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Meeting abstract

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Recent progress in the treatment of multiple myeloma: updates and highlights from ASH 2008

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The treatment of multiple myeloma has rapidly evolved over the past 8 years. During this period we have seen the introduction of two immunomodulatory drugs and a proteasome inhibitor for the treatment of myeloma. Each of these drugs has shown to be effective as single agent as well as in combinations in relapsed and/or refractory myeloma. And the optimum use of these drugs upfront, both for transplant eligible as well as transplant ineligible patients has been the focus of intense clinical investigations as reported by the investigators from US as well as Europe in the last ASH meeting.

A series of large randomized trials have established the addition of a novel agent, either thalidomide or bortezomib, to melphalan and prednisone as the standard of care for transplant ineligible patients. With longer follow-up for a median of 25.9 months VISTA trial showed continued survival benefit for patients randomized to receive upfront bortezomib; three year OS was 72% for VMP compared to 59% for MP. VMP improved outcome in all patients, whether under or over age 75 years, with or without modest renal impairment, as well a patient with adverse prognostic features by cytogenetics or fish. These improvements in outcome came with no difference in hematologic toxicity or HZV infection, but higher incidence of peripheral sensory neuropathy (grade ≥ 3 13%) from bortezomib.

Addition of thalidomide to MP had been shown to improve the progression-free and OS among transplant ineligible patients. However, recent updates of 3 different studies, Italian study (GIMEMA), the Dutch study (HOVON 49) and the Scandinavian study showed improvement in progression-free survival but not OS. This may be related to differences in the dose intensity and tolerability of the treatment, lack of efficacy of thalidomide in high-risk cytogenetic group and availability of other novel agent to rescue upon relapse.

The addition of thalidomide to VMP regimen (VMPT) was compared to VMP in a large randomized trial. In the preliminary analysis after a short follow-up showed no improvement in the PFS or OS but notable increase in toxicity for the four drug combination. The same study showed that weekly administration of bortezomib was well tolerated with much lower incidence of grade ≥ 3 peripheral neuropathy of 2% without significant loss of efficacy.

Earlier reports on ECOG trial E4A03 comparing lenalidomide with low-dose or high-dose dexamethasone highly favored low-dose dexamethasone arm for EFS and OS. However, with longer follow-up (median 36 months) the updated results of the trial showed identical 3-year survival outcome of 75%; but progression-free survival favored low-dose dexamethasone arm. When land mark analysis is performed at the end of four cycles, 3-year survival of patients who proceeded to transplant immediately (N = 90) was 92%; while those who stayed on the primary therapy whether high-dose or low-dose dexamethasone, their 3-year survival was 79%. Thus, lenalidomide and dexamethasone is highly active in newly

diagnosed myeloma patients both as an induction therapy pre-transplant for newly diagnosed myeloma as well as primary therapy for patients ineligible for stem cell transplantation.

Lenalidomide was unable to overcome the adverse prognostic features identified by cytogenetics, FISH or labeling index as noted by a single institutional study of 100 patients with lenalidomide and weekly dexamethasone.

Two large randomized trials have shown bortezomib based induction therapies pretransplant improve the response rate before and after stem cell transplantation and with short follow-up there is improved progression-free survival at 2 years. The first trial was performed by the French investigators (IFM) which compared four cycles of bortezomib and dexamethasone against four cycles of VAD chemotherapy. At the end of induction therapy 39% were in >VGPR after bortezomib-dexamethasone compared to 16% after VAD ($p < 0.0001$). With a median follow-up of 28 months the progression-free survival was superior for the bortezomib and dexamethasone arm with 2 year PFS of 69% vs. 60% for the VAD arm (p0.011).

The second trial was reported by the Italian group which compared 3 cycles of thalidomide and dexamethasone (TD) to the same regimen with added bortezomib (VTD). Again, the addition of bortezomib to thalidomide and dexamethasone significantly improved the response rates pretransplant; VGPR or better was 62% for VTD compared to 29% for TD. With a short median follow-up time of 15 months the projected two-year PFS was 90% for VTD arm compared to 80% for TD arm ($p = 0.009$). Other studies have shown replacing the vincristine in the VAD regimen with either thalidomide (TAD) or bortezomib (PAD) also improves the response rate and progression-free survival after transplantation.

In conclusion, advent of novel agents has substantially improved the outcome of patients with newly diagnosed myeloma. MP plus thalidomide or bortezomib should be the choice of therapy for transplant ineligible patients. Brief induction with bortezomib containing regimen is the treatment of choice for transplant eligible patients. Lenalidomide and low-dose dexamethasone is an excellent treatment option for both transplant eligible as well as ineligible patients. Bortezomib has been shown clearly to improve the outcome of patients with high-risk genetic features.