Managing Myeloma

Maintenance Therapy with the Oral Proteasome Inhibitor (PI) Ixazomib Significantly Prolongs Progression-Free Survival (PFS) Following Autologous Stem Cell Transplantation (ASCT) in Patients with Newly Diagnosed Multiple Myeloma (NDMM): Phase 3 Tourmaline-MM3 Trial

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Today, I will be reviewing the data of the phase III TOURMALINE-MM3 trial maintenance therapy with the oral proteasome inhibitor ixazomib in patients with newly diagnosed multiple myeloma who have received high-dose therapy.

Maintenance therapy has been extensively used as a strategy for prolonging the duration of disease control and potentially survival following high-dose therapy. To date, only lenalidomide has been approved for this indication. However, we know that approximately 30% of patients receiving lenalidomide maintenance after high-dose therapy, they cannot tolerate this drug and they have to discontinue because of side effects. Furthermore, we know that proteasome inhibitors are a backbone of multiple myeloma treatment and bortezomib-based maintenance has shown promising activity after high-dose therapy, although formal studies have not been performed so far. There is a need for an oral proteasome inhibitor maintenance therapy that can be administered for a prolonged period of time to improve the depths of response without cumulative or late-onset toxicity, and with improvement of the convenience of the patient.

In the TOURMALINE 3 trial, patients were eligible if they had newly diagnosed multiple myeloma, they were candidates for high-dose therapy. They received the induction therapy with a proteasome inhibitor and/or an immunomodulatory agent. They have responded to high-dose melphalan at a dose of 200 mg/m^2. At that time, they were randomized on a 3:2 ratio to receive ixazomib or matched placebo on days 1, 8, and 15 of a 28-day cycle for up to two years or until there was evidence of progressive disease or unacceptable toxicity. Randomization was stratified by induction regimen, baseline ISS stage, and response after high-dose therapy. The primary endpoint was PFS but the key secondary endpoint is overall survival.

The main findings of the study indicate that both regimens were very well tolerated. It is important to note that discontinuation due to adverse event was low, 7% for ixazomib versus 5% for placebo. Side effects were mild and essentially equally distributed between ixazomib and placebo. With ixazomib there was higher incidence of gastrointestinal toxicity, nausea, vomiting, diarrhea, and arthralgias. It is important to note that there was no signal for secondary primary malignancies and incidence was low, 3% in both arms. Furthermore, global quality of life's course on ixazomib was similar to placebo. The main finding of the study is a significant improvement of the progression-free survival with the hazard ratio of 0.72 and a *P*-value of 0.002. The median PFS with ixazomib was 26.5 months and with placebo was 21.3 months.

Thus, the study demonstrated a 39% improvement in PFS with ixazomib maintenance with deepening of responses and increased conversions of MRD negativity over control. Furthermore, there was a very favorable safety profile including no risk for second primary

malignancies, low rates of peripheral neuropathy, and this data supported ixazomib as a valuable option for maintenance therapy after high-dose melphalan in patients with myeloma.

Reference

Dimopoulos M, Gay F, Schkesvold F, et al. Maintenance Therapy with the Oral Proteasome Inhibitor (PI) Ixazomib Significantly Prolongs Progression-Free Survival (PFS) Following Autologous Stem Cell Transplantation (ASCT) in Patients with Newly Diagnosed Multiple Myeloma (NDMM): Phase 3 Tourmaline-MM3 Trial. ASH 2018. Abstract 301.