Reduced relapse rate in upfront tandem autologous/reduced-intensity allogeneic transplantation in multiple myeloma only results in borderline non-significant prolongation of progression-free but not overall survival

Results of Allogeneic Stem Cell Transplantation (Allo-SCT) as part of first-line therapy for multiple myeloma (MM) are conflicting.[1-7] The 96 month long-term follow-up of the EBMT trial showed a significantly prolonged PFS and OS for Auto-/Allo-SCT as compared to double Auto-SCT, both in the intention-to-treat analysis and in the patients who actually received their allocated treatment.[8] One of the conclusions from that study was that a follow-up of longer than 5 years is necessary for a correct interpretation of the value of Auto-/Allo-SCT in MM. Here we present the long-term follow-up (median 113 months) results of the donor *versus* no-donor (DvND) comparison of patients who were included in the HOVON-50 study.[9] In this study the effect of thalidomide combined with Auto-SCT after high-dose melphalan 200 mg/m^2 (HDM200) was evaluated. PFS and OS were not statistically different, neither in the donor *versus* no-donor comparison nor in the patients that received their allocated therapy, i.e. the Allo-SCT or maintenance (α-interferon or thalidomide, given until relapse or progression) following the Auto-SCT. Despite the extended follow-up time, there was no benefit observed for using Allo-SCT as part of first-line therapy in myeloma.

Out of 536 patients randomized in the HOVON-50 study, 260 patients were eligible for the DvND analysis; 122 patients with and 138 patients without an HLA-identical donor (Figure 1). Eligibility criteria included treatment with Auto-SCT, and for inclusion in the donor group patients had to have a fully matched 10/10 sibling donor. M-protein type, ISS stage, median age and remission status were well balanced.[6] The data for this update were analyzed as available on August 15th, 2014. Conditioning for the Allo-SCT was low-dose total body irradiation (TBI; 2 Gy) and GvHD prophylaxis consisted of cyclosporine and mycophenolate mofetil. The HOVON-50 study was approved by the ethics committees of the participating centers and was conducted in accordance with the Declaration of Helsinki. The trial was registered at www.trialregister.nl (NTR238; ISRCTN06413384).

The European Group for Blood and Marrow Transplant criteria were used to evaluate response. The primary endpoints were progression-free survival (PFS) and overall survival (OS) from Auto-SCT. The secondary endpoints were the impact of prognostic factors, and PFS and OS from the start of treatment for those patients who received their allocated therapy, that is, Allo-SCT or maintenance therapy with thalidomide or α-interferon (denoted herein as PFStr and OStr). For some of the endpoints the Kaplan-Meier survival curves were crossing (Figure 2) indicating a violation of the proportional hazards assumption. In that case, a standard log-rank test and Cox regression analysis are not optimal statistical methods.[10] Therefore we used the so-called restricted mean survival time (RMST) method[11,12] for all analyses to compare PFS and OS between donor *versus* no-donor, which has been implemented in Stata[13] (StataCorp. 2013. Stata: Release 13. Statistical Software. College Station, TX: StataCorp LP). The difference in RMST within 10 years (RMST$_{10y}$) was calculated, together with the 95% confidence interval (CI). In view of the fact that in the HOVON-50 trial patients had been randomized to induction treatment with either VAD or TAD, a treatment arm was included as a covariate. To compare our results with those previously published, we also evaluated the prognostic value of donor availability for the VAD and TAD subgroups separately, as well as in subgroups according to ISS stage (I *vs.* II *vs.* III), β-2 microglobulin (β-2M; ≤ 3 *vs.*> 3 mg/l) and the presence or absence of deletion 13 (determined by FISH and/or by karyotyping).[14] Kaplan-Meier curves were generated to illustrate differences between subgroups. All reported *P* values are two-sided and have not been adjusted for multiple testing, and a significance level alpha = 0.05 was used.

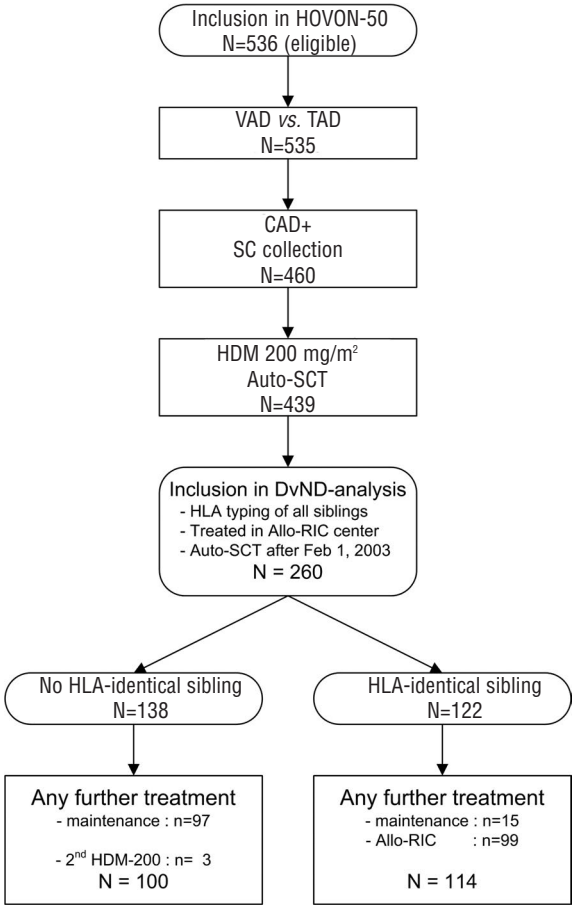

Figure 1. Design of the study and patient flow.

The best response as determined by CR was 43% for patients with a donor and 38% for patients without a donor (*P*= 0.41). The 8-year and 10-year PFS were 25% and 17%, respectively, for patients with a donor and 18% and 16%, respectively, for the patients without a donor (Figure 2A). RMST$_{10y}$ was 6 months longer in the donor group (95% CI -5 to 16, *P* =0.29), which was not statistically significant. RMST$_{10y}$ was also not significantly different between donor and no-donor in the subgroups of VAD and TAD patients. β-2 M> 3mg/L was associated with an 11 month lower RMST$_{10y}$ (95% CI 0 to 22, *P*=0.04), but in the DvND comparison no significant difference in PFS was found for patients with low or high β-2 M. This was also apparent for ISS stage and the presence or absence of deletion 13, determined either by FISH (available for 61 % of no-donor and 57 % of donor patients) or by karyotyping (available for 82 % of no-

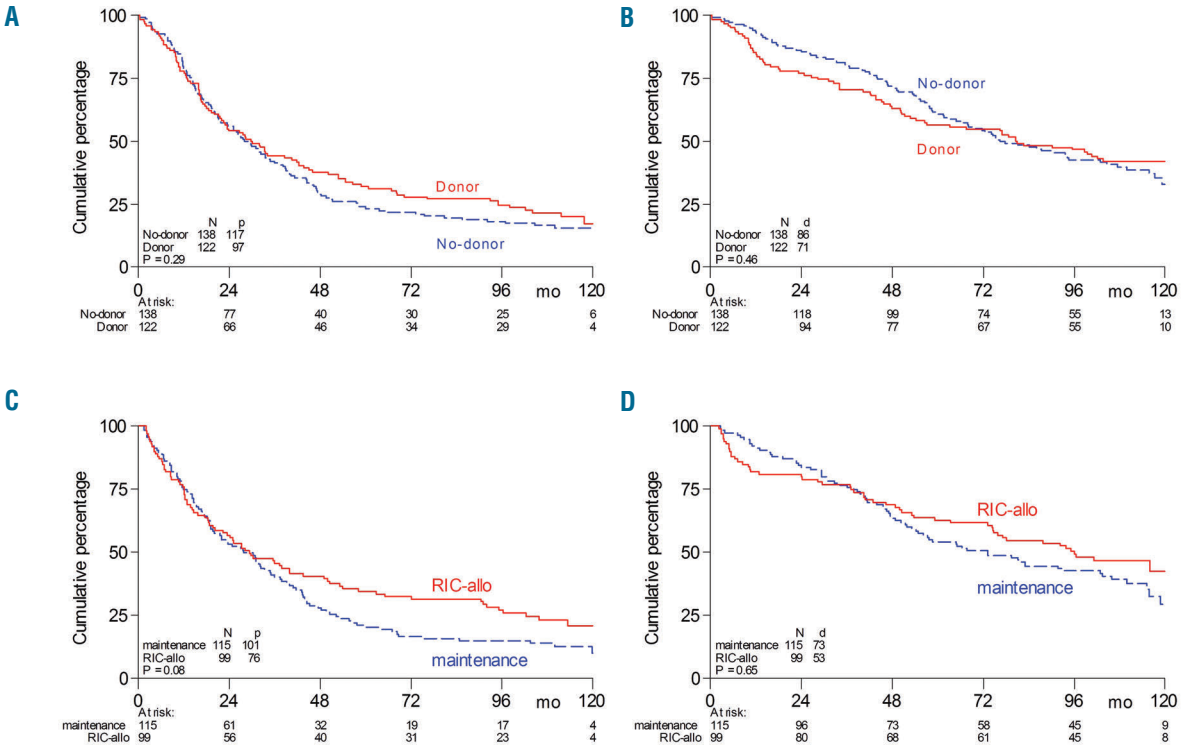

Figure 2. Kaplan-Meier survival curves. Actuarial rates of PFS (A) and OS (B) according to availability of an HLA-identical sibling of patients included in the HOVON-50 study. PFS and OS are presented as from the date of autologous SCT. Actuarial rates of PFStr (C) and OStr (D) according to treatment started after Auto-SCT, ie, Allo-SCT *versus* maintenance with thalidomide or α-interferon. PFStr and OStr are presented as from the date of Allo-SCT or start of maintenance, whichever was applicable. The reported *P* values are those obtained with the RMST method.

donor and 83 % of donor patients).

The 8-year and 10-year OS were 47% and 42%, respectively, for patients with a donor and 43% and 33%, respectively, for the patients without a donor (Figure 2B). $RMST_{10y}$ was 4 months longer in the no-donor group (95% CI -15 to 7, *P*=0.46). This non-significant 4.1 months longer $RMST_{10y}$ for OS in the no-donor patients was also observed within the subgroups of VAD and TAD patients, both *P*=0.6. β-2 M > 3 was associated with a 17 month lower $RMST_{10y}$ (95% mg CI 6 to 28, *P*=0.003), but the difference in $RMST_{10y}$ between donor and no-donor patients in each of the low or high β-2 M subgroups was less than 1 month (*P*=0.9). There was also no significant difference in PFS within the subgroups according to ISS and the presence or absence of deletion 13. The cumulative incidence of non-relapse mortality at 96 months after Auto-SCT was 16% in the donor group *versus* 3% in the no-donor group (*P*<0.001) and the cumulative incidence of relapse at 96 months was 77% in the no-donor arm *versus* 55% in the donor arm (*P*=0.001), (Figure 3A,B).

We also compared the outcome of the 99 patients who received their allocated Allo-SCT with the 115 patients who started with their allocated maintenance therapy after Auto-SCT. Response status (ORR, CR and VGPR) was comparable in both groups. The 8-year and 10-year PFStr were 27% and 21%, respectively, for the Auto-/Allo-SCT patients and 15% and 10%, respectively, for the Auto/maintenance patients (Figure 2C). A non-significant 10 month increase in $RMST_{10y}$ (95% CI -1 to 21, *P*=0.08) was observed in the Auto-/Allo-SCT patients. While $RMST_{10y}$ was 17 months longer in the patients treated with VAD (*P*=0.04), it was only 6 months longer in the TAD patients (*P*=0.47). Furthermore, an increase in $RMST_{10y}$ of 25 months in the Auto-/Allo-SCT patients was observed in patients without deletion 13 (*P*=0.009).

The 8-year and 10-year OStr were 50% and 42%, respectively, for Allo-SCT patients and 43% and 29%, respectively, for the Auto/maintenance patients (Figure 2D). A non-significant increase in $RMST_{10y}$ of 3 months (95% CI -9 to 15, *P*=0.65) was observed in the Auto-/Allo-SCT patients. Thalidomide was not associated with improved outcome. β-2 M > 3 predicted for reduced survival (*P*=0.02). However, no benefit for Allo-SCT as compared to maintenance was found in this patient category. Neither ISS nor deletion 13 had a significant impact on OStr.

With the longest follow-up (median 113 months after Auto-SCT therapy) in published studies as yet, we found no benefit for Allo-SCT as part of first-line therapy on PFS and OS. The positive graft-*versus*-myeloma effect as demonstrated by the significantly reduced incidence of relapse in the donor arm did not compensate for the higher TRM (Figure 3). As in our previous analysis there was a trend for prolonged PFS in patients treated with the allocated Allo-SCT, however due to late relapses this did not lead to a significant benefit when compared to patients receiving maintenance following Auto-SCT. The absence of a benefit in our updated study may be due to better outcome for the no-donor group as compared with the Italian and EBMT studies, while the outcome with regard to PFS and OS of patients with a donor seemed rather similar. Our study was initiated later, therefore bortezomib and lenalidomide could be routinely given to patients with relapsed disease. It may be that the availability of these new anti-myeloma agents for relapse

explains the comparable survival of the patients who did receive their allocated therapy, although the PFS curves diverge after 30 months in favor of the Allo-SCT group. There were 6 patients who had progressive disease at a time point of more than eight years, and we are aware that these patients were still alive between 3 and 25 months following the occurrence of the progressive disease.

An important query is whether in this era of effective MM strategies, Allo-SCT should be completely abandoned or whether it could still be an option for patients with high risk features like 17p deletion or patients with an early first relapse.[15] In the case that this topic is explored, alternative procedures are essential to allow effective and safe post Allo-SCT strategies to prevent both TRM and early relapse and the initiation of specific graft-*versus*-myeloma effects.

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Funding: The study was supported by a grant from Dutch Cancer Society (KWF).

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doi:10.3324/haematol.2015.128728

Key words: myeloma, allogeneic stem cell transplantation, prognosis.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

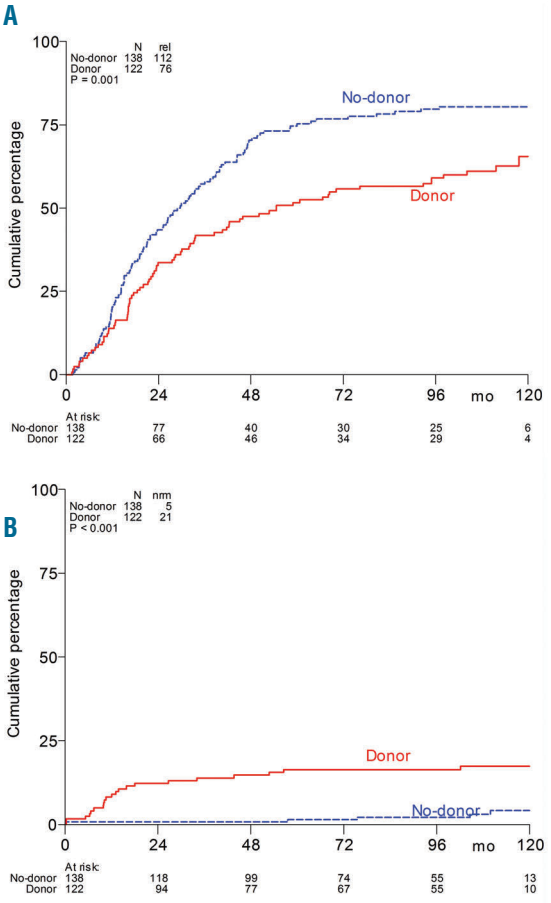

Figure 3. A. The cumulative incidence of relapse at 96 months was 77% in the no-donor arm *versus* 55% in the donor arm (*P*=0.001). B. The cumulative incidence of non-relapse mortality at 96 months was 3% in the no-donor arm *versus* 16% in the donor arm (*P*<0.001).

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