ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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First-line Treatment of Elderly Multiple Myeloma Patients

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H&O What is the standard of care for induction therapy in newly diagnosed myeloma patients older than 65 who are not eligible for autologous transplant?

AP In Europe, the standard of care for these patients is a combination of melphalan, prednisone, and thalidomide (Thalomid, Celgene) or a combination of melphalan, prednisone, and bortezomib (Velcade, Millennium). In the United States, there is a broader use of other agents in combination, including bortezomib, dexamethasone, and lenalidomide (Revlimid, Celgene).

H&O What was the trial design for the study examining bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) for initial treatment of elderly multiple myeloma patients?

AP This phase III trial examined the 4-drug combination of VMPT followed by maintenance with VT. This intensive treatment was compared with the standard bortezomib, melphalan, and prednisone regimen as was presented in the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone) trial. The patients, who were ages 65 years or older, were randomized to receive VMPT followed by VT (n=254) or VMP without maintenance (n=257). The primary endpoint was progression-free survival. Initially, the VMPT regimen consisted of induction with nine 6-week cycles (bortezomib: 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32 in cycles 1–4 and on days 1, 8, 22, and 29 in cycles 5–9; melphalan: 9 mg/m^2 on days 1–4; prednisone: 60 mg/m^2 on days 1–4; and thalidomide: 50 mg on days 1–42) followed by maintenance (bortezomib: 1.3 mg/m^2 every 15 days and thalidomide: 50 mg/day). The patients in the VMP without maintenance group received bortezomib, melphalan, and prednisone at the same doses and schedules as those in the VMPT group. In March 2007, the schedule was changed so that all patients in both groups received bortezomib infusion once weekly.

H&O What were the study results?

AP We found that the addition of thalidomide in the induction regimen and the use of maintenance with bortezomib and thalidomide significantly improved progression-free survival in comparison not with the melphalan and prednisone combination alone, but with the combination of VMP, which is considered at present the standard of care. The VMPT group had superior response rates as compared with the VMP without maintenance group, in terms of patients who achieved a partial response or better (89% vs 81%; *P*=.01), a very good partial response or better (59% vs 50%; *P*=.03), and a complete response (38% vs 24%; *P*=.0008). The response to induction was not increased in the VMPT group. After a median follow-up of 22 months, the 3-year progression-free survival was 60% in the VMPT group and 42% in the VMP group (*P*=.007). Overall survival at 3 years was 89% in both groups. Chromosomal abnormalities did not affect progression-free survival in either group.

H&O What did you conclude from the study?

AP The message from this study is that a 4-drug combination may increase the response rate, while maintenance with bortezomib and thalidomide seems to increase progression-free survival.

H&O What toxicities were observed in the study?

AP Patients in the VMPT group experienced a higher incidence of grade 3/4 neutropenia (38% vs 28%; *P*=.02) and cardiac complications (10% vs 5%; *P*=.04). The incidence of grade 3/4 peripheral neuropathy was 8% in VMPT and 5% in VMP (*P*=.19).

An important result of this study involves the use of a weekly infusion of bortezomib instead of a twice-weekly infusion, from a 1-4-8-11 infusion schedule to a 1-8-15-22 infusion schedule. The weekly infusion of bortezomib significantly reduced the rate of peripheral neuropathy from 15% to 3–4%, without affecting efficacy. Basically, peripheral neuropathy can no longer be considered a problem with bortezomib if a weekly infusion schedule is used. We found that the cumulative dose of bortezomib was identical in patients receiving the twice-weekly infusions versus patients receiving the once-weekly infusion. In the patients who received the once-weekly infusion, the discontinuation rate was much lower, so these patients had a prolonged period of treatment. The cumulative treatment was identical in both patient groups.

H&O Do you believe that the results of this study have the potential to change clinical practice?

AP The VMPT combination is the only one showing superior results in comparison to the 3-drug combinations including novel agents. The results should change the clinical practice from this point of view. What has already been clearly changed in terms of standard of care and clinical practice is that a majority of physicians are already currently moving from a twice-weekly infusion of bortezomib to a once-weekly infusion of bortezomib.

H&O Could you describe the future directions of myeloma therapy?

AP One direction is the development of maintenance treatment, which can improve progression-free survival. Bortezomib could represent an alternative to lenalidomide, especially if a subcutaneous injection becomes available. Another approach is a more intense induction regimen, which is certain to increase the rate of patients who achieve a complete response. For example, in this study, the 4-drug combination doubled the rate of complete response from 20% to 40%. This approach might further increase the opportunity to achieve a prolonged remission duration and even increase the cure rate in these patients.

Suggested Readings

Boccadoro M, Bringhen S, Gaidano G, et al. Bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) for initial treatment of elderly multiple myeloma patients. *J Clin Oncol*. 2010;28. Abstract 8013.

Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol*. 2010;28:2259-2266.