Immunotherapy

Noopur Raje, MD
Associate Professor of Medicine
Harvard Medical School
Director, Center for Multiple Myeloma
Massachusetts General Hospital
Boston, Massachusetts

Hi, my name is Noopur Raje. I am the Director of the Multiple Myeloma Program at Massachusetts General Hospital in Boston and I am also an Associate Professor of Medicine at Harvard Medical School. I am here live at the 58th Annual American Society of Hematology Meeting and what I what I will be doing today is reviewing five abstracts presented in the immunotherapy section for multiple myeloma. There has been a lot of excitement around multiple myeloma and immuno-oncology, and we will be talking about some of these abstracts today.

The first one that I am going to be talking to you about is in kind of precursor disease states which is smoldering multiple myeloma. So, there is a phase 2 study of elotuzumab which is an antibody against SLAMF7 in combination with lenalidomide and dexamethasone in high-risk smoldering multiple myeloma patients. Really, the rationale for trying to do a study in smoldering myeloma, specifically high-risk smoldering myeloma, is the fact that these patients will eventually develop multiple myeloma and the goal here is to try and prevent the active disease which as of today is still an incurable cancer. We have new ways of defining smoldering multiple myeloma now, and based on this study at least they have incorporated those high-risk features for smoldering myeloma. The way one defines smoldering myeloma is anybody who has a bone marrow plasmacytosis of 10%, that is the minimum requirement, and then in addition to that you need at least one other feature. This has been published now by Dr. Vincent Rajkumar in *Blood* of last year. What he has said out there is that anybody with an M-protein of greater than 3 grams or immune paresis and abnormal serum-free light-chain ratio of more than 8 but less than 100, as well as abnormal cytogenetics, MRI abnormalities in terms of increased MRI intensity, as well as just about one focal lesion; so having one of these in addition to 10% plasmacytosis allows you to be defined as high-risk. What Dr. Ghobrial has done in this abstract is treated patients with smoldering multiple myeloma, close to about 40 patients, and what was seen out here was a clinical benefit rate in the majority of patients, with an overall response rate of about 70%. I think this is an important initial study in the smoldering myeloma space. What the study does show is obviously we are using active drugs, and active drugs work in the space. I think in the future we would have to try and compare this lenalidomide, elotuzumab, and dexamethasone with the patients who were not treated with this and try and see if we are truly changing the natural history of smoldering multiple myeloma patients.

The next trial that I am going to be talking about is the CASTOR study. The CASTOR study is a combination of the monoclonal antibody daratumumab with bortezomib and dexamethasone. We are all very excited that daratumumab has gotten its approval only this past week, both in combination with bortezomib as well as in combination with lenalidomide based on what was published and presented in the *New England Journal of Medicine* this past year. What the investigators here have done is a subgroup analysis where they have looked at lines of treatment. Now, remember the CASTOR study was a study which looked at 1 to 3 prior lines of treatment. What Dr. Mateos has done out here is subdivided these patients and also specifically looked at

cytogenetics, so high-risk cytogenetics as defined by deletion 17p, 4;14, or the 14;16 translocation. Obviously, the overall response rate, everybody is familiar with this. It is more about 89% for the DVd arm, which is the daratumumab, bortezomib, and dexamethasone arm, compared to about 74% in the Vd arm. What is striking out here is the hazard ratio of 0.38 favoring the triplet in the standard risk versus a hazard ratio of 0.46 in the high-risk patient group, suggesting that this treatment should in fact be incorporated for high-risk patients going forward in the treatment of myeloma.

What about some of the other interesting things which are being looked at during this meeting? Well, I am going to talk a little bit about some of what everybody is excited about and these are the CAR T-cell studies. There were two studies which have been presented at this year's ASH meeting. Both of these studies are being presented by the investigators at Penn. The first one is on the anti-CD19 CAR T-cells, and this is generally after salvage autologous stem cell transplant. They have treated about 10 patients, 12 were eligible I believe, and they have treated about 10. They did not see a lot of toxicity with CD19 CAR T-cells. Most of the toxicity was the toxicity seen with the high-dose melphalan and the autologous stem cell transplant. What they did show here was the PFS did correlate with peak bone marrow CTL019, so if you have CAR T-cells which are CD19 positive within the bone marrow, that in fact correlated with the progression-free survival. So, CD19 CAR T-cells are something which is a good proof of principle. The majority of myeloma does not really quite express CD19. So, we will have to figure out where the place of CD19 CAR T-cells is in the context of myeloma. But, more exciting was their abstract on a Phase 1 study using the B-cell maturation antigen CAR T-cell, so BCMA CAR T-cells again presented by the Penn group. Now to me, this is a much more interesting approach. BCMA or the B-cell maturation antigen, as you all know, is pretty much ubiquitously expressed on multiple myeloma cells. So, the majority of patients should have BCMA expression, and what was seen here is, again it is early data, but at least in the six patients they have treated based on BCMA expression, they have seen very good responses. A word of caution though, along with those responses, given that a lot of myeloma patients do express BCMA, there is toxicity. The most important toxicity to think about here is the cytokine release syndrome, which was seen in five of these patients who had responses as well, and there was a dose-limiting toxicity. This is PRES that was seen, which stands for posterior reversible encephalopathic syndrome, and really nobody quite understands why this happens and this did resolve after supportive care use of antiepileptics. It happened in just one patient, but that is something to think about. The other toxicities were pretty straightforward, lymphopenias and thrombocytopenias, but I do think this BCMA CAR T-cell is a really exciting approach since the majority of myeloma patients do in fact express BCMA.

There is another monoclonal antibody which is being tested, and there is data being presented at this meeting by Marc Raab. This is a phase 1 2A study using again CD38, so very similar to what we have seen with daratumumab as well as with isatuximab, but this time it is MOR202. This MOR202 was tested either alone or in combination with pomalidomide and lenalidomide. What they saw here was infusion-related reactions were really quite minimal and that may be because of lack of CDC (complement-dependent cytotoxicity) so cellular toxicity is not noted supposedly with MOR202 and the investigators were actually able to give this antibody over a 2-hour period. As monotherapy, they saw response rates of about 19%, partial response rates with VGPR seen in about 13% of patients, and when they combined it with both lenalidomide and pomalidomide, obviously they saw much higher response rates. So, the bottom line, MOR202 could be given much faster over 2 hours and at least did not see the same sort of infusion-related reactions, which we typically see only with the first or second dosage of either daratumumab or isatuximab.

So, we will have to see how this drug gets developed in the future but here again we have another antibody targeting CD38, and we have already demonstrated how effective CD38 monoclonal antibodies are in the context of myeloma.

So with that, I would like to thank you for viewing this activity, and for obvious additional resources, please be sure to view other educational activities on *ManagingMyeloma.com*.