

Highlights from the 2007 Annual Meeting of the American Society of Hematology

In Focus: Phase III Trials in Multiple Myeloma

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H&O What were the most important findings in the phase III trials reported at the 2007 annual meeting of the American Society Hematology?

MC Several interesting phase III studies performed in both young and elderly patients with newly diagnosed multiple myeloma were presented at the 2007 annual meeting of the American Society of Hematology (ASH). In my opinion, two presentations in the setting of young patients were promising, one reported by the French Intergroupe Francophone du Myélome (IFM) and another by the Italian GIMEMA (Gruppo Italiano per lo studio delle Malattie EMatologiche dell'Adulto) Myeloma Network. In both studies, it was shown that the use of regimens including bortezomib (Velcade, Millennium) in preparation for autologous stem cell transplantation (ASCT) significantly improved the complete remission (CR) rate in comparison to either conventional chemotherapeutic regimens, such as vincristine, doxorubicin, and dexamethasone (VAD), or novel regimens, such as thalidomide (Thalomid, Celgene) plus dexamethasone. In particular, following 3–4 courses of bortezomib-containing regimens (bortezomib-dexamethasone in the French study and bortezomib-thalidomide-dexamethasone in the Italian study), the rate of CR increased up to the values previously reported with use of single or double ASCT. In the French study, the rate of CR after primary induction therapy was approximately

21%, and the corresponding value in the Italian study averaged 36%. The second most important finding was that the increased rate of CR effected by novel agents (eg, bortezomib) in preparation for ASCT translated into a significantly increased probability of CR following the first ASCT. In both studies, the rate of CR or of at least very good partial response (VGPR) was in the range of 62–77%. Moreover, in the French study, most of the patients who achieved at least a VGPR did not require a second ASCT. In my opinion, these presentations were important because they demonstrated that by incorporating novel agents, such as bortezomib, in the primary induction regimen, it is possible to maximize the speed and degree of tumor reduction, both before and after ASCT.

There was a third important study, presented by the Eastern Cooperative Oncology Group, aimed at comparing lenalidomide (Revlimid, Celgene) plus either high-dose or low-dose dexamethasone (RD vs Rd, respectively) for a total of four 28-day courses. The overall response rate, including the probability of at least VGPR, within four cycles was significantly higher in the RD arm (82% and 44%, respectively) as compared to Rd (70% and 26%, respectively). Nevertheless, overall survival at 1 and 2 years was significantly lower for patients randomized to RD (88% and 75%, respectively) in comparison with the Rd group (96% and 87%, respectively) due to a higher frequency of deaths (41/222 vs 23/219, respectively) because of disease progression or toxicities, such as thromboembolic events, infections, and cardiac complications. In my opinion, several issues raised by this study deserve further comments. Specifically, a subgroup analysis failed to show a survival advantage in favor of Rd among patients less than 65 years of age. These patients might reasonably receive RD, eventually reducing the total dose of dexamethasone on odd cycles, as preparation for subsequent ASCT. In addition, the disappointingly low CR rate at 4 months (2% with RD and 1% with Rd) may have been underestimated due to the lack of bone marrow biopsies to confirm CR. Finally, it is difficult to explain why, in comparison to Rd, in RD arm of the study (which yielded a higher response rate) the frequency of deaths due to disease progression was higher.

H&O What toxicities were seen in the IFM and GIMEMA studies?

MC Both the IFM and the GIMEMA studies showed that, in younger patients, the use of bortezomib as part of an induction regimen given for a limited period of time

was associated with an acceptable toxicity profile. In these studies, the frequency of grade 3–4 peripheral neuropathy was approximately 6–7% and the rate of discontinuation due to any adverse event was in the range of 3–7%. In the Italian study, more than 90% of patients received all planned administrations of bortezomib, and, more importantly, no patient experienced disease progression during induction therapy. Moreover, there were no early deaths during primary induction therapy with bortezomib-thalidomide-dexamethasone.

There are several other important findings related to toxicity that need to be emphasized. In both studies, it was shown that the frequency of thromboembolic complications was low, even when bortezomib was combined with thalidomide (3% vs 6.5% in the arm that did not contain bortezomib in the Italian study). Another important finding was that the use of bortezomib as primary therapy did not adversely affect subsequent peripheral blood stem-cell collection. Indeed, in both studies it was possible to collect sufficient amounts of stem cells to support two sequential courses of high-dose therapy in the majority of patients.

H&O What were the important findings in patients with myeloma over 65 years of age?

MC With respect to elderly patients, the most important presentation included the results of an interim analysis of the VISTA trial. This trial was a large, multicenter international phase III study aimed at comparing standard melphalan and prednisone (MP) with MP plus bortezomib (MPV) for the treatment of elderly patients with myeloma. Results of an interim analysis performed in September 2007 showed a clear superiority of the bortezomib-containing regimen over MP alone with respect to all efficacy endpoints, including time to progression, response rate, CR rate, event-free survival, overall survival, and time to next therapy. Based on a 52% reduction in risk of progression and a 39% improvement in overall survival with MPV, along with a CR rate of 35%, an independent committee analyzing the data recommended early closure of the study to allow patients in the MP arm to receive MPV. As a result of these findings, the MPV regimen for the treatment of elderly myeloma patients is currently under review for approval by the US Food and Drug Administration.

At the 2007 ASH annual meeting, a presentation by the IFM demonstrated that even among myeloma patients over 75 years of age, there was a clear advantage of MP plus thalidomide (MPT) over MP in terms of rates of response, event-free survival, and overall survival. At present, MPT is considered the standard of care for elderly patients with myeloma. Within the coming months, MPV will likely

become another reference therapy for elderly patients or those who are not candidates for ASCT.

H&O Where will future research go as a result of the findings you have discussed?

MC I believe future research will address several issues. One of these concerns the identification of the optimal induction regimen offering the highest CR rate at the price of the lowest toxicity. An example of ongoing research in this field is a phase I/II study that showed promising results by combining bortezomib with lenalidomide and dexamethasone. Another possibility is to add an alkylating agent, such as cyclophosphamide, to the regimen including bortezomib, thalidomide, and dexamethasone in preparation for ASCT. Great efforts are being made to try to maximize the rate of CR before transplantation because it has been shown that achievement of this objective translates into an even higher probability of CR posttransplantation. Another area of research will be to investigate whether novel agents can replace ASCT for the treatment of younger myeloma patients. In my opinion, ASCT will continue to play a major role because applying high-dose therapy with stem-cell support after an induction regimen based on the use of novel agents allows clinicians nearly to double the rate of CR in comparison to that obtained with novel agents alone. As CR is a surrogate marker of prolonged survival, it is likely that incorporation of novel agents into ASCT will further extend the duration of survival, both progression-free and overall. Nevertheless, I believe that several groups will try in the near future to compare upfront ASCT following induction therapy with novel agents to transplantation applied at the time of relapse after the use of novel agents alone. Another issue currently under investigation is the role of novel agents as consolidation of remission or as maintenance therapy, with the goal of further increasing the rate and durability of response. It is possible that a proportion of patients with suboptimal response even after ASCT can upgrade their response status and achieve a CR, even at the molecular level, after receiving consolidation therapy. Another possibility is to prolong the duration of remission by administering bortezomib or lenalidomide as maintenance therapy, although at this time it is undefined whether these agents may play a role in all patients or only in those who failed CR/VGPR. In summary, I believe optimizing response by modifying the combinations and sequence of novel agents will be the focus of future research. In addition, the question of whether ASCT can be delayed until relapse occurs following induction therapy with novel agents without lessening overall outcomes will soon be investigated.

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Suggested Readings

Cavo M, Patriarca F, Tacchetti P, et al. Bortezomib (Velcade)-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (TD) in preparation for autologous stem-cell (SC) transplantation (ASCT) in newly diagnosed multiple myeloma (MM). *Blood*. 2007;110(11 pt 1): Abstract 73.

Hulin C, Facon T, Rodon P, et al. Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients 75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01/01. *Blood*. 2007;110(11 pt 1): Abstract 75.

Rajkumar SV. Controversies regarding the use of dexamethasone in patients with multiple myeloma. *Clin Adv Hematol Oncol*. 2008;6:103-104, 141.

Rajkumar SV, Jacobus S, Callander N, et al. A randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *Blood*. 2007;110(11 pt 1): Abstract 74.

San Miguel JF, Schlag R, Khuageva N, et al. MMY-3002: A phase 3 study comparing bortezomib-melphalan-prednisone (VMP) with melphalan-prednisone (MP) in newly diagnosed multiple myeloma. *Blood*. 2007;110(11 pt 1): Abstract 76.

Waage A, Gimsing P, Juliusson G, Turesson I, Fayers P. Melphalan-prednisone-thalidomide to newly diagnosed patients with multiple myeloma: a placebo controlled randomised phase 3 trial. *Blood*. 2007;110(11 pt 1): Abstract 78.

Zonder JA, Crowley J, Hussein MA, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): results of the randomized, double-blinded, placebo-controlled SWOG trial S0232. *Blood*. 2007;110(11 pt 1): Abstract 77.