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Balancing act for elderly myeloma

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In this issue of *Blood*, Waage and colleagues present a phase 3 study comparing the combination melphalan-prednisone-thalidomide (MPT) with melphalan-prednisone plus placebo (MP) for the treatment of elderly patients with multiple myeloma. Though responses were in favor of MPT, they did not translate in prolonged progression-free or overall survival.

In the past few years, the so-called novel agents including thalidomide, the proteasome inhibitor bortezomib, and lenalidomide have been introduced in the treatment of multiple myeloma. Thalidomide has shown antiangiogenesis immunomodulatory and anti-inflammatory properties, and was first introduced 12 years ago for the treatment of multiple myeloma.[1,2] The use of novel agents has increased the treatment options for myeloma patients, with significant clinical benefits. Waage and colleagues present a trial, conducted by the Nordic group, on 363 elderly patients who were randomly assigned to be treated with the MPT combination or MP.[3] This study reported a significantly higher response rate with MPT: at least a very good partial response was achieved in 23% of patients assigned to MPT, while the corresponding figure for MP was only 7%. Unfortunately, such improvement did not translate into prolonged median progression-free survival (15 months with MPT and 14 months with MP; $P = .16$) or enhanced median overall survival (29 months vs 32 months; $P = .16$).

These findings should be compared with similar studies: a randomized study conducted in Italy compared MPT with MP in patients aged 60 to 85 years. Median progression-free survival with MPT was significantly longer than with MP ($P < .001$), whereas median overall survival did not considerably differ between the 2 groups, and was 45.0 months with MPT and 47.6 months with MP ($P < .79$).[4,5] A French study on patients aged 65 to 75 years detected a significant improvement with MPT not only in progression-free survival ($P < .001$) but also in overall survival, where medians were 51.6 months with MPT and 33.2 months with MP ($P < .001$).[6] In a separate French study conducted in patients older than 75 years, median progression-free survival was longer with MPT than MP ($P = .001$), and median overall survival was 44.0 months with MPT and 29.1 months with MP ($P = .028$).[7] In a Dutch trial including patients older than 65 years, MPT significantly prolonged event-free survival ($P < .001$) and marginally prolonged progression-free survival ($P = .08$) in comparison with MP, but no overall survival benefit was evident ($P = .28$).[8]

Waage's study seems to report the lowest efficacy outcomes. However, these results deserve further scrutiny. The different inclusion criteria of these trials led to the selection of different study populations, especially in the mix of relative fit and frail elderly patients enrolled. In the Nordic trial, 30% of patients had WHO performance status 3-4 compared with 6%, 8%, and 6% in the Italian and French studies. Age is another crucial factor that should be considered: during the first 6 months of treatment, Waage and colleagues reported 35 deaths, 23 among patients older than 75 years of age. The median age of patients treated with MPT was 74.1 in Waage's study, relatively higher than 72 years in the Italian and Dutch trials, or 69 years in the French trial. The older median age of the Nordic study population, together with the higher incidence of comorbidities typical of the elderly population, may have negatively affected efficacy outcomes. Of note, the thalidomide-dose was considerably high in the present study: 400 mg in the treatment phase and 200 mg during maintenance. The dose of thalidomide was lower in the Italian and the French studies.[4–6] In the Nordic trial, the increased toxicity led 56% of patients to discontinue thalidomide after 1 year of treatment. By contrast, the rate of thalidomide discontinuation in the Italian and French studies ranged between 30% and 40%. A high and early discontinuation rate of the MPT combination not

only cancels the advantages of the addition of thalidomide, but also the benefits of the MP administration. These data suggest that the Nordic schema is too toxic for the elderly and relatively frail study population, and that a gentler approach with reduced doses of thalidomide seems wise. Indeed, the Nordic authors suggest a dose of thalidomide of 100 to 200 mg, as well as a further dose reduction in patients older than 75 years and with WHO performance status 3-4, or even their exclusion.

In the Italian study, the incidence of thromboembolic events was 12% with MPT and 2% with MP (P = .001); in the French study, thromboembolic events were 12% in the MPT arm and 4% in the MP arm (P = .008). In the Nordic study, the incidence of thromboembolic events was 8% with both MPT and MP treatments, probably because 40% of patients in both groups received antithrombotic prophylaxis.

In conclusion, MPT remains an efficacious tool and is one of the new standards of care for elderly patients with multiple myeloma. In a recent meta-analysis on survival of 1682 individual patients treated with MPT or MP in 6 different randomized studies, including the trials previously reported, the addition of thalidomide to MP significantly improved progression-free survival and overall survival.[9] Similar data have been presented in a meta-analysis of published data.[10] The potential benefits of the MPT combination must be balanced against increased rates of toxicities. Efficacy may be decreased by older age, comorbidities, and elevated thalidomide doses that in turn induce higher toxicity rates and early treatment discontinuations. When MPT becomes too toxic for an elderly population, a less effective therapy, such as MP, becomes competitive and similar to MPT.

What is the lesson coming from the Nordic study? Although the biologic age may considerably differ from the chronologic age, we should remember that elderly patients may be divided into 2 groups: those 65 to 75 years of age, usually more fit, where full-dose chemotherapy should be delivered, and those older than 75 years of age, usually with significant comorbidities, where reduced dose-intensity chemotherapy should be adopted. In these subjects, the melphalan dose should be reduced from 0.25 mg/kg to 0.18 mg/kg or even to 0.13 mg/kg; similarly, the thalidomide dose should be reduced from 100 mg/d to 50 mg/d to even 50 mg every other day. These dose reductions may significantly reduce toxicity rate and drug discontinuation. To keep patients on treatment is the first condition for delivering effective therapy.

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