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New approaches to front-line therapy in multiple myeloma patients aged over 60 years

High dose therapy followed by autologous stem cell support (ASCT) represents the standard of care for younger myeloma patients. However, half of MM patients are >70 years at diagnosis and other have comorbidities which preclude ASCT. For more than 30 years Melphalan-Prednisone (MP) has been the standard treatment for elderly MM patients, although the response rate (RR) is only 40–50% and complete responses (CR) are rare. Median duration of response to MP is 1.5 years and median O.S is 2–3 years. Therefore, there is an urgent need for new more active therapies for elderly MM patients. Palumbo *et al.*¹ initially conducted a pilot study to assess the efficacy and tolerability of the combination of MP plus Thalidomide (MPT) in 49 patients. The RR was 73% and 18% achieved CR, 6% near CR (nCR) and 49% a partial response (PR). In a subsequent randomized study of six 4-week cycles of MPT vs MP;² using thalidomide at 100 mg/day continuously, they have confirmed a significant benefit for MPT compared with MP: response rate of 76% (16% CR, 12% nCR) vs 47% (2% CR) and this is associated with longer EFS (29 vs 13.6 months) and OS (80% vs 64% at 3 years). The IMF group³ has compared MPT (thalidomide up to 400 mg) vs MP vs double autologous transplant with Melphalan 100 mg in patients between 65 and 75 years old. Again MPT arm was superior to the two other arms: response rate: 81% (15% CR) vs 40% (2%) vs 72% (17% CR); PFS (29,7 vs 17 vs 19 months) and OS (NR vs 30 vs 38,6 months). In both studies the most relevant toxicity was DVT (12% and 9% in the French and Italian study respectively), together with peripheral neuropathy and haematological toxicity. Ludwig *et al.*⁴ have compared Thalidomide/Dexamethasone versus MP in 168 patients with a median age of 72 years. Thalidomide was given at 200 mg/day up to 400 mg/day and Dex at 40 mg two pulses on even cycles and one on odd cycles. The RR is 43% (5% CR) vs 38% (3% CR) with a median PFS in both arms of 17.6 months. Thromboembolic events and neuropathy were the most rel-

evant side effects. At the last ASH meeting, the Italian group (Palumbo *et al.*, *abstr.785 in Blood 2005;106*) reported on another pilot study based on the combination of escalating doses of Lenalidomide (5–10 mg/day ×21 days) and MP. The RR was 70% with 10% CR and the most important toxicity was neutropenia (grade 4 in 20%). The feasibility and efficacy of combining Bortezomib with MP has been explored by the Spanish group.⁵ Sixty patients with a median age of 75 years have been recruited at a final dose of Bortezomib of 1.3 mg/m². The RR was 86% with 32% CR plus 11% nCR. Interestingly, half of CR patients achieved immunophenotypic remission, and responses were independent of the presence of cytogenetic abnormalities (13q deletions or IgH translocations). The principal toxicities were peripheral neuropathy, gastrointestinal and haematological and were more evident during early cycles and in patients aged >75 years.

On the basis of these promising results, a new standard of care has emerged for elderly myeloma patients. Interestingly, the old MP remains as part of the backbone of these new regimens, in which the addition of the novel drugs (either IMiD's or proteasome inhibitors) results in a significant synergistic effect.

References

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