Philippe Moreau, MD
University Professor of Clinical Hematology
Nantes Faculty of Medicine
Hematology Department
University Hospital of Nantes
Nantes, France

The Role of Transplant and Doublet vs. Triplet Salvage Therapy

Hello, my name is Philippe Moreau. I am a Professor of Clinical Hematology at the University Hospital of Nantes in France, and I am reporting to you live at ASCO 2016 in Chicago from the *Managing Myeloma* booth. Today, I am going to discuss with you brief highlights of some of the most exciting advances in multiple myeloma, and I will review some of the new data released here at ASCO.

We have heard about a very important study presented by Michele Cavo, a prospective randomized study in young patients with myeloma eligible for stem cell transplantation. This study, the EMN2 study, was a multi-centered study international one, enrolling patients from Italy, from the Netherlands, from Germany, from Greece, from the Czech Republic, and a very large number of patients, more than 1000 patients, were enrolled to receive VCD as part of front-line treatment, bortezomib, cyclophosphamide, and dexamethasone, and then patients were randomized to receive VMP conventional treatment without stem cell transplantation or to receive a single or a tandem stem cell transplantation. And the aim of the study was to look at the progression-free survival in patients treated without stem cell transplantation but with novel agent based-only combinations or patients treated with induction plus stem cell transplantation, so a very large number of patients. These data are preliminary. It is the first time that we have heard about some results, and Dr. Cavo nicely showed that the progression-free survival was highly increased in patients receiving VCD followed by stem cell transplantation as compared with patients treated with VCD followed by VMP. This is also true, not only for standard-risk patients but also for high-risk patients, and the conclusion of this very important study is that in the context of novel agent-based induction regimens, stem cell transplantation still remains front line and high-dose treatment still remains the standard of care. Of course, we have to wait for a longer followup to look at overall survival data, but PFS is really in favor of early stem cell transplantation.

In the same session, we have heard about the results of a meta-analysis looking at the impact of lenalidomide maintenance following stem cell transplantation. This study was proposed by Dr. Attal and Dr. Phil McCarthy who was the speaker, and he showed that lenalidomide following stem cell transplantation versus placebo was able to increase not only the progression-free survival but also overall survival. In this study, the meta-analysis merged the data from three randomized trials comparing placebo versus lenalidomide maintenance following stem cell transplantation, one from the US, the CIGB study; one from France, IFM 2005-02; and the last one coming from Italy. Overall, we have a very large number of patients, and the conclusions are rather clear in fact. Lenalidomide maintenance is improving progression-free survival but also overall survival by 2.5 years, in fact. Some subgroups of patients are benefiting less from lenalidomide maintenance, especially patients with ISS3, patients with high-risk cytogenetics. But overall, this trial, this meta-analysis is now showing that in the future we should use lenalidomide maintenance systematically.

The third study was presented by Paul Richardson. That is a sub-analysis of the Tourmaline-MM1 trial. Paul Richardson looked at the impact of ixazomib, an oral proteasome inhibitor, in patients in the relapsed setting with 1 to 3 prior lines of treatment. Patients were receiving either lenalidomide-dexamethasone-placebo or lenalidomide-dexamethasone-ixazomib, and he focused on the subgroup of patients with high-risk cytogenetics, 17p, and patients with translocation 4;14. These patients overall are representing 20% of the patient population enrolled in this phase 3 randomized study, and he showed that the progression-free survival with the addition of ixazomib is very important, from 9-10 months with lenalidomide-dexamethasone placebo up to 20- 21 months with lenalidomide-dexamethasone-ixazomib. So, this trial is clearly establishing that for patients with high-risk cytogenetics in the relapsed setting, we need to use a triplet combination including lenalidomide, an IMiD, and ixazomib, an oral proteasome inhibitor.

The fourth trial that I want to share with you is also a meta-analysis proposed by Dr. Nooka. In fact, he is working at Emory in the US, and he looked at the comparison of two drugs versus three drugs in the relapsed setting. That again is a meta-analysis of prospective phase 3 trials using two drugs versus three drugs, and he has pooled all patients treated with a triplet and pooled all patients treated with a doublet, lenalidomide-dexamethasone versus lenalidomide-dexamethasone-ixazomib, lenalidomide-dexamethasone-elotuzumab, lenalidomide-dexamethasone-carfilzomib, or bortezomib-dexamethasone versus bortezomib-dexamethasone-panobinostat. So, the patients treated with two drugs are patients treated either with lenalidomide-dexamethasone or with bortezomib-dexamethasone, and the patients treated with three drugs are patients treated with bortezomib-dexamethasone plus panobinostat or lenalidomide-dexamethasone plus either ixazomib, elotuzumab, or carfilzomib. And overall, the results are really in favor of the triplet combination, not only for the response rate, also for progression-free survival, and we have a huge trend for an overall survival benefit for patients receiving a triplet combination. So, the message here is that, when possible, in the relapsed setting we should use a triplet combination instead of two drugs in order to improve the quality of the response and also the duration of the response.

And finally, one poster looked at pomalidomide and low-dose dexamethasone in very advanced patients, and we have pooled the data from different trials to MM-03 study, the MM-02 study, and also a post approval study, STRATUS study. We looked at the toxicity of pomalidomide and low-dose dexamethasone on a very large number of patients. This study is clearly showing that using pomalidomide and low-dose dexamethasone in very advanced patients, patients progressing on bortezomib, patients progressing on lenalidomide, the toxicity profile, the safety profile of this combination is rather good. We do not have any issue in terms of peripheral neuropathy. The most important toxicity is the hematologic toxicity, as expected. We have to be careful regarding the neutrophil counts and also the platelet counts, this is very well known. And we also looked at all the toxicities, for example DVT. We know that with the use of IMiDs, we have to be careful with the induction of thrombosis, and in fact when all patients are receiving a DVT prophylaxis, the DVT rate is very, very low, less than 5%. So overall, pomalidomide and low-dose dexamethasone is quite well established and really manageable. So, this is the summary of the data that I wanted to share with you, five good abstracts, five good presentations, during the ASCO meeting 2016.