EHA Highlights from María-Victoria Mateos, MD, PhD

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Welcome to *Managing Myeloma*. I am Dr. María-Victoria Mateos and I will be reviewing two abstracts that were presented at the European Hematology Association 2018 Annual Congress in Stockholm. I will review the results of the randomized phase 3 A.R.R.O.W. study which evaluated once-weekly versus twice-weekly carfilzomib plus dexamethasone in patients with relapsed and refractory multiple myeloma, and I will report also on a subgroup analysis of a phase 1b study looking at daratumumab, carfilzomib, and dexamethasone in lenalidomide-refractory patients with relapsed multiple myeloma.

We will focus on the A.R.R.O.W. study. This is a phase 3 randomized trial in which the standard approach to use carfilzomib as a single agent in relapsed and refractory myeloma (20/27 mg/m^2 twice weekly) was compared with the administration of carfilzomib (only once-weekly at dose of 70 mg/m^2) in both cases in combination with dexamethasone. The background for this study is that of the CHAMPION-1 study, which was a phase 1/2 trial conducted in relapsed and refractory myeloma patients in which the weekly administration of carfilzomib was evaluated.[1] In this study, 70 mg/m^2 was the maximum tolerated dose defined for the administration of carfilzomib once weekly.

In the A.R.R.O.W. study, almost 500 patients were included, all of them relapsed and refractory after two to three prior lines of therapy. Important to note, all patients had been previously exposed to a proteasome inhibitor (PI) and IMiD. Patients were 1:1 randomized to receive carfilzomib plus dexamethasone, but carfilzomib 70 mg/m^2 just once weekly versus carfilzomib 20/27 mg/m^2 twice weekly. The treatment was given until disease progression or unacceptable toxicity. The primary endpoint for this trial was progression-free survival and the secondary endpoints included overall response rate, overall survival, and safety profile.

The median follow up for this study is approximately one year and the primary endpoint, the median progression-free survival, was significantly superior for carfilzomib 70 mg/m^2 once weekly in comparison with carfilzomib 20/27 mg/m^2 twice weekly. Median progression-free survival was 11.2 months for weekly administration versus 7.6 months for the twice-weekly administration. In addition, the benefit or the superiority of carfilzomib 70 mg/m^2 once weekly was sustained across the different subgroups of patients. Patients exposed to proteasome inhibitor, exposed to immunomodulatory drugs, and even patients refractory to bortezomib or refractory to lenalidomide showed a greater benefit when they received carfilzomib once weekly. The secondary endpoint

of overall response rate also showed superiority for carfilzomib once weekly: 63% overall response rate versus 40.8% for carfilzomib 27 mg/m^2 twice weekly. In fact, the complete response rate or better was also superior for carfilzomib once weekly.

In this study, one important point to evaluate was the safety profile. It's important to mention that in spite of the higher dose for carfilzomib given in a weekly scheme, the safety profile was very similar. In fact, the incidence of grade 3/4 adverse events was 67.6% in the weekly arm versus 62% in the twice-weekly arm. When we evaluated the incidence of hematological or non-hematological adverse events, the incidence of adverse events of all grades or grade 3/4 was very similar. If we focus on specific adverse events of interest like hypertension, cardiac failure, or renal impairment, I can say that the incidence was very similar for carfilzomib 70 mg/m^2 weekly versus carfilzomib 27 mg/m^2 twice weekly.

The conclusion of the A.R.R.O.W. study was that once-weekly carfilzomib 70 mg/m^2 significantly improved the progression-free survival by 3.6 months and reduced the risk of progression or death by 30.7%, compared with the twice-weekly carfilzomib at 27 mg/m^2. In addition, patients who received carfilzomib once weekly also showed a significantly higher overall response rate as well as complete response rate. The overall safety profile was comparable between the two treatment groups and no new safety signals were identified. Thus, in comparison with twice-weekly carfilzomib, once-weekly carfilzomib at 70 mg/m^2 showed a favorable benefit risk profile for patients with relapsed and refractory multiple myeloma. In addition, it provides a more convenient schedule and can improve access to an efficacious therapy for patients unable to make twice-weekly visits to the clinic.

The second abstract that I would like to discuss here is based on a subanalysis conducted in a phase 1b trial in which daratumumab, the CD38 monoclonal antibody, was combined with carfilzomib and dexamethasone. We know that lenalidomide is an immunomodulatory drug, and it is very common to see in patients with myeloma that all of them usually had been previously exposed to lenalidomide, and most of them are usually lenalidomide-refractory. This subanalysis showed the efficacy and the safety profile of this combination in patients refractory to lenalidomide.

Eighty-five carfilzomib-naïve patients and after one to three prior lines of therapy were included in this study. The treatment included the administration of carfilzomib once-weekly at a dose of 70 mg/m^2 in combination with the dexamethasone and the monoclonal antibody daratumumab given in a conventional scheme. Importantly, 75 patients split the first dose of daratumumab (the conventional dose is 16 mg/kg but that these patients received 8 mg/kg on cycle one/day one and cycle one/day two). All patients were lenalidomide-refractory, defined as progression during treatment with lenalidomide or within 60 days of completion of the last line of therapy, and in this case receiving lenalidomide.

Fifty-one patients included in this trial were lenalidomide-refractory. The median age was 66 and all patients had a good performance status. The median number of prior lines of therapy were two, and almost all patients had been previously treated with bortezomib (a PI). Almost 20% of the patients had been also previously exposed to pomalidomide, a second-generation immunomodulatory drug. After a median follow-up of 8.3 months, the median progression-free survival was 14.1 months, indicating that this combination of carfilzomib, dexamethasone plus daratumumab is very effective in this heavily pre-treated population, and in fact all of them refractory to lenalidomide. In fact at one year, almost 70% of the patients remain alive and free of progression. The overall response rate was also a secondary endpoint, and 80% of the patients receiving carfilzomib, daratumumab, and dexamethasone responded to this combination and achieved at least partial response. What is important is that more than 60% of the patients achieved at least very good partial response (VGPR). Minimal residual disease was indeed evaluated in this study and the median time to minimal residual disease negative rate was approximately five months, and approximately 8% of the patients were able to achieve minimal residual disease negativity. In terms of safety profile, I would say that the safety profile was consistent with the well-known safety profile for daratumumab and carfilzomib. In fact, infusion-related reactions occurred in approximately 37% of the patients, but in most of them it was grade 1 and 2. In fact, no patients developed infusion-related reactions grade 3/4.

In summary, I would say that the results of this subanalysis conducted in lenalidomide-refractory myeloma patients showed a significant benefit for this specific combination based on the monoclonal antibody daratumumab plus carfilzomib in a population that had been previously exposed to lenalidomide. In addition, all of them were refractory to lenalidomide. Split-dose daratumumab is feasible and may improve the patient convenience for initial dose. Finally, you should know that there is currently an ongoing phase 3 randomized trial comparing carfilzomib and dexamethasone with daratumumab, carfilzomib, and dexamethasone (CANDOR study). The results of this trial may be positive, and we will have a new standard of care for the management of relapsed and refractory multiple myeloma. I finish here my presentation to say thanks for joining this recording, and I hope you have enjoyed this presentation.

Abstracts

Mateos MV, Moreau P, Berenson J, et al. Once-weekly vs twice-weekly carfilzomib (K) dosing plus dexamethasone (d) in patients with relapsed and refractory multiple myeloma (RRMM): Results of the randomized phase 3 study A.R.R.O.W. EHA 2018. Abstract S849.
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Moreau P, Martinez-Lopez J, Mateos MV, et al. Daratumumab, Carfilzomib, and Dexamethasone (D-Kd) in Lenalidomide (Len)-Refractory Patients with Relapsed Multiple Myeloma (MM): Subgroup Analysis of MMY1001. EHA 2018. Abstract PF579. *https://learningcenter.ehaweb.org/eha/2018/stockholm/215029/philippe.moreau.daratumumab.arfilzomib.and.dexamethasone.28d-kd29.in.html?f=ce_id=1346*ot_id=19065*media=3*

Reference

1. Berenson JR, Cartmell A, Bessudo A, et al. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. *Blood.* 2016;127(26):3360-3368.