Managing Myeloma

Anti-BCMA CAR-T Cell Therapy in RRMM and RVd Lite in Transplant Ineligible MM

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Welcome to *Managing Myeloma*. I am Dr. Noopur Raje and I am live at the ASH Annual Meeting in Atlanta, Georgia. What I will be doing today is presenting an updated multicenter study of BB2121, an anti-BCMA CAR-T cell therapy. We are very excited about this data which is going to be presented at this meeting, and this is using cellular therapy to target a protein called BCMA which stands for B-cell maturation antigen. Now, most of us know that BCMA is pretty much present on all plasma cells as well as very mature B-cells. What we have learned over the last several years is that BCMA is a great target for treatment in multiple myeloma. The approach here is using cellular therapy which is using CAR-T cells. These are second generation CAR-T cells wherein we have included CD3 zeta activation domain and the BB212 costimulatory domain to create these CARs recognizing this protein called BCMA. We had presented data on 21 patients early on at ASCO this year, and at this meeting, we are presenting updated results of this clinical trial.

Patients who were accrued onto this clinical trial were patients who had had at least three lines of treatment and they had to have been relapsed and refractory, and refractory to their last line of treatment. The majority of patients had received an IMiD as well as a proteasome inhibitor and were, in fact, refractory to both of these, and a large proportion of these had received a CD38 monoclonal antibody as well. All patients on this trial had received a stem cell transplant. The CAR-T cells were generated after isolating peripheral blood mononuclear cells and then they were processed and created at an outside lab facility. After giving patients lymphodepletion (which was done in-house with both Cytoxan (cyclophosphamide) and fludarabine) these transfected T-cells were injected back into people. We did a classic phase 1 dose escalation CAR-T cell approach in this situation. We started off with 50 million cells and went all the way up to 800 million cells. When you look at the data in aggregate in over 20 patients (close to 21 patients now), we found that the response rate was about 80% plus. However, when you look at the doses which were relevant – which is more than 150 million cells given to patients – we saw a 100% response rate in these patients. What was also striking in this was that responses were early: we saw bone marrow clearing of BCMA-positive plasma cells as early as day 15 on bone marrow exams. When you look at response rates, we saw 100% of patients responding with in excess of 70% with a VGPR or better, with a significant number of patients who were very refractory to previous treatments becoming MRD-negative.

The obvious next question in this situation is: What is the toxicity associated with such an approach? We were fortunate to see that the toxicity was generally manageable. We did see cytokine release syndrome (CRS) in the majority of patients, but most of the CRS was grade 1 and 2. We did see a couple of patients who had grade 3 CRS as well, and the antidote to CRS (an anti-IL-6 receptor antibody called tocilizumab) was used only in four of these patients. We are going to be presenting some updated toxicity information as well, but we did not up until recently see a whole lot of neurotoxicity. We did see one patient in this population with grade 4

neurotoxicity which was appropriately managed with steroids and with tocilizumab, and the patient is doing quite well. Another question considered in this kind of situation is: Who are the patients who would quality for this kind of an approach? As of right now, we have had patients as old as 74 and 75 on this clinical trial, and we have seen that because of the manageable toxicity, we have been able to deliver the strategy to these patients. Going forward, we will have to see how sustained these responses are. We have a median response duration of close to a little over four months, but we have gone out in excess of one year in patients who had been on this treatment.

What we are presenting at this meeting is updated results on a combination approach in non-transplant-eligible patients, using a combination of lenalidomide, bortezomib, and dexamethasone. We call this the RVd lite regimen because we have dose-modified this since this is an elderly patient population. We know that triplet therapies have shown a benefit in terms of progression-free survival in myeloma; now based on the SWOG data, we have seen an overall survival advantage in this patient population. We therefore have modified this triplet regimen wherein we are using bortezomib on a weekly schedule in a subcutaneous fashion. We are using lenalidomide at a slightly lower dose of 15 mg for 21 days, and we are dose adjusting the dexamethasone based on the age of the patient. If you are above the age of 75, you get an attenuated dose of dexamethasone. If you are below the age of 75, you are getting the higher dose of dexamethasone. These results are being presented at this meeting by my colleague Dr. Betsy O'Donnell from Massachusetts General. What she has shown very nicely in close to 53 patients is that this is a generally very well-tolerated regimen, with a little bit of dose adjustment based on either fatigue or neuropathy. What was most striking about this triplet combination in this patient population was that the oldest patient treated was 90 years old, and we saw a very nice overall response rate of 92%, with more than 70% of patients achieving a very good partial response (VGPR) or better. This very nice response rate with very tolerable toxicity translated into a progression-free survival benefit of about 36 months, and the overall survival median has not yet been reached. We believe that this RVd lite regimen (or a dose-adjusted regimen of this triplet formulation) for non-transplant eligible patients is a very well-tolerated regimen, and should be considered the standard of care for newly diagnosed multiple myeloma patients.

References:

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