Managing Myeloma

Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

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Welcome to *Managing Myeloma*. I am Dr. Shaji Kumar and I am live at the 60th ASH Conference in San Diego, California. Today, I will be reviewing the results of an oral presentation, looking at the results of a Phase II study of venetoclax and carfilzomib with dexamethasone in patients with relapsed/refractory myeloma.

Venetoclax is a small-molecule inhibitor of BCL-2 which is an antiapoptotic protein that is critical for survival of a variety of different tumor cells including myeloma cells. Initial studies using single-agent venetoclax had demonstrated an overall response rate of 21% in patients with relapse disease and a response rate of about 40% in patients carrying a translocation 11;14 abnormality. Subsequent studies have looked at the combination of venetoclax with dexamethasone showing that the response rate can be as high as 65% in patients who have the translocation 11;14. More importantly, pre-clinical studies with proteasome inhibitors like bortezomib and carfilzomib have demonstrated that the combination can be quite synergistic, thought to be as a result of the inhibition of the Mcl-1 by the proteasome inhibitor which when combined with the BCL-2 inhibition from venetoclax leads to significant synergy. So, venetoclax has been combined with bortezomib and dexamethasone in a Phase II trial that demonstrated a response rate of 70% to 90% in various subgroups of patients with and without translocation 11;14. Based on this, there is an ongoing Phase III trial of bortezomib and dexamethasone with or without venetoclax in patients with relapsed myeloma. The results of which are awaited currently.

Given the significant activity of carfilzomib, a second-generation proteasome inhibitor, a Phase II trial was designed to look at the efficacy of carfilzomib combined with venetoclax and dexamethasone. The current study is a Phase I/II trial which initially looked at the best tolerated dose of venetoclax that can be combined with carfilzomib and dexamethasone, and an expansion phase that is designed to look at the efficacy of this combination. The Phase I trial was completed and the dose that was thought to be the best was 70 mg/m^2 of carfilzomib given once-weekly along the lines of what has been seen with weekly dosing of carfilzomib in combination with venetoclax and dexamethasone. The best tolerated dose was the 70 mg given with 800 mg of venetoclax and dexamethasone. The venetoclax is given on a daily basis, the dexamethasone is given on a weekly basis, and the carfilzomib is 70 mg/m^2 weekly dosing. In the dose-expansion phase, the response rates were about 70% across all the different subgroups of patients. When you look at the subgroup of patients that had a translocation 11;14, over 90% of these patients actually had an overall response rate and most importantly, nearly two-thirds of these patients had a complete response or a very good partial response. So clearly, the combination appears to be quite effective in patients with relapse disease. The tolerability of the regimen was excellent. The toxicity was along the lines of what would have been anticipated for the carfilzomib and also what we saw with single-agent venetoclax in the

previous studies and is primarily hematological toxicity. There was some hypertension that was noticed in approximately 10% of patients which is likely related to the carfilzomib.

Overall, the triplet regimen of carfilzomib, venetoclax, and dexamethasone appears to be promising with good efficacy and manageable toxicity in patients with relapse disease. Ongoing studies are looking at specific biomarkers within this subgroup of patients to see who benefits the most.

Reference

Costa L, Stadtmauer E, Morgan G, et al. Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma. ASH 2018. Abstract 302.