200 mg/m² melphalan – the gold standard for multiple myeloma

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Palumbo and co-authors report on the results of a randomised trial comparing two doses of melphalan in patients with symptomatic multiple myeloma. Overall complete response rates, median progression-free survival and projected five-year overall survival were significantly higher among patients receiving the higher melphalan dose. These results confirm that for this patient population melphalan 200 mg/m² should remain the gold standard conditioning regimen.

Despite multiple attempts to design alternative therapies, autologous transplantation with high-dose melphalan remains the standard of care for transplant-eligible patients with multiple myeloma. A recent article by Palumbo et al.[1] reports on the results of a randomised trial that assessed treatment with two doses of melphalan in patients with newly diagnosed multiple myeloma, and was performed at Italian institutions from 2001 to 2006. The study was powered to demonstrate a 20% improvement in survival with 320 patients; however, owing to slow accrual only 298 patients participated in the trial.[1] This is the second randomised trial to confirm that melphalan 200 mg/m² should continue to be considered the gold standard conditioning regimen for patients undergoing single or tandem autologous transplant for myeloma. A previous study by Moreau et al.[2] demonstrated that melphalan 200 mg/m² was better tolerated and improved progression-free survival when compared to the combination of melphalan 140 mg/m² with 8 Gy of total body irradiation. Palumbo et al.[1] hypothesised that similar disease control could be achieved with fewer toxic effects if the dose of melphalan used for conditioning was reduced. At the time it was proposed this was an interesting question; however, since the initiation of the trial in 2001 the advent of bortezomib, thalidomide and, more recently, lenalidomide-based induction therapy for myeloma meant that this trial had lost much of its impact.

Despite the advent of novel therapies, some features of the recent Palumbo trial are worth mentioning. First, all patients received a standard combination of vincristine–adriamycin–dexamethasone as induction therapy with almost three quarters of the patients achieving at least a partial response after tandem transplants, regardless of the randomisation group. However, almost twice as many patients achieved a complete remission in the melphalan 200 mg/m² group compared with patients in the melphalan 100 mg/m² group (15% vs 8%; P=0.07). These results stand in contrast with the data from the studies by Cavo et al.[3] and Harousseau et al.[4] (published in abstract form) of randomised trials comparing bortezomib-based induction therapy to either thalidomide–dexamethasone or vincristine–adriamycin–dexamethasone induction displayed in the table.

If complete remission in myeloma is considered one of the most important surrogate endpoints for long-term disease control, studies that do not include modern induction therapy (such as bortezomib-based treatment) have a limited impact.[5] Despite this limitation, the Palumbo et al.[1] study is still important because it examined how much tolerance to high-dose melphalan can be improved by a 50% dose

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in *Nature Reviews Clinical Oncology* 2010 vol.7 no.9, and is republished with permission. doi:10.1038/nrclinonc.2010.104, www.nature.com/nrclinonc

POST-TRANSPLANT BEST RESPONSE IN PATIENTS RECEIVING MELPHALAN CONDITIONING THERAPY

Study	Induction regimen	Conditioning therapy	Complete remission (%)	Very good partial remission or better (%)	Partial remission (%)
Palumbo et al. (2010)[1]	Vincristine–adriamycin–dexamethasone	Melphalan 100 mg/m^2 vs melphalan 200 mg/m^2	8 vs 15 (P = 0.07)	22 vs 37	50 vs 42
Cavo et al. (2008)[3]	Thalidomide–dexamethasone vs bortezomib–thalidomide–dexamethasone	Melphalan 200 mg/m^2	20 vs 41 (P <0.001)	53 vs 75 (P <0.001)	Not reported
Harousseau et al. (2007)[4]	Vincristine–adriamycin–dexamethasone vs bortezomib–dexamethasone	Melphalan 200 mg/m^2	28 vs 38 (P = 0.127)	50 vs 66 (P = 0.021)	88 vs 87

reduction. In this study, the 50% reduction in melphalan dose did not reduce transplant-related mortality (3% in each group), hospitalisation after engraftment or duration of severe (grade 3–4) neutropenia. Although the incidences of severe neutropenia and infections were higher in the melphalan 200 mg/m^2 group as well as the incidence of at least one nonhaematologic grade 3 or 4 adverse event, this difference was not as dramatic as the reduction in complete remissions in the 100 mg/m^2 group. Therefore, strategies to reduce the burden of treatment that occurs with high-dose melphalan should not focus on dose reduction (since this study demonstrates that even a 50% dose reduction was associated with similar toxic effects but a much lower complete response and disease-control rate), but rather look at other novel strategies of reducing symptom burden; rational strategies to explore would be increased stem-cell doses or the use of anti-interleukin-6 blockade treatment.[6,7]

Even with modern induction therapy and autologous transplant, many patients fail to achieve a complete remission and experience relapse before succumbing to their disease. A variety of strategies have been explored to try to improve upon the results of high-dose melphalan, including adding other agents and dose escalation with cytoprotectants, such as amifostine.[8,9] Of these, only tandem transplantation has been demonstrated in randomised trials to improve outcomes; however, more recently, the addition of post-transplant therapies with thalidomide or lenalidomide have also demonstrated efficacy and a potential survival benefit.[10]

Finally, the conclusion stated by Palumbo et al.[1] that melphalan 200 mg/m^2 should not be recommended for patients between the ages of 60 and 65 years is not supported by the data provided. This recommendation is based on an unplanned *post hoc* analysis of a subgroup consisting of fewer than 50 patients in each arm and was, therefore, underpowered to justify this conclusion. However, this analysis should provide impetus for studying the question of the ideal post-induction therapy for patients over 60 years of age. In summary, although associated with more toxic effects, melphalan 200 mg/m^2 continues to be the gold standard conditioning regimen for multiple myeloma autografts.

For future improvement of therapy in this patient population the role of single or tandem transplants in the context of bortezomib-based and lenalidomide-based therapies needs to be re-explored with large randomised trials, such as the one being planned by the International Myeloma Foundation and the Dana Farber Group as well as the recently initiated Blood and Marrow Transplant Clinical Trials Network Study looking at the role of tandem transplant versus consolidation versus maintenance therapy alone as post-transplant therapy for myeloma.

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

This study confirms that for patients younger than 65 years of age melphalan 200 mg/m^2 should remain the gold standard conditioning regimen to which other regimens need to be compared.

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Competing interests: The author has acted as a consultant for and received honoraria from the following companies: Celgene, Genzyme, Millenium Pharmaceuticals and Novartis