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

by Henk M. Lokhorst, Bronno van der Holt, Jan J. Cornelissen, Marie Jose’ Kersten, Marinus van Oers, Reinier Raymakers, Monique C. Minnema, Sonja Zweegman, Gerard Bos, Nicolaas Schaap, Shulamiet Wittebol, Okke de Weerdt, Rianne Ammerlaan, and Pieter Sonneveld

Haematologica 2015 [Epub ahead of print]

doi:10.3324/haematol.2015.128728

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in print on a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Reduced relapse rate in upfront tandem autologous/reduced intensity allogeneic transplantation in multiple myeloma only results in borderline non-significant prolongation of progression free and not of overall survival

Henk M. Lokhorst,1 Bronno van der Holt,2 Jan J. Cornelissen,3 Marie José Kersten,4 Marinus van Oers,4 Reinier Raymakers,5 Monique C. Minnema,5 Sonja Zweegman,1 Gerard Bos,6 Nicolaas Schapa,7 Shulamiet Wittebol,8 Okke de Weerdt,9 Rianne Ammerlaan,2 Pieter Sonneveld,3

1 Department of Hematology, VU University Medical Center Amsterdam, The Netherlands
2 HOVON Data Center, Erasmus MC Cancer Center – Clinical Trial Center, Rotterdam, The Netherlands
3 Department of Hematology, Erasmus Medical Center, Rotterdam, The Netherlands
4 Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands
5 Department of Hematology, University Medical Center Utrecht, The Netherlands
6 Department of Hematology, Academic Hospital Maastricht, The Netherlands
7 Radboud University Nijmegen Hospital, Nijmegen, The Netherlands
8 Meander Medical Center, Amersfoort, The Netherlands
9 Antonius Hospital, Nieuwegein, The Netherlands

Corresponding author:
Henk Lokhorst
Department of Hematology
VU University Medical Center
De Boelelaan 1117
1087 Amsterdam
The Netherlands
Email: h.lokhorst@vumc.nl
Tel: 0031631798795
Fax: 0031204442601

The study was supported by a grant from Dutch Cancer Society (KWF)
Results of Allogeneic Stem Cell Transplantation (Allo-SCT) as part of first line therapy for multiple myeloma (MM) are conflicting. The 96 months 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 analyses and in the patients that actually received their allocated treatment. One of the conclusions from that study was that follow up longer than 5 years is necessary for a correct interpretation of the value of Auto/Allo-SC 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. In this study the effect of thalidomide combined with Auto-SCT after High Dose Melphalan 200mg/m² (HDM200) was evaluated. PFS and OS were not statistically different as well as in the donor versus no donor comparison as 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. Also with the extended follow-up there was no benefit for 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: design of the study and patient flow). Eligibility criteria included treatment with Auto-SCT and for inclusion in the donor group having a 10/10 sibling donor. M-protein type, ISS stage, median age and remission status were well balanced. The data for this update were analysed 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 mophetil. The HOVON-50 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. Secondary endpoints were impact of prognostic factors, and PFS and OS from start allocated treatment for the patients who received their allocated therapy, that is, Allo-SCT or maintenance therapy with thalidomide or -interferon (denoted here as PFS and OS). 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, standard logrank test and Cox regression analysis are not optimal statistical method. Therefore we used the so-called restricted mean survival time (RMST) method for all analyses to compare PFS and OS between donor versus no-donor, which has been implemented in Stata (StataCorp. 2013. Stata: Release 13. Statistical Software. College Station, TX: StataCorp LP). The difference in RMST within 10 years (RMST) was calculated, together with 95% confidence interval (CI). Because in the HOVON-50 trial patients had either been randomized to
induction treatment with VAD or TAD, 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-2 M; ≤ 3 vs > 3 mg/l) and presence or absence of deletion 13 (determined by FISH and/or by karyotyping).\textsuperscript{14} Kaplan-Meier curves were generated to illustrate differences between subgroups. All reported P values are 2-sided and have not been adjusted for multiple testing, and a significance level alpha = 0.05 was used.

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% for patients with a donor and 18% and 16% for the patients without a donor (Figure 2A). \text{RMST}_{10y} was 6 months longer in the donor group (95% CI -5 to 16, P=0.29), which was not statistically significant. \text{RMST}_{10y} was also not significantly different between donor and no-donor in the subgroups of VAD patients and TAD patients. β-2 > 3 was associated with an 11 months lower \text{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 either determined by FISH (available for 61% of no donor and 57% of donor patients) or determined by karyotyping (available for 82% of no donor and 83% of donor patients).

The 8-year and 10 year OS were 47% and 42% for patients with a donor and 43% and 33% for the patients without a donor (Figure 2B). \text{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 \text{RMST}_{10y} for OS in the no-donor patients was also observed within the subgroups of VAD patients and TAD patients, both P=0.6. β-2 M > 3 was associated with a 17 months lower \text{RMST}_{10y} (95% CI 6 to 28, P=0.003), but the difference in \text{RMST}_{10y} between donor and no-donor patients in each of the low or high β-2 M subgroups was less than one months (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), see Figures 3A and 3B.

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 PFS\textsubscript{a} were 27% and 21% for the Auto/Allo-SCT patients and 15% and 10% for the Auto/maintenance patients (Figure 2C). A non-significant 10-months increase in \text{RMST}_{10y} (95% CI -1 to 21, P=0.08) was observed in the Auto/Allo-SCT patients. While \text{RMST}_{10y} was longer 17 months 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 OS, were 50% and 42% for Allo-SCT patients and 43% and 29% 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. ß-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 since Auto-SCT) of published studies until now 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 the 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, so that 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 explain the comparable survival of the patients who did receive their allocated therapy, although the PFS curves diverge after 30 months in favour of the Allo-SCT group. There were 6 patients with progressive disease after 8 years. None of them have died, with follow up between 3 and 25 months later.

A major question 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. In case this is explored alternative strategies are essential to allow effective and safe post Allo-SCT strategies to prevent both TRM, early relapse and initiation of specific graft versus myeloma effects.

**Authorship Contributions:** H.M.L., B.v.d.H. and P.S. contributed to study conception and design; H.M.L., B.v.d.H., J.J.C., M.-J.K., M.v.O., R.R., M.C.M., S.Z., G.B., N.S., S.W., O.d.W., R.A., and P.S. collected and assembled the data; H.M.L., B.v.d.H., R.A., and P.S. conducted data analysis and interpretation; and all authors were involved in manuscript writing and approved the final version of the manuscript.

**Disclosures of Conflict of interest:** H.M.L served as a consultant and received research support from Genmab and Janssen. P.S has received research support from Onyx, Janssen and Celgene. M.I.K. has
received research support from Celgene and honoraria from Celgene and Janssen. S.Z has received from and served on the advisory boards of Janssen, Celgene and Millenium. M.v.O: consultant Roche, GSK and Genmab. G.B has received research support from Celgene. M.C.M served as a consultant for Janssen, Amgen and Novartis. N.S. Advisory board Novartis. R.R. Advisory board Novartis, Roche. All other authors have nothing to disclose.

References


Figure legends

Legend to figure 1
Design of the study and patient flow

Legend to 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 PFS\textsubscript{u} (C) and OS\textsubscript{u} (D) according to treatment started after auto-SCT, ie, Allo-SCT versus maintenance with thalidomide or α-interferon. PFS\textsubscript{u} and OS\textsubscript{u} are presented as from the date of Allo-SCT or start maintenance, whichever applicable. The reported P-values are those obtained with the RMST-method.

Legend to figure 3A
The cumulative incidence of relapse at 96 months was 77% in the no-donor arm versus 55% in the donor arm (p=0.001).

Legend to figure 3B
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).
Inclusion in HOVON 50 N = 536 (eligible)

VAD vs TAD N = 535

CAD + SC collection N = 460

HDM 200 mg/m² + Auto-SCT N = 439

Inclusion in DvND-analysis
- HLA typing of all siblings
- Treated in Allo-RIC center
- Auto-SCT after Feb 1, 2003 N = 260

No HLA-identical sib N = 138
- Any further treatment
  - maintenance : n=97
  - 2nd HDM-200 : n=3
  N = 100

HLA-identical sib N = 122
- Any further treatment
  - maintenance : n=15
  - Allo-RIC : n=99
  N = 114