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Combination Melphalan/Prednisone Plus Thalidomide Outperforms Standard Treatment for Elderly Patients with Multiple Myeloma

Findings from the French Francophone Myeloma Intergroup (IFM) 99-06 trial clearly establish the superiority of melphalan/prednisone in combination with thalidomide (MPT) over other regimens for elderly patients with newly diagnosed multiple myeloma who are not candidates for high-dose therapy ([Abstract 1](#)). The regimen not only produced better overall survival and progression-free survival in patients than the old standard of melphalan/prednisone (MP), but it also outperformed high-dose therapy in combination with autologous stem cell transplantation (ASCT).

"The MPT combination could be the reference treatment at the present time for patients with newly diagnosed myeloma ineligible for high-dose therapy," said Thierry Facon, MD, of the Hospital Claude Huriez, Lille, France, who presented the results of the trial on behalf of IFM at the Sunday Plenary Session. The researchers designed the trial to determine whether other treatment regimens could improve the median 3-year overall survival achieved with MP in elderly patients with multiple myeloma, a population typically not eligible for ASCT. "We were also interested in exploring a transplant procedure that was adapted to elderly patients: melphalan 100 mg/m² supported by peripheral blood stem cells, instead of melphalan 200 mg/m² used in younger patients," Dr. Facon said. A total of 447 patients aged 65 to 75 with newly diagnosed multiple myeloma were randomly selected 3:2:2 to receive 12 courses of standard MP every 6 weeks, MP plus the maximum tolerated dose of thalidomide not exceeding 400 mg/day, or high-dose therapy. High-dose therapy consisted of two courses of dexamethasone, vincristine, and doxorubicin, followed by cyclophosphamide treatment during stem cell harvest, and then high-dose melphalan (100 mg/m²) prior to double ASCT (MEL100). Enrollment into the trial was stopped after the third interim analysis in August 2005 when the superiority of the MPT regimen emerged. The primary endpoint of the study was overall survival; progression-free survival and the response to treatment were secondary endpoints.

After a median follow-up of 37 months, patients on MPT achieved a median overall survival time of 53.6 months compared with only 32.2 months for MP patients and 38.6 months for MEL100 patients (Fig. 1). This translated to a significantly greater risk of death with MP compared with MPT (hazard ratio [HR] = 1.8; p = 0.001) and a greater risk of death with MEL100 compared with MPT (HR = 1.7, p = 0.004). MPT patients also demonstrated longer median progression-free survival compared with the other treatment arms: 27.6 months compared with 17.1 months for those receiving MP and 19.4 months for those receiving MEL100.

Patients in the MPT and MEL100 arms responded similarly to treatment, which was significantly better than the response among MP patients. After 12 months of therapy, 16% of MPT patients and 17% of MEL100 patients achieved a complete response compared with only 2% of MP patients ($p < 0.0001$). Likewise, 50% of MPT patients and 43% of MEL100 patients attained at least a 90% response to treatment compared with only 8% of MP patients ($p < 0.0001$).

Dr. Facon noted that the toxicity of the MPT regimen was acceptable but higher than that observed with MP. Significantly more patients on MPT experienced grade 3 or higher neutropenia, thrombosis, peripheral neuropathy, constipation, and other nonhematologic effects. As a consequence, he suggested that efforts be made to reduce thrombosis with either heparin or aspirin prophylaxis; neuropathy could be reduced with lower doses of thalidomide and/or a shorter treatment duration.

Although the MPT results prove promising, Dr. Facon said, "In the near future, the MPT combination will be challenged by other combinations of MP with new drugs, especially the MP/bortezomib and the MP/lenalidomide combinations. The different combinations will have to be carefully compared in terms of efficacy and toxicity."

Expanding on this latter point, discussant Kenneth Anderson, MD, of the Dana-Farber Cancer Institute, highlighted other novel treatment combinations that are revolutionizing outcomes in affected patients, such as MP/bortezomib and lenalidomide/dexamethasone. "Just as with thalidomide and with bortezomib, and now with lenalidomide, the simple addition of novel drugs to conventional therapies is making a major difference," Dr. Anderson said. "The important conclusions in my view of this wonderful study by Thierry Facon and colleagues from the IFM are... that melphalan/prednisone/thalidomide is now a standard comparator option for all future trials of novel therapies in elderly patients with newly diagnosed myeloma, and that the integration of novel agents – whether it be thalidomide, bortezomib, lenalidomide, and several others coming – with conventional therapy is active and ongoing in disease (myeloma) and is already showing promise at improving efficacy while at the same time decreasing toxicity."

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