Managing Myeloma

Efficacy and Safety of Once-Weekly vs Twice-Weekly Carfilzomib Plus Dexamethasone: Subgroup Analysis of the Phase 3 A.R.R.O.W. Study (NCT02412878) By Prior Lines

María-Victoria Mateos, MD, PhD
Associate Professor of Medicine
University of Salamanca
Salamanca, Spain

I am here in San Diego attending the American Society of Hematology Congress 2018 and I will show you a subanalysis done in the Phase III A.R.R.O.W. study in which the efficacy and safety of once-weekly versus twice-weekly carfilzomib plus dexamethasone was evaluated, and this specific analysis will be conducted based on the number and type of prior lines of therapy. The A.R.R.O.W. study was a Phase III randomized trial conducted in 478 relapsed or refractory myeloma patients after two or three prior lines of therapy. All patients had been previously exposed to IMiD and PI. In this study, patients were randomized 1:1 to receive carfilzomib plus dexamethasone once-weekly at a dose of 70 mg/m^2 versus carfilzomib plus dexamethasone twice-weekly at a dose of 27 mg/m^2 and I would say that the twice-weekly carfilzomib and dexamethasone was the control arm.

In this subanalysis, when we evaluated the baseline characteristics of the patients according to the number and type of prior lines of therapy, I would say that 50% of patients had received one or two prior lines of therapy in both arms. Important to note that 84% of patients has been previously exposed to the immunomodulatory drug lenalidomide and baseline characteristics of the patients were generally well balanced between both groups. The proportion of patients older than 75 years was higher in Kd 70 mg/m^2 weekly versus Kd 27 mg/m^2 twice-weekly, especially in the group of patients who had received three prior lines of therapy. When we evaluated the efficacy in terms of overall response rate and complete response rate in once-weekly versus twice-weekly according to the number of prior lines of therapy, I can say that the results are consistent and always once-weekly Kd 70 mg/m^2 is superior to twice-weekly Kd 27 mg/m^2. If we focused on patients who had received just two prior lines of therapy, the overall response rate was 63% versus 41% for once-weekly versus twice-weekly, respectively. When we focused on patients who had received three prior lines of therapy, we see the same magnitude of benefit, 63% of overall response rate for once-weekly Kd 70 mg/m^2 versus 40.7% in the twice-weekly Kd 27 mg/m^2 arm. The same picture is observed in terms of complete response rate, and I would like to remark that 10% of patients achieved the complete response rate when they received a once-weekly carfilzomib 70 mg/m^2 after just two prior lines of therapy.

This benefit in terms of overall response rate and complete response rate translated when we evaluated the progression-free survival, and in fact when we focused on patients who had received just two prior lines of therapy, carfilzomib and dexamethasone administered once-weekly at a dose of 70 mg/m^2 resulted significantly superior in comparison with twice-weekly carfilzomib 27 mg/m^2 with median progression-free survival 12.1 months versus 7.6 months. When we evaluated the same effect in patients who received the three prior lines of therapy, there is also a superiority, although it is true that this patient population are more heavily pretreated and the benefit is more marginal and the PFS for once-weekly carfilzomib was nine months versus eight months for twice-weekly carfilzomib 27 mg/m^2.

As I previously said, in this patient population, most of them almost 80% of the patients have been previously exposed to lenalidomide. When we evaluated what was the effect of prior treatment with lenalidomide, we can say that the carfilzomib and dexamethasone once-weekly at the dose of 70 mg/m^2 was superior to carfilzomib and dexamethasone twice-weekly at the dose of 27 mg/m^2 in both groups of patients who have received two or three prior lines of therapy. I think that this information is relevant because we are facing right now more and more patients previously exposed to lenalidomide and we can confirm with this subanalysis that carfilzomib and dexamethasone, especially weekly and at a dose of 70 mg/m^2, is an excellent option.

I would conclude saying that the results of this subgroup analysis of A.R.R.O.W. indicated that the convenient once-weekly carfilzomib 70 mg/m^2 dosing has a better benefit-risk profile than twice-weekly carfilzomib at 27 mg/m^2 dosing, regardless of the number of prior lines of therapy or prior lenalidomide exposure. Overall response rates in the Kd at 70 mg/m^2 weekly were higher than those in the Kd at 27 mg/m^2 twice-weekly for patients with two and three prior lines of therapy. The median progression-free survival extended by 4.5 months in patients with two prior lines of therapy and by just one month in patients with three prior lines of therapy. The superiority was also observed regardless of the lenalidomide exposure. Safety profile was consistent with that reported in the overall population and is consistent with previous reports that patients with fewer prior therapies achieved a greater benefit with carfilzomib therapy, suggesting that the carfilzomib efficacy can be optimized by earlier administration in the disease course for patients with relapsed and refractory multiple myeloma.

Reference

Moreau P, Stewart K, Lazzaro A, et al. Efficacy and Safety of Once-Weekly vs Twice-Weekly Carfilzomib Plus Dexamethasone: Subgroup Analysis of the Phase 3 A.R.R.O.W. Study (NCT02412878) By Prior Lines. ASH 2018. Abstract 3244.