Managing Myeloma

Efficacy and Safety of Carfilzomib at 56 mg/m^2 with Cyclophosphamide and Dexamethasone (K56Cd) in Newly Diagnosed Multiple Myeloma Patients Followed By ASCT or K56Cd Consolidation: Initial Results of the Phase 2 Cardamon Study

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Welcome to *Managing Myeloma*. Today I will be reviewing the results of the study titled "Efficacy and Safety of Carfilzomib at 56 mg/m^2 with Cyclophosphamide and Dexamethasone in Newly Diagnosed Multiple Myeloma Patients Followed by Stem Cell Transplant or K56 Cytoxan and Dexamethasone Consolidation: The Initial Results of the Phase 2 Cardamon Study." Most carfilzomib-based regimens in the newly-diagnosed setting have used bi-weekly dosing ranging anywhere between 27 mg/m^2 to 36 mg/m^2 in combination with immunomodulatory agents of thalidomide and lenalidomide as well as alkylating agents of cyclophosphamide. The ENDEAVOR trial is the first trial that compared carfilzomib at 56 mg/m^2 twice-weekly in the relapse setting in comparison to the other proteasome inhibitor bortezomib, and the dosing of carfilzomib was deemed to be extremely effective and promising in this study, leading to unprecedented rates of PFS benefits of greater than 18 months. The biweekly dosing of 56 mg/m^2 is relatively unexplored in the frontline setting, hence the rationale for investigating the higher doses of carfilzomib at 56 mg/m^2 in newly-diagnosed multiple myeloma. The study had primary endpoint of VGPR pre-randomization upon patients receiving carfilzomib, Cytoxan, and dexamethasone for four cycles of induction, and patients were then randomized to receive a single stem cell transplant or receiving carfilzomib (Kyprolis), Cytoxan, and dexamethasone for four cycles of consolidation. MRD was measured in both arms after the transplant and after the consolidation. The co-primary endpoint includes two-year PFS after patients received the stem cell transplant or K56 Cytoxan, dexamethasone consolidation in patients who received carfilzomib maintenance for a period of 18 cycles. A total of 281 patients were enrolled, of which 252 patients completed the induction and were enrolled accessible for response. One hundred patients were randomized to receive a single autologous stem cell transplant and 101 patients received KCD consolidation. One hundred and thirty-three patients went on to receive carfilzomib in the maintenance phase for a total of 18 cycles. The median age of the patients was 58 years, 91% had an ECOG performance status of 0 to 1. ISS stage I was seen in 45.2% of the patients and a quarter of the patients, 24.7%, had adverse risk cytogenetics. If you include 1q+/1p this number increases to 48.5%. Responses to induction were really phenomenal with this combination, rather than VGPR rates were seen in 59.2% of the patients. CR rates in 4.8%, stringent complete responses in 2.8%, VGPR response rates were seen in 51.6%

of the patients. Overall response rate of 87.6% was seen, 23.2% of the patients had MRD negativity by flow cytometry with a sensitivity level of 10^{-5}.

Reviewing the safety events, anemia was seen in 36.3% of the patients which was grade 1 to 2, and grade 3 anemia was seen in 10.1%. Lymphopenia was seen in a quarter of the patients, which is 25% of the patients, had a grade 3 event. Overall, the adverse events were very well tolerable from a hematological standpoint. From a non-hematological standpoint hypertension of grade 1 to 2 was seen in 20% of the patients and grade 3 was seen in 10% of the patients, which was commonly seen with all the carfilzomib-based regimens, at least any grade event of hypertension of close to 30%. Respiratory infections seen in 15% of the patients, acute kidney injury seen in close to 4% of the patients, and grade 3 events accounted for 3% of these. Ten patients progressed during or at the end of induction and 12 were withdrawn for toxicities. There were four deaths in the study during the induction, one from myocardial infarction, three from cardiac arrest associated with bronchopneumonia and sepsis. Twenty-five percent of the patients are currently reported to have received a dose modification during the induction.

In summary K56 Cytoxan and dexamethasone is an effective induction regimen in newly-diagnosed myeloma patients eligible for stem cell transplant. Overall response rates of close to 90%, VGPR rates of close to 60%, MRD negativity rates of close to 25% were seen with this combination post-induction therapy. Discontinuation rates were low, around 5%, and the safety of this combination was comparable to other frontline carfilzomib regimens. Thank you for reviewing this activity.

Reference:

Yong K, Popat R, Wilson W, et al. Efficacy and Safety of Carfilzomib at 56 mg/m^2 with Cyclophosphamide and Dexamethasone (K56Cd) in Newly Diagnosed Multiple Myeloma Patients Followed By ASCT or K56Cd Consolidation: Initial Results of the Phase 2 Cardamon Study. *Blood.* 2019;134 (Supplement_1): 861. https://ashpublications.org/blood/article/134/Supplement_1/861/427107/Efficacy-and-Safety-of-Carfilzomib-at-56mg-m-2?searchresult=1