Managing Myeloma

Minimal Residual Disease and Biomarkers

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Welcome to *Managing Myeloma*. My name is Dr. Paul Richardson and I am the R.J. Corman Professor of Medicine at Harvard Medical School and the Director of Clinical Research and Clinical Program Leader at the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute in Boston, Massachusetts. I am here at the 58th American Society of Hematology Annual Meeting in San Diego, California, and today, I will be reviewing with you four abstracts presented on variety of exciting topics in multiple myeloma.

Now, the first one we are going to discuss this afternoon is the evaluation of minimal residual disease in relapsed/refractory myeloma patients treated with daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone. This work has been led by my colleague, Dr. Hervé Avet-Loiseau. So when we first think about the study, it is important to note that these trials were remarkable studies in which it was demonstrated clearly the combination of daratumumab either with lenalidomide and dexamethasone, or with bortezomib and dexamethasone resulted in substantial progression free and survival benefits in favor of the three-drug combination over the two. Now in terms of the hazard ratios involved with PFS, these were striking, in the region of 0.35 and point 0.37 for both studies. With this kind of backdrop, it is important to recognize the clinical benefit derived from these combinations. What was also very important in both of these trials is, in those patients who achieved complete remission, MRD testing was particularly informative. Now how was this done? Well, basically MRD was assessed at the time of complete remission and at 3 months and 6 months post remission. MRD was assessed using a special clonal sequence assay and sensitivities were 10^{-4}, 10^{-5}, and 10^{-6} in terms of their ability to assess tumor burden. Now what we saw was that in the POLLUX trial when we compared daratumumab, lenalidomide, and dexamethasone to lenalidomide and dexamethasone, the sensitivity threshold was 29% for the three-drug combination versus 8% for the two, showing the rates of MRD were over three-fold higher for the three-drug combination. Similar degree of improvement was seen at 10^{-5} and 10^{-4}. For example, at 10^{-5}, 5% of patients were MRD negative with Rd alone whereas in contrast, 22.5% were MRD negative with the three-drug combination. When one looked at the 10^{-6} threshold, 2% were MRD negative amongst those who achieved complete response versus 10% in those patients receiving DRd. What is also very interesting is if you look at the CASTOR data, similar differences in favor of the three-drug combination were seen. For example, approximately 14% of the patients were MRD negative at 10^{-4} versus 3% at the same level of sensitivity for bortezomib and dexamethasone alone. Similarly at 10^{-5}, 7% were MRD negative versus just 2% for the control group, and finally 10^{-6} just 4% were MRD negative with the three drugs versus less than 1% for the control. What was very important was at each of these levels they translated into progression-free survival benefit, and very importantly the most sensitive was at 10^{-6}. So, I think these data in aggregate tell us that MRD testing on the one hand is feasible in this setting and is prognostically meaningful in this group of patients. But most importantly, it shows the real benefit of the three-drug combination compared to the two in the study for those patients achieving complete remission. Very excitingly, I think as we go forward, this particular type of testing may have an increasing impact in practice in the future.

At the moment, however, it must be I think emphasized that this remains primarily a research tool and will be very useful in the context of drug approval finding studies; for example, for endpoints that are of importance and have surrogate value. But in the context of day-to-day clinical practice, while they can be informative, it is probably reasonable to say that for the moment it will remain part of our research domain primarily. Nonetheless, this is clearly emerging as an important new tool that we can use in our practice, be it in research or standard of care going forward.

Now, the next abstract I wanted to review with you is a really interesting study. A phase 1B study actually assessing subcutaneous delivery of daratumumab in patients with relapsed/refractory multiple myeloma and comparing this to intravenous delivery of daratumumab in the same study population. The rationale for investigating subcutaneous daratumumab is to improve the ease of administration of this important new monoclonal antibody, shorten infusion time, and improve convenience and tolerability in that same context. What was very exciting in this trial, led by Dr. Saad Usmani and colleagues, was that essentially the safety data were very favorable, comparable to what we see with the IV, and in fact, if not somewhat better. What was very interesting was that we were able to demonstrate that this was a feasible approach with half an hour infusion under the abdominal wall into the abdominal skin combined with hyaluronidase in a way that was both convenient and actually very feasible for all patients. The two-dose level study compared very favorably, and in this same context the use of subcutaneous daratumumab was very comparable to intravenous daratumumab, with equal efficacy in this relapsed/refractory population. Now, how will the subcutaneous form of daratumumab impact the clinical practice? I myself think hugely, because at the end of the day it will allow us to much more conveniently administer daratumumab going forward. While intravenous daratumumab is now a very exciting new addition to our armamentarium, with not only approval last year for relapsed/refractory disease and the accelerated approval pathway, but now with this full approval in combination with both lenalidomide and bortezomib, we will start to see intravenous therapy gradually be replaced in my view by subcutaneous delivery, which may be much more convenient and just as good for our patients. So, I think it is a very exciting study, very informative, and I actually congratulate the investigators on successfully completing this so quickly, because there is no doubt in my mind that this will be very helpful in changing clinical practice going forward and improving the convenience of the administration for this really important and arguably breakthrough monoclonal antibody.

Now, the next abstract that I wanted to review with you is one by my colleague, Dr. Alessandra Di Bacco. She looks at the association of higher c-MYC expression with progression-free survival benefit in patients with relapsed/refractory myeloma treated as part of the phase 3 TOURMALINE-MM1 study. Just to remind you of this trial, this study looked at the combination of ixazomib, lenalidomide, and dexamethasone compared with placebo, lenalidomide, and dexamethasone in a patient population who received one to three prior lines of treatment. Just to also remind you, this study showed an impressive 6-month progression-free survival benefit in favor of the three-drug combination versus the two. An excitement of this combination was it was obviously all-oral. Ixazomib was generally very well tolerated, and it would provide therefore an important new therapeutic option for patients. This was further exemplified by the fact this drug got FDA approval in combination at the end of last year and European approval this year. Now, what is c-MYC and why is it relevant in multiple myeloma? c-MYC is a proto-oncogene that encodes a transcription factor that regulates cell growth, proliferation, protein translation, metabolism, and apoptosis. Importantly, increased c-MYC expression is involved in myeloma pathogenesis and progression, and what Alessandra showed very nicely was that higher levels of c-MYC expression was seen in patients with more advanced disease. Very interestingly, the three-drug combination of ixazomib,

lenalidomide, and dexamethasone was more active in this group of patients than in those who had lower c-MYC expression. Now does this mean one would not use this combination in the patients with low c-MYC expression? No, I think that is not the case. However, I think it is particularly interesting to see the three-drug combination was particularly active in this higher-risk worst biology group and this might easily explain why, for example, in the context of the TOURMALINE trial, more benefit was seen in patients who had 2 to 3 prior lines of therapy versus those who only had one. Having said that, the benefit of the combination overall remains quite impressive, particularly as we think about the excellent tolerability of this approach.

The last abstract I want to review with you this afternoon is one presented by my dear friend and colleague, Dr. Thierry Facon, from the Intergroupe Francophone Myélome, or IFM, and he is principal investigator. He is presenting a final analysis of overall survival from the FIRST trial. This study is a unique study in which there was a comparison of melphalan, prednisone, and thalidomide as a control group compared to either lenalidomide and dexamethasone continuously or lenalidomide and dexamethasone given for 18 months. Just to remind you, this was published in the *New England Journal of Medicine*. It was a paper in which PFS difference was clearly apparent for the lenalidomide and dexamethasone continuously. The impact in Rd for 18 months was somewhat less, but both Rd arms outperformed MPT, which was the previous control. The study therefore confirmed the use of lenalidomide and dexamethasone is a new standard of care in the upfront setting and FDA approval also followed on the basis of this data. Now in this context what is really exciting about the final analysis from the FIRST trial is the following. Basically, at 4-year, progression-free survival percentage remained the highest for Rd continuous at 33%, with Rd for 18 months being around 14%, and MPT being around 13%. Now if you look at the updated PFS, they are 26 months for the Rd continuous, 21 months for Rd18, and MPT remain 21 months. So, the hazard ratio here is 0.69 and highly significant. What is also very interesting from this analysis, however, is the median overall survival benefit in which 59-month median survival was seen to Rd continuous, versus 62.3 months for Rd18, and 49.1 for MPT. This suggests that both Rd continuous and Rd18 for overall survival are superior to MPT with a hazard ratio of 0.78. What is particularly interesting as well is that the impact on second progression after relapse was noteworthily favorable for the Rd combinations. So in conclusion, Rd continuous significantly prolonged progression-free and overall survival and improved other secondary endpoints compared with MPT in this older population who were transplant ineligible with newly diagnosed disease. Rd continuous also showed a progression-free survival benefit compared with Rd18, delaying the time to next therapy. PFS2 outcome suggests that Rd does not induce resistant relapses, and very importantly second primaries were rare in the Rd arms and incidence of second primaries were similar between Rd continuous and Rd18. In this context, therefore, these data confirm that Rd continuous remains an important standard of care for transplant-ineligible patients with newly diagnosed multiple myeloma. In terms of future directions, it is important to note that with the addition of proteasome inhibitors to the Rd backbone upfront, data are now showing this to be yet another new standard in this setting. Of course in older patients, this may well become more of an important approach. Having said that, the long-term outcome data from the FIRST trial firmly confirm that Rd, as I mentioned, is the standard of care in this older transplant ineligible population.

So, thank you so much for viewing this activity, and I hope the information we have shared with you this afternoon is helpful. For additional resources, please be sure to view the other educational activities on *ManagingMyeloma.com*.