

## A new standard of care for elderly patients with myeloma

New biologically-derived agents have changed the treatment of myeloma in the past 10 years. Thalidomide, the first-in-class proteasome inhibitor bortezomib, and lenalidomide have all yielded encouraging results in overcoming drug resistance and improving outcome in relapsed and refractory patients with multiple myeloma.<sup>1-3</sup> Melphalan and prednisone (MP) have previously been the standard treatment for patients older than 65 years.<sup>4</sup> However, we now have extensive and confirmed evidence that MP plus thalidomide (MPT) is better than MP and should be the new standard of care for elderly patients with myeloma.

In today's *Lancet*, the Intergroupe Francophone du Myélome (IFM) group<sup>5</sup> present a large trial that randomly assigned newly diagnosed myeloma patients, aged 65–75 years, to MPT, MP, or tandem melphalan-based (melphalan 100 mg/m<sup>2</sup>) autologous stem-cell transplantation (MEL100). After a follow-up of 51.5 months, patients who received MPT had a significantly higher overall survival (median 51.6 months) and progression-free survival (27.5 months) than did those who received MP or MEL100. Our group showed much the same results in newly diagnosed patients, aged 65–85 years, who were randomly assigned to MPT or MP.<sup>6</sup> Although the follow-up was shorter in our study than in today's study, MPT significantly improved 2-year event-free survival (54% vs 27%) but failed to improve 3-year overall survival (80% vs 64%) compared with MP. In a third study (IFM 01–01), patients aged 75–85 years were randomly assigned to either MPT or MP.<sup>7</sup> MPT was again associated with better progression-free and overall survival than was MP. These three studies have unanimously shown better progression-free survival, and two of three also reported better overall survival in the MPT group. Concordance of results from different randomised studies represents the strongest evidence-based medicine.

In an interim analysis of a randomised study, elderly patients were assigned to receive the thalidomide-dexamethasone combination or standard MP; event-free and overall survivals were much the same in both groups.<sup>8</sup> Again, melphalan remains an essential component of every induction treatment, even though such induction incorporates new agents. A new standard of care has been defined. However, the optimum dose

of thalidomide, the number of cycles, and the need for maintenance therapy with single-agent thalidomide still need to be investigated. In the IFM study,<sup>5</sup> patients were aged 65–75 years and the median dose of thalidomide was 200 mg a day. The other two studies included older patients (aged 75–85 years), and the dose of thalidomide was 100 mg a day. 100 mg daily might be an appropriate dose for patients older than 75 years. In the IFM study,<sup>5</sup> the median duration of thalidomide treatment was confined to the first seven 6-week cycles of MPT (median duration 11 months). In our study,<sup>6</sup> the median duration of thalidomide treatment included all the six 4-week cycles of MPT and was shorter overall (median duration 8 months) than today's IFM study. If these findings are confirmed by other studies, a number of MPT cycles ranging from six to nine, a treatment duration shorter than 1 year, or a treatment delivered up to the achievement of a plateau phase should be considered.

We should always balance potential benefits with increased risks of toxic effects. MPT is associated with

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MRI showing myeloma (box) in femur

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higher risk of thromboembolism and peripheral neuropathy than is MP, but we should also consider that we have learned how to manage these adverse events. The introduction of anticoagulants, such as enoxaparin at 40 mg a day for the first 4–6 months of treatment, has reduced the rate of thromboembolism to less than 5%.<sup>6,9</sup> Similarly, improved education of patients about how thalidomide dose can immediately be reduced or discontinued when paraesthesia is complicated by pain, motor deficit, or interference with daily function, will further decrease the frequency and severity of peripheral neuropathy.

After 50 years of unsuccessful attempts to find new and more effective treatment approaches suitable for most patients, we now have extensive evidence to support the introduction of MPT as the standard of care for elderly patients with multiple myeloma.

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## Day or night blood pressures to predict cardiovascular events?



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Measurements of office blood pressure do not always correlate with 24-h blood pressure. The predictive value of 24-h blood pressure for cardiovascular events is greater than that seen for office blood-pressure values in populations, as well as in people with untreated and treated hypertension.<sup>1–4</sup> The 2007 guidelines for the management of arterial hypertension<sup>5</sup> state that, although office blood pressure should be a reference for diagnosis of hypertension, ambulatory blood-pressure monitoring could improve prediction of cardiovascular risk in patients with untreated and treated hypertension. Indeed, 24-h blood pressure correlates more closely with hypertension-related organ damage than does office blood pressure; changes in such blood pressures after treatment are even more closely correlated.<sup>6,7</sup>

Ambulatory blood-pressure monitoring provides information not only about 24-h average blood pressure but also about specific periods such as day, night, or morning. In 1988, O'Brien and colleagues<sup>8</sup> reported that patients in whom the nocturnal decrease in blood pressure was blunted had a greater prevalence

of organ damage and a less favourable outcome than those whose blood pressure dropped at night. Several studies then confirmed the higher prognostic value of night-time blood pressure than daytime blood pressure for cardiovascular events.<sup>1–4</sup> Because these studies considered only fatal outcomes, the question arises as to whether the higher predictive value of night-time blood pressure applies also to non-fatal cardiovascular events.

In today's *Lancet*, José Boggia and colleagues<sup>9</sup> report a meta-analysis of individual data for ambulatory blood-pressure monitoring in more than 7400 patients from many countries. They challenge the common view that night-time measurements have the best prognostic value and show indeed that the predictive accuracy of the daytime and night-time values and night-to-day ratio depends on the outcome. For fatal endpoints, they confirmed that night-time blood pressure predicted outcome better than daytime blood pressure, and showed that the night-to-day ratio predicted total, cardiovascular, and non-cardiovascular mortality. By