MultipleMyelomaHub

Patients eligible for transplant

EBMT 2018 | Pre-transplant Induction in MM

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The MM Hub attended the 44th Annual Meeting of the European Society for Blood and Marrow Transplantation held in Lisbon, Portugal, from 18–21 March 2018. On Sunday 18 March 2018 an Intergroupe Francophone du Myélome (IFM) non-profit symposium was held entitled: *Multiple myeloma in 2018: the IFM global perspective*. It was acknowledged that a global perspective on Multiple Myeloma (MM) now needs to be taken, as treatment regimens are relevant to physicians in all countries, and that many initiatives are now established on a global basis.

The session was moderated by Mohamad Mohty, from the Hospital Saint-Antoine and University Pierre & Marie Curie, Paris, France and Jean Luc Harousseau, from the University of Nantes, France. The first talk was presented by Joan Bladé, from the Amyloidosis and Myeloma Unit, from the Hospital Clínic of Barcelona, Spain, on the topic of *Pre-transplant Induction in Multiple Myeloma*.

Professor Bladé introduced his talk by explaining that induction regimens require high anti-myeloma activity and low toxicity. In the past, chemotherapy regimens included vincristin, adriamycin, dexamethasone (VAD); cyclophosphamide and dexamethasone (CyDex); Vincristine, carmustine, melphalan, cyclophosphamide, prednisone (VBMCP) or vincristine, carmustine, doxorubicin and high-dose dexamethasone (VBAD). Other regimens combined dexamethasone with either thalidomide (thal) or bortezomib (bor). With these regimens, 10% of patients achieved a complete response (CR) pre-autologous stem cell transplantation (ASCT), while 25-35% achieved a CR post-ASCT and around 5-10% of patients displayed a continuous CR for more than 10 years post-transplant.

Currently, the treatments approved for transplant-eligible patients include induction with a three-drug regimen, containing one of the following combos: bortezomib, thalidomide, and dexamethasone (VTD); bortezomib, cyclophosphamide, and dexamethasone (VCD); lenalidomide, bortezomib, and dexamethasone (RVD), and bortezomib, doxorubicin, and dexamethasone (PAD), followed by melphalan at 200mg/m^2, ASCT and lenalidomide maintenance.

A recent pooled meta-analysis, with data derived from three randomized trials, showed that significant improvements in overall survival (OS) and progression-free survival (PFS) could be achieved with the use of bortezomib-based regimens, specifically PFS of 36 *vs* 26.8 months (p<0.001) and OS (3-yr) benefit of 79.7% *vs* 74.7% (p = 0.04) Additionally, the IFM2013-04 trial (NCT01971658), led by Philippe Moreau, showed that four cycles with VTD was superior to four cycles with VCD, with 13% of patients achieving CR, 66.3% of the patients achieving a very good partial response (VGPR), and only 92.3% with partial response to induction.

In the Pethema/GEM phase III study, the efficacy of bortezomib, lenalidomide, and dexamethasone (VRd) was assessed as a pre-transplant induction regimen, with the administration of 35 mg of lenalidomide on a daily basis for 21 days in 455 newly diagnosed multiple myeloma (NDMM) patients. A CR was achieved in 38% and a VGPR in 29% of patients, with 35% of these patients negative for minimal residual disease (MRD), as assessed by New Generation Flow (NGF). The overall response rate (ORR) was 85%. This was accompanied by only minor toxicity for peripheral neuropathy, neutropenia and thrombocytopenia.

In a time to response analysis of the GEM05 phase III trial, an increase in response over time in parallel with an increase in the number of cycles, was observed. Similarly, the IFM2013-04 trial showed a clear increase in the number of patients achieving CR with different cycles over time. For example, 16% of patients had a CR after three cycles while 35% of the patients had a CR after six cycles. Additionally, Professor Bladé emphasized the importance of the GEM12menos65 trial, which assessed the MRD status of NDMM patients after each stage of treatment: induction, transplant, and consolidation. An increase in MRD negativity was observed after each treatment, which translated into a significant improvement in PFS.

Professor Bladé then touched on the concept of consolidation, which he defined as full drug dosing for short periods, usually 2-4 cycles after transplant, which he believes is optimal. He mentioned that such consolidation regimens are very promising in reducing tumor burden and believes this will become part of standard therapy in the future.

Finally, he also gave some insights into the use of novel therapies to improve induction regimens, which will include triplet regimens with proteasome inhibitors (PIs) such as carfilzomib and ixazomib, with lenalidomide and dexamethasone (KRd), as well as adding daratumumab on top of VTD, VRD. Future studies will inevitably be designed to assess the impact of such combos on OS and MRD.

References

1. Bladé J. *et al*. Pre-transplant Induction in Multiple Myeloma. 44th Annual Meeting of the European Society for Blood and Marrow Transplantation. IFM Symposium March 2018, #IST-1.