Managing Myeloma

Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) Induction, Autologous Transplantation and Post-Transplant, Response-Adapted, Measurable Residual Disease (MRD)-Based Dara-Krd Consolidation in Patients with Newly Diagnosed Multiple Myeloma

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Welcome to *Managing Myeloma.* Today I will be reviewing the results of the study titled "Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone Induction, Autologous Stem Cell Transplant and Post-Transplant, Response-Adapted, Measurable Residual Disease-Based Dara-KRd Consolidation in Patients with Newly Diagnosed Multiple Myeloma." Daratumumab is a CD38 monoclonal antibody approved for myeloma in relapsed/refractory multiple myeloma as well as newly diagnosed settings. In this study daratumumab was combined with the most potent proteasome inhibitor, carfilzomib, lenalidomide, and dexamethasone with an intent to establish the safety of this combination and assess its activity among patients with newly diagnosed myeloma. In addition, we assessed the feasibility of using MRD by next generation sequencing. The clonoSEQ® method which measured sensitivity of 10^{-5} in the study to inform the use and duration of post-transplant Dara-KRd consolidation. The primary endpoint for the study was rate of MRD negative responses which are 10^{-5} utilizing next-generation sequencing in patients treated with Dara-KRd induction, autologous stem cell transplant and MRD-based response-adapted Dara-KRd consolidation. There were several secondary endpoints that were considered: toxicity of this combination, frequency of imaging plus MRD negative CR, impact of stem cell transplant and MRD. The correlation with the traditional IMWG responses and outcomes of observations without maintenance upon the confirmation of MRD negativity. To date, 81 patients have been enrolled at a median follow-up is 7.4 months. All patients have completed induction of greater than two cycles, 42 patients have completed post-transplant assessments, median age were 61 years. Patients were ranged anywhere between 38 years to 79 years, 20% of the patients had ISS stage III disease, 29% had high-risk chromosomal abnormalities of deletion 17p, translocation 4;14 or translocation 14;16. This includes gain of 1q as a high risk chromosomal abnormality, more than half of the patients had high-risk chromosomal abnormalities. The MRD was trackable by next-generation sequencing clonoSEQ® in 78 out of 81 patients that were enrolled in the study which is 96% of the patients, 100% of the patients had datapoints with trackable MRD; 40% of the patients post-induction had MRD negativity of less than 10^{-5} and post-transplant these responses have escalated to 73% of the patients achieving MRD negativity, and after MRD-directed consolidation 82% of patients had MRD negativity. No patients

discontinued therapy due to toxicity in the study. There were two deaths. One patient died from a metapneumovirus post-transplant and there was one unwitnessed sudden death 58 days after the stem cell transplant, but both of these were not considered to be related to the investigational agents. Most common grade 3 to 4 adverse events included neutropenia that was seen in one-third of the patients, around 35%, infection seen in 58% of the patients. Eighteen serious adverse events including pneumonia seen in five patients, fever and neutropenia seen in two patients, pulmonary embolism in one patient, atypical hemolytic uremic syndrome in one patient, atrial fibrillation in one patient, one of the most common ones. Twenty-six patients had received confirmed MRD negativity and entered the observational MRD surveillance, at a median follow-up observation of 4.9 months, no relapse or resurgence of MRD was noted. Dara-KRd is deemed to be a very safe regimen, much deeper and rapid responses were seen. MRD-negative responses were seen in newly-diagnosed multiple myeloma with this combination. The NGS, MRD-based response-adapted therapy was deemed to be feasible in at least 96% of patient in this study. What is still yet to be known are the long-term outcomes with this MRD-directed discontinuation of therapy in the surveillance period. The study is continuing to accrue and will reach 123 patients to further inform outcomes by the cytogenetic status.

Reference:

Costa L, Chhabra S, Godby K, et al. Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd) Induction, Autologous Transplantation and Post-Transplant, Response-Adapted, Measurable Residual Disease (MRD)-Based Dara-Krd Consolidation in Patients with Newly Diagnosed Multiple Myeloma (NDMM). *Blood.* 2019;134 (Supplement_1): 860. https://ashpublications.org/blood/article/134/Supplement_1/860/427102/Daratumumab-Carfilzomib-Lenalidomide-and?searchresult=1