Managing Myeloma

Highlights from the ASPIRE and PETHEMA/GEM2012 Trials

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It is my pleasure to share with you today the final analysis from the randomized phase 3 ASPIRE trial in which carfilzomib with lenalidomide and dexamethasone (KRd) has been compared with lenalidomide and dexamethasone (Rd).

The initial result showed significant benefit in progression-free survival (PFS) with a hazard ratio of 0.69, which was associated with a complete response rate of 32% in the KRd arm versus 9% in the Rd arm. As a reminder, the KRd was based on carfilzomib at 27 mg and the standard dose of lenalidomide and dexamethasone. A total of 792 patients were included. All these patients were relapsed or refractory myeloma patients who have received one to three prior lines of therapy; 46% of the patients were stage III, high-risk cytogenetic was observed in 12% of the patients, and 66% of the patients were previously exposed to bortezomib. The primary endpoint was progression-free survival. In the initial report, we saw already that there was a significant benefit for the experimental arm, and now the progression-free survival assessed by the Independent Review Committee confirmed almost 10 months' difference. This is also being confirmed in the progression-free survival assessed by the investigator and updated the information with 26 months versus 16.6 months in the control arm, at a hazard ratio of 0.66. Probably the most exciting data that is being presented corresponds to the overall survival. The overall survival is significantly better in the experimental arm; 48 months versus 40 months for the control arm, and this is a highly significant benefit for the KRd treatment. This benefit in overall survival is observed across all specified subgroups. Patients receiving one or more than two prior lines of therapy, patients previously exposed to bortezomib, and non-responses or responses to bortezomib were equally effective when they were treated with carfilzomib, lenalidomide, and dexamethasone. It should be noted that the overall survival is associated with the quality of the response; patients that achieved a complete response or better enjoyed a significantly longer overall survival.

The challenge is always the analysis of survival beyond progression, and this study shows that the use of carfilzomib is not associated with more-resistant disease because the survival beyond progression is equal in the KRd and Rd arms. Finally, you can see the incidence of adverse event is almost identical in both arms, except for more frequent hypokalemia in patients receiving carfilzomib. If we concentrate now in adverse cardiovascular events, we can see that the incidence is higher, as has been reported, with carfilzomib: more cardiac failure, more hypertension, but the same rate of peripheral neuropathy. The good news is that we have learned now how to handle these cardiovascular events. Therefore, I can conclude that this second phase 3 trial in relapsed/refractory patients using carfilzomib demonstrates a significant benefit in overall survival, and the same was previously shown for carfilzomib-dexamethasone in the ENDEAVOR trial. We have two randomized trials in which carfilzomib is associated not only with a benefit in progression-free survival, but also a benefit in overall survival. The KRd efficacy advantage is most pronounced in first relapse with 11-month improvement in overall survival, and safety is consistent with prior findings.

Now let me share with you today the data on minimal residual disease that has been presented by Bruno Paiva on behalf of the Spanish group.

What should be the goal of therapy in myeloma patients? Should we just search for an appropriate balance between treatment efficacy, toxicity, and cost? But if cure is the goal, then we need to eradicate all tumor cells in order to achieve and maintain the best possible response. What is the best possible response? Minimal residual disease (MRD) negativity. In this meeting, we are going to see two very important presentations. The first one is from the French group. In this randomized trial, they have analyzed the impact of minimal residual disease after consolidation and after maintenance by using next-generation sequencing. Herve Avet-Loiseau has previously reported that, in patients that achieved minimal residual disease negativity at a level of 10^{-6}, the progression-free survival is significantly longer than patients that achieved minimal residual disease negativity in the level of 10^{-5} or 10^{-4}. This was independent of prior treatment. Patients that achieved MRD-negativity post-maintenance in both treatment arms obtained a significantly longer survival. At this meeting, Herve Avet-Loiseau has updated the final analysis of this very important trial; 269 patients were evaluated for minimal residual disease using the clonoSEQ approach, and they showed that the progression-free survival is significantly longer for patients that achieved MRD-negativity not reached versus 29 months. The treatment arm shows that more patients in the transplant arm achieved MRD-negativity but no difference among MRD-negative cases. In addition, high-risk cytogenetic patients who achieved MRD-negativity presented a significantly better outcome than standard risk patients who did not achieve MRD-negativity. This study also illustrates a very important point: MRD-negativity is also associated with significantly longer overall survival.

The clinical data of the Spanish study, which I alluded to before that is going to be presented by Laura Rosinol, is based on six induction cycles with bortezomib-lenalidomide-dexamethasone (VRd), followed by autologous transplant with either melphalan 200 or busulfan melphalan and consolidation with two VRd cycles. MRD is analyzed after induction, after transplant, and after consolidation. The data on MRD correspond to 419 patients over 1000 bone marrow samples that have been analyzed in this study. The approach is the new next-generation flow (NGF) cytometry that allowed a limit of detection of 10^{-6} that was reached in 88% of the samples. After induction, 35% of the patients achieved MRD-negative status. After transplant, the figure increased to 54%, and 58% after consolidation. In MRD-negative patients, similar to what Herve Avet-Loiseau had shown by the next-generation sequencing, here with the next-generation flow, MRD-negative patients have significantly longer progression-free survival. Once again, the depth of the MRD-negativity is associated with longer survival. Patients that achieve MRD-negativity or an MRD-negative level between 10^{-6} and 10^{-5} have significantly longer progression-free survival. This benefit is observed across all sub-groups in advanced stage and, very important, in high-risk patients. In fact, high-risk patients that achieve MRD-negativity do as well as standard-risk patients with also MRD-negativity, and much better than standard-risk patients who remained MRD-positive.

Finally, we have already observed some relapses, and interestingly, the relapses correspond to patients with extramedullary disease. This reinforces the need to analyze MRD-negativity, both inside the bone marrow and outside the bone marrow. These are my conclusions. This is the largest MRD study. NGF is feasible in large multicenter trials, has high sensitivity, and allows the identification of hemodiluted bone marrow samples. The sensitivity for 10^{-5} and 10^{-6} confer

significantly better survival, and MRD-negativity is probably the most relevant endpoint both in standard- and high-risk transplant-eligible patients.

Thank you very much for your attention.

References:

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