Managing Myeloma

Carfilzomib in Relapsed or Refractory Multiple Myeloma Patients with Early or Late Relapse Following Prior Therapy: An Analysis of Overall Survival in Subgroups from the Randomized Phase 3 Aspire and Endeavor Trials

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I am here attending the 60th American Society of Hematology Congress in San Diego. I will present the results of a subanalysis conducted in the Phase III randomized trials ASPIRE and ENDEAVOR, evaluating the efficacy of carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy. Both ASPIRE and ENDEAVOR were Phase III randomized trials conducted in relapsed and refractory myeloma patients in which carfilzomib, lenalidomide, and dexamethasone, or carfilzomib and dexamethasone alone were compared with two standards of care: lenalidomide and dexamethasone in the ASPIRE study; and bortezomib and dexamethasone in the ENDEAVOR trial. Both studies have shown in the overall series of patients a significant benefit in terms of progression-free survival that was the primary endpoint as well as in terms of overall survival.

In this subanalysis, we are going to focus on the outcome of these patients included in this study according to the type of relapse, early versus late relapse, and I would say that early relapse includes those patients who relapsed within the first year from initiating the most recent prior line of therapy. In ASPIRE, 29% of the patients in the KRd and 26% of patients in the Rd arm had a relapse within the first year from initiation of the most recent prior line of therapy. In ENDEAVOR, 27% and 25% of patients in the Kd and Vd arms respectively, experienced earlier relapse. Concerning baseline characteristics of the patients, I would say that there were not significant differences in both studies and in both arms according to the early versus late relapse. I would like you to know that the greater percentage of patients with early versus late relapse had a prior bortezomib or lenalidomide therapy in ASPIRE, high-risk cytogenetic abnormality seen in ENDEAVOR, and three prior regimens in the ASPIRE study. As I previously said, both ASPIRE and ENDEAVOR showed significant benefit in terms of PFS and overall survival. If we focus first on progression-free survival, we can say that in the ASPIRE study, patients having early or late relapses, when they received carfilzomib, lenalidomide and dexamethasone, they had a significant benefit in comparison with lenalidomide and dexamethasone alone. Of note, patients receiving KRd with early relapses have a median progression-free survival of 21.4 months, and I think that it is important to know that in the ASPIRE, patients receiving KRd and late relapses had a median progression-free survival of almost 30 months. When we evaluated this benefit in the ENDEAVOR study, we see a similar picture on patients receiving carfilzomib and dexamethasone at a dose of 56 mg/m^2. If they have early or late relapses, they had a significant benefit in comparison with bortezomib and dexamethasone. Again, early relapses receiving carfilzomib and dexamethasone with median progression-free survival of 14 months, and patients receiving Kd and late relapses had a benefit in progression-free survival with a median PFS of almost two years.

This benefit in terms of progression-free survival is important, but I think it is much more relevant the benefit so-far reported in terms of overall survival, and in both ASPIRE and ENDEAVOR, carfilzomib-based combination resulted into a significant benefit in terms of overall

survival. I would like to note that early relapses receiving KRd had a median overall survival of three years, and when we focused on these patients receiving KRd but late relapses, the median overall survival is 53 months. In the ENDEAVOR study, median overall survival for early relapses was approximately 29 months and what is important is the median always has not been reached yet in ENDEAVOR receiving carfilzomib and dexamethasone late relapses.

I would say that relapsed and refractory myeloma patients who received the carfilzomib-based combination had a longer overall survival compared with those who received lenalidomide/ dexamethasone or bortezomib and dexamethasone respectively, regardless of whether they had early or late relapse, following the most recent line of therapy. Progression-free survival and overall response rate were also improved with the carfilzomib-based combination. As suspected, outcomes were improved in patients with late relapse. Early relapse was predictive of worst outcomes, but this is similar to the results reported in other studies. In ASPIRE, median overall survival was improved by 8.3 months among patients with early relapse and by one year in late relapses. In ENDEAVOR, median overall survival was improved by almost seven months among patients with early relapse and the median was not reached versus 42.3 months for late relapses.

I would conclude by saying that the benefit of carfilzomib-based combinations were found to be consistent regardless of whether patients had an early or late relapse after the most recent prior line of therapy.

Reference

Mateos M, Goldschmidt H, San-Miguel J, et al. Carfilzomib in Relapsed or Refractory Multiple Myeloma Patients with Early or Late Relapse Following Prior Therapy: An Analysis of Overall Survival in Subgroups from the Randomized Phase 3 Aspire and Endeavor Trials. ASH 2018. Abstract 1964.