Managing Myeloma

Evaluating Long-term Prognosis in MM Patients: Lenalidomide, Maintenance and MRD

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Welcome to *Managing Myeloma*. My name is Dr. Philip McCarthy, and I am Professor of Oncology and Director of the Blood and Marrow Transplant Program at the Roswell Park Cancer Institute in Buffalo, New York. Today, I am here to discuss a few abstracts, some related to the role of maintenance therapy and some to other issues related to what is found in community practice. Today, when we look at lenalidomide maintenance, we have a poster presentation looking at the crossover effect in the CALGB-100104 study. In this study, originally a 461-patient study, about half received placebo and the other half lenalidomide. Because the primary endpoint was met, which was progression-free survival, the study was unblinded. At the time of unblinding, there were about 128 patients who had not progressed on placebo therapy, and about 86 of them crossed over to receive lenalidomide. This crossover effect confounded the analysis because the analysis was originally done as an intent-to-treat investigation. We had to try and balance out the effect of the crossover, because now we had placebo patients who were receiving lenalidomide, yet were being considered as placebo patients. This is a rank-preserving structural failure time model and iterative parameter estimation, which are both statistical techniques that allow us to account for this crossover. What it essentially showed is that the placebo arm had a smaller progression-free survival because of the crossover, and the lenalidomide arm of course remained the same because there was no crossover. What this showed is that there was probably an even greater impact for the use of lenalidomide maintenance. This is in concordance with what was found with the FDA approval; as you probably know, both the FDA and the European Medicines Agency (EMA) approved lenalidomide maintenance until progression because of both the French and the American studies, (the CALGB-100104) and the Italian study. We are very pleased that this crossover analysis also demonstrates the continued impact of lenalidomide maintenance, as well as allowing us to understand better the effect of the crossover.

What is also interesting here at EHA is there is a very large British Study, the Myeloma XI study, which was reported at the last ASH meeting. This time, they looked at the effect of two induction regimens. This is about 1000 patients per arm, and the two inductions were cyclophosphamide-thalidomide-dexamethasone versus cyclophosphamide-lenalidomide-dexamethasone. What they showed is that the overall response rate was superior in the patients receiving a lenalidomide-based induction. When they looked at maintenance, they found that maintenance lenalidomide was superior when compared to no maintenance in the patients receiving a lenalidomide

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induction, but the effect was magnified over patients who got a thalidomide-based induction and then got lenalidomide maintenance. Now, one concern about this study is patients were not exposed to bortezomib as part of their induction. They could have received a bortezomib-cyclophosphamide-dexamethasone-based consolidation prior to transplant. It made a little bit complicated, and there were some patients who never received bortezomib. I think that we will have to see how this sorts out relative to the French and American determination trials which do look at the both an IMiD and a bortezomib as part of induction therapy. The key take-home message from this is that patients still benefit from lenalidomide maintenance when looking at a different induction regimen.

Finally, there is a minimal residual disease (MRD) study presented by the EMN02 investigators; this is a large cooperative group trial in Europe. They looked at MRD by multiparametric flow cytometry, and what they found is that in patients who had achieved a very good partial response (VGPR) or better (about 300 patients out of 1200) that a large percentage attained MRD negativity. What was even more important was that of the patients who were MRD positive, 44% of them attained MRD negativity within a year of maintenance treatment. What is very exciting about this is that even patients who are MRD positive could become MRD negative with prolonged maintenance therapy. I think the key element from this study is that lenalidomide maintenance remains a valid indication in this particular study, and that by incorporating MRD measurement of the bone marrow, we will be able to determine how well somebody is going to do long term. Indeed, the goal is to find a surrogate endpoint, an earlier endpoint for overall survival, because we now have patients who are living for many years on maintenance therapy. It is a good problem for the patient, but it is difficult for investigators as we would have to keep the studies open for 10 years to figure out if there is an overall survival benefit. What we hope to do is find these early surrogates to allow us to be able to move on to new studies incorporating new agents, as we have multiple agents that could be tested for maintenance therapy in the future. Thank you for viewing this activity. This is Philip McCarthy speaking to you today from Madrid, Spain at the European Hematology Association.

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