Managing Myeloma

Ixazomib in the Maintenance Setting

Robert Z. Orlowski, MD, PhD
Professor, Chair Ad Interim
Department of Lymphoma/Myeloma
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Welcome to *Managing Myeloma*. My name is Dr. Robert Orlowski and I am here live at the ASH Annual Meeting in surprisingly snowy Atlanta, Georgia. I am going to review the results of two studies today which focus on maintenance therapy using ixazomib, which is the orally available proteasome inhibitor. The first abstract is an update on a phase 2 trial combining lenalidomide and ixazomib for patients who have undergone autologous stem cell transplantation, a study that was performed at MD Anderson. Following that will be a summary of an integrated analysis of four different phase 1 and 2 studies, looking at long-term efficacy and safety of ixazomib as maintenance in patients who have not undergone stem cell transplantation.

The first study which was Abstract 437 combined lenalidomide and ixazomib. The rationale, of course, is that lenalidomide is now a widely accepted standard of care for posttransplant maintenance therapy. Even with that, patients do relapse and some patients do not achieve complete remission (CR) or minimal residual disease (MRD) negativity, and we had hoped that by adding ixazomib to lenalidomide, we could prolong progression-free survival as well as MRD-negativity. Again, these were patients in the posttransplant setting who were usually started between three and six months after their first stem cell transplant. Lenalidomide was used at the standard dose ranging from 5 to 15 mg (with 10 mg as the starting dose) and ixazomib was typically started at 3 mg and given orally on days 1, 8, and 15 of each 28-day cycle. The safety data with this combination were excellent. As you probably know with ixazomib, you can have some GI effects with a little bit of nausea or a little bit of diarrhea (especially with the first dose). That typically resolves with later doses and relatively few patients required any dose reductions of either one or the other agent. In terms of outcomes, we were able to see so far that the estimated progression-free survival at two years is around 81% or 82%. Those data really compare favorably with what has been seen with lenalidomide only as maintenance, although in fairness this was not a randomized study, and hopefully that will be obtained in the future. We also saw a good rate of conversion of patients to complete remission and MRD-negativity, although, again, I think we have to have a randomized study. For community practitioners, we hope soon to have ixazomib approved as a maintenance therapy, and I would definitely consider using it as a maintenance after transplant in a number of different settings. First of all, there are patients who cannot tolerate lenalidomide, for example because of diarrhea or cytopenias or rash, and you want to have them on some type of maintenance, so definitely, ixazomib would be a worthy consideration. The second group I would consider are patients with high-risk disease where we know that lenalidomide is less active, whereas proteasome inhibitors can be beneficial, so I would definitely add ixazomib to lenalidomide in high-risk patients for maintenance. One group is still a little bit hypothetical; if patients do not achieve minimal residual disease negativity on lenalidomide alone, it could be of interest to add something like ixazomib to try to push the disease further down because we know that MRD-negativity is associated with a superior outcome.

Moving on to the next study, the previous trial was presented by Krina Patel, and this one was presented by Meletios Dimopoulos. What Dr. Dimopoulos and his colleagues did was take data from four different phase 1/2 studies which used ixazomib-based induction therapy, and then continued ixazomib afterwards as a single agent as maintenance. This is in the non-transplant patient population. Here again, lenalidomide is the standard of care, but there is good reason to think that a proteasome inhibitor would be better. I mentioned earlier that our study is underway to look at ixazomib as maintenance and probably sometime in 2018, we will have data from randomized phase 3 studies looking at ixazomib versus placebo as a posttransplant maintenance, and also as a postinduction maintenance. But getting back to this particular study, it added ixazomib as a maintenance after an ixazomib-based induction. The toxicities were similar to what I mentioned earlier, which included really low-level GI events and some cytopenias. What was found is that the aggregate progression-free survival after initiation of maintenance was on the order of 18 months, which is really a very positive finding. We will get randomized data from phase 3 studies soon, but in the meantime, I would definitely think about continuing ixazomib as maintenance in transplant ineligible patients after their induction, especially if they have either high-risk disease, if they have been on lenalidomide maintenance and it has not been of sufficient benefit to get down to CR and MRD-negativity, or possibly if you are MRD-positive to convert to MRD-negativity.

Thank you very much, and I hope that this activity will be helpful for you in managing your patients.

References:

Patel KK, Shah JJ, Feng L, et al. Update on a Phase II Study of Ixazomib with Lenalidomide As Maintenance Therapy Following Autologous Stem Cell Transplant in Patients with Multiple Myeloma. *Blood*. 2017;130. Abstract 437.

Dimopoulos MA, Laubach J, Asuncion M, et al. Efficacy and Safety of Long-Term Ixazomib Maintenance Therapy in Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Not Undergoing Transplant: An Integrated Analysis of Four Phase 1/2 Studies. *Blood*. 2017;130. Abstract 902.