

To the editor:

## Long-term follow-up results of IFM99-03 and IFM99-04 trials comparing nonmyeloablative allotransplantation with autologous transplantation in high-risk de novo multiple myeloma

Recent pilot studies combining a cytoreductive autologous stem cell transplantation (ASCT) with a reduced-intensity conditioning regimen (RIC) allograft have reported encouraging results in patients with de novo multiple myeloma (MM).<sup>1,2</sup> However, it remains to be determined whether single autograft followed by RIC allograft approaches are superior to double ASCT programs. Until now, only 3 prospective studies comparing the combination of ASCT followed by RIC allograft with tandem ASCT have been reported, one from the Intergroupe Francophone du Myélome (IFM),<sup>3</sup> one from Italy,<sup>4</sup> and one from Spain.<sup>5</sup> The Italian group reported a significant survival advantage in favor of allo-RIC, both for event-free survival (EFS) and overall survival (OS).<sup>4</sup> In the Spanish trial, there was a trend toward a longer progression-free survival in favor of allo-RIC, but both EFS and OS were not significantly different between second ASCT and allo-RIC.<sup>5</sup>

Here we report the updated results of the IFM study.<sup>3</sup> At the reference date of July 1, 2008, on an intent-to-treat basis and considering the entire population of 284 patients with a median follow-up of 56 months, the EFS did not significantly differ from tandem ASCT to single autograft followed by allo-RIC (median 22 vs 19 months,  $P = .58$ ). Nevertheless, there was a trend for a superior OS in the double ASCT trial (median 48 vs 34 months,  $P = .07$ ; see Figure 1). When considering the comparison of the results of the 166 patients out of 219 who completed the whole tandem ASCT protocol with those of the 46 patients out of 65 who underwent the entire auto/allo-RIC program, no difference was observed regarding EFS (median 25 vs 21 months,  $P = .88$ ), but there was again a trend for a superior OS in favor of double ASCT (median OS, 57 vs 41 months,  $P = .08$ ), due to a longer survival after relapse in the tandem ASCT arm.

Our results differ significantly from those reported by Bruno<sup>4</sup> and Rosinol.<sup>5</sup> This can be explained through the different study design. Our study focused on patients with high-risk disease, that is, elevated  $\beta 2$ -microglobulin plus chromosome 13 abnormalities,

and the conditioning regimen before allo-RIC consisted of busulfan, fludarabine and high-dose ATG, possibly eliminating part of the GVM effect.<sup>6,7</sup> In the Italian trial,<sup>4</sup> all patients irrespective of the prognostic factors were included, the conditioning regimen before allo-RIC consisted of 2 Gy TBI, and the results of the tandem ASCT arm were surprisingly poor, with a median OS of 58 months in patients who completed the double autograft protocol, which is clearly inferior to the results of other recently reported series of double ASCT.<sup>8,9</sup> In the recent Spanish trial, only chemosensitive patients failing to achieve complete or near-complete response after a first ASCT were treated with either a second ASCT or an allo-RIC based on the availability of an HLA-identical sibling donor.<sup>5</sup> Moreover, in this study the number of patients in the allogroup was small and the preparative regimens for autotransplant patients were not uniform.

Our long-term results may indicate that, in a subgroup of high-risk patients with de novo MM, a tandem ASCT procedure is at least equivalent or even superior to a combination of autologous followed by RIC allogeneic SCT. In patients with standard-risk and/or chemosensitive disease RIC allograft could be an interesting option. Results of 2 recently completed prospective phase 3 trials in North America and Europe comparing double ASCT with single ASCT followed by nonmyeloablative allogeneic SCT are eagerly awaited.

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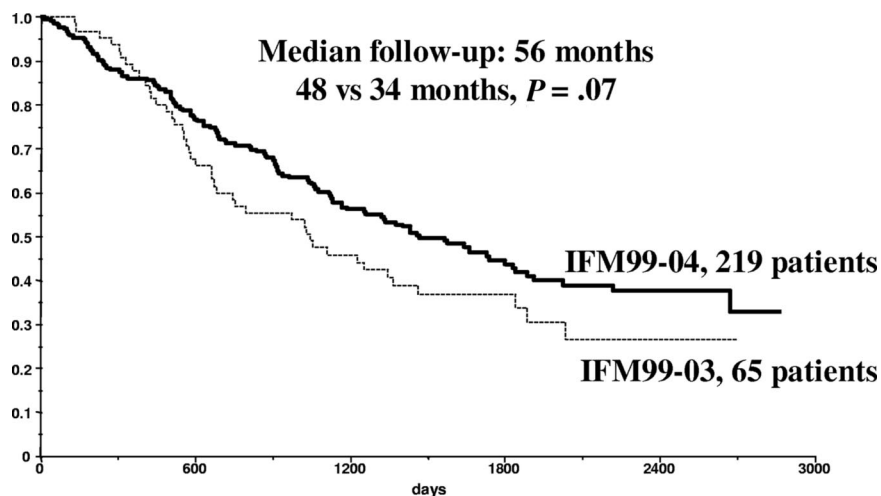


Figure 1. Overall survival, intent-to-treat.

## References

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1. Kröger N, Schwerdtfeger R, Kiehl M, et al. Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. *Blood*. 2002;100:755-760.
2. Maloney D, Molina A, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood*. 2003;102:3447-3454.
3. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood*. 2006;107:3474-3480.
4. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;356:1110-1120.
5. Rosiñol L, Pérez-Simón JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*. 2008;112:3591-3593.
6. Lokhorst H. No RIC in high-risk myeloma? *Blood*. 2006;107:3420-3421.
7. Crawley C, Iacobelli S, Björkstrand B, et al. Reduced intensity conditioning for myeloma: lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. *Blood*. 2007;109:3588-3594.
8. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354:1021-1030.
9. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol*. 2007;25:2434-2441.