3 trials for patients with one to three prior lines of therapy in relapsed multiple myeloma. So, this is a difficult choice in terms of management of myeloma patients, which regimen is best? I will say that the idea or the concept of combining a proteasome inhibitor, such as bortezomib or carfilzomib in the past and now ixazomib, with an alkylating agent such as cyclophosphamide in the relapsed setting has a long historical precedent and has proved to be an effective regimen for patients with relapsed myeloma. I think it is an attractive option for individuals mindful of the fact that one does need to be aware of potential toxicities as was shown in this trial, particularly with the hematologic toxicity.

Now, we will turn to two abstracts that involved individuals with newly diagnosed multiple myeloma. The first of these was a phase 2 trial led by Dr. Wester and colleagues evaluating carfilzomib, thalidomide, and low-dose dexamethasone, or CARTHADEX, as induction and consolidation therapy in transplant-eligible patients with newly diagnosed disease. This was a dose escalation study in which patients received thalidomide 200 mg/m^2 continuous and low-dose dexamethasone 40 mg once weekly in combination with carfilzomib at escalating doses ranging from 20/27 mg/m^2 up to 20/56 mg/m^2 on the standard carfilzomib dosing schedule on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. In terms of the efficacy, the overall response rate for the group of patients treated with this regimen as a whole was 95%. After induction therapy, the rate of complete response was 16%, after transplant 31%, and after consolidation therapy 64%, pointing to the benefit of sequential therapy with induction, carfilzomib, thalidomide, and dexamethasone, followed by transplant, followed by consolidation therapy. In terms of how the cohorts compared with respect to response rates, they were quite comparable across the four dosing cohorts. In terms of safety data pertaining to the three-drug regimen of carfilzomib, thalidomide, and low-dose dexamethasone, there were a number of grade 3 and 4 nonhematologic toxicities including, respiratory disorders which occurred in 15% of patients, GI disorders which occurred in 13% of patients, and skin lesions interestingly which occurred in roughly 10% of patients. Cardiac adverse events were relatively rare with heart failure occurring in two patients, hypertension in two patients, and chest pain in one patient. The toxicity profile across the various cohorts was quite similar as well. In terms of how this combination of carfilzomib, thalidomide, and dexamethasone may fit into the current option for management of newly diagnosed myeloma, it will be interesting to see. I think as far as historical standards of care in the United States for newly diagnosed disease, lenalidomide,

bortezomib and dexamethasone, and cyclophosphamide, bortezomib and dexamethasone have long been considered a standard of care. Based on more recent data, the combination of carfilzomib, lenalidomide, and dexamethasone can also be considered an emerging standard of care particularly for patients with high-risk disease. This was obviously a very well-conducted trial, and the three-drug regimen involving thalidomide seemed to be well tolerated as well. So, it will be interesting to see where the investigators with this trial choose to go with this regimen moving forward.

Finally, we will consider the phase 2 IFM study, a frontline therapy with carfilzomib, lenalidomide, and dexamethasone followed by autologous transplant; carfilzomib, lenalidomide, and dexamethasone consolidation; and lenalidomide maintenance in newly diagnosed myeloma. These were newly diagnosed patients, they received carfilzomib at the dose of 20/36 mg/m^2 on the standard carfilzomib dosing schedule, lenalidomide at 25 mg days 1 through 21 of a 28-day cycle, and dexamethasone 20 mg on days of carfilzomib. They then underwent stem cell mobilization with cyclophosphamide followed by high-dose therapy with melphalan 200 mg/m^2, and thereafter four cycles of consolidation with carfilzomib, lenalidomide, and dexamethasone followed by one year of maintenance therapy with lenalidomide at 10 mg. In terms of the efficacy for this particular trial, the overall response rate after consolidation therapy was 97%, and this included 70% of patients achieving a complete response or better, so very effective in terms of depth of response. In addition to that, minimal residual disease was evaluated in this study by both multiparameter flow cytometry and next-generation sequencing for patients who achieved at least a very good partial response. Among patients who achieved a very good partial response and underwent MRD assessment by flow, 90% of these patients were MRD negative. A smaller percent of patients underwent MRD evaluation by next-generation sequencing, and in that cohort of patients, the MRD negativity rate was around 60%. In terms of safety data for this study, the overall rate of grade 3 or 4 toxicities was around 60%, most of these were hematologic or infectious as might be expected. There were no grade 3 or 4 incidences of sensory peripheral neuropathy. Four patients permanently discontinued therapy as a result of treatment-emergent adverse events; including one patient who developed heart failure, one pneumonia, one jugular vein thrombosis, and one lethal septic event. In terms of a cardiovascular toxicity profile for the study, there were eight cardiovascular events that met the criteria of serious adverse events including two patients with congestive heart failure, one with bradycardia, two with pulmonary embolisms, and three with thrombosis despite adequate prophylaxis. In terms of other serious adverse events, infections occurred in 26% of patients and musculoskeletal disorders in 17% of patients. So, the question comes up, how could this combination impact the standard of care, keeping in mind that other regimens are being developed in this space as well? Well, as I mentioned before, I think based on the results of the SWOG trial that were presented at last year's meeting comparing lenalidomide, bortezomib, and dexamethasone to lenalidomide and dexamethasone; lenalidomide, bortezomib, and dexamethasone is considered a standard of care in this population. There is a significant amount of data now with the use of carfilzomib, lenalidomide, and dexamethasone in upfront disease as well, and it has been clearly demonstrated that this regimen achieves very high levels of stringent complete response and MRD negativity. So, for many settings, it is now considered a standard of care to consider this regimen for patients with high-risk disease in the newly diagnosed setting in particular.

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