Managing Myeloma

What is the rationale for utilizing quadruplet therapy for frontline treatment of myeloma?

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The current standard of care for newly diagnosed myeloma is to use three-drug combinations, including proteasome inhibitors, immunomodulatory drugs and dexamethasone. Now, with the introduction of the new classes of drugs, particularly the monoclonal antibodies, the question that has come up is whether we can replace the bortezomib with a monoclonal antibody, or are we better off adding that newer class of drug to the existing three-drug combination to create a four-drug regimen? That led to several clinical trials.

The CASSIOPEIA trial[1] was the first trial that looked at a four-drug combination, particularly in the setting of transplant-eligible patient population. The trial randomized patients to getting a bortezomib, thalidomide, dexamethasone triplet versus adding daratumumab to the VTD regimen. That trial also had a second randomization to a daratumumab maintenance versus no maintenance. What we know from the results so far is that adding daratumumab to VTD clearly improved the progression-free survival. We are still waiting for the overall survival data. Also, the impact of the maintenance of daratumumab versus no maintenance is still awaited as well.

Now, given that VTD is not a commonly used regimen, especially in the US setting, the GRIFFIN trial,[2] which randomized patients to VRD vs a daratumumab/VRD, is more pertinent to the US practice. That trial also demonstrated that by adding daratumumab to bortezomib, lenalidomide, and dexamethasone, given for four cycles before stem cell transplant, two cycles of consolidation and then continuing on maintenance with lenalidomide with or without daratumumab, you significantly improve the depth of response. You have more, two to threefold higher proportion, of patients getting to be MRD negative compared to the VRd. We still don't have data in terms of the progression-free survival or overall survival, as we don't have long term-follow up. Now, a similar approach has been taken in phase 2 studies,[3,4] where daratumumab has been added to ixazomib, lenalidomide, dexamethasone, as well as bortezomib, cyclophosphamide, dexamethasone. Both of them have been studied in phase 2 setting. It certainly demonstrates a high rate of response, and also deep responses, suggesting that four-drug combinations are highly effective.

In the non-transplant patient population, daratumumab has also been added to bortezomib, melphalan, prednisone (VMP) that had been the backbone for these older patients until the new drugs came along. The ALCYONE trial,[5] which randomized patients to getting the Dara + VMP versus VMP, showed that there was an improved progression-free survival, and with longer-term follow-up, an improved overall survival as well.

So, the overall data that we have from these multiple trials suggest that adding a monoclonal antibody to the existing three-drug combinations seems to improve the outcome of patients, both in terms of depth of response, and the durability of response, though overall survival data is awaited. Identification of the patients who derives the most benefit from these combinations will allow more personalized approaches.

References:

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