Published in final edited form as:

Br J Haematol. 2013 January ; 160(2): 199–206. doi:10.1111/bjh.12123.

Late Relapses Following Reduced Intensity Allogeneic Transplantation in Patients with Multiple Myeloma: a long-term follow-up study

Firoozeh Sahebi^{1,2}, Yan Shen³, Sandra H. Thomas¹, Amalia Rincon³, Joyce Murata-Collins⁴, Joycelynne Palmer³, Amrita Y. Krishnan¹, Chatchada Karanes¹, Myo Htut¹, George Somlo¹, and Stephen J. Forman¹

¹Department of Hematology, City of Hope, Duarte, CA

³Department of Information Sciences, City of Hope, Duarte, CA

⁴Department of Cytogenetics, City of Hope, Duarte, CA

²Southern California Kaiser Permanente Medical Group, Los Angeles, California

SUMMARY

We analysed the long-term outcomes of 60 multiple myeloma patients who underwent reduced intensity allogeneic stem cell transplantation between August 2000 and March 2008. Regimens included fludarabine and melphalan conditioning (flu-mel regimen) for allogeneic haematopoietic cell transplant (HCT) or a planned tandem regimen consisting of high-dose melphalan conditioning for autograft followed by low-dose total body irradiation conditioning for allogeneic HCT (auto-allo regimen). Donors included human leucocyte antigen-matched siblings (n=55) or matched unrelated donors (n=5). With a median follow-up of 9.8 years, 7-year overall survival (OS) and progression-free survival (PFS) were 60% and 31%, respectively. By multivariate Cox regression analysis, disease status of complete response (CR) or partial response (PR) at transplant and the presence of chronic graft-versus-host disease were significantly associated with improved OS. Only disease status was significantly associated with improved PFS. We noted a surprising number of very late relapses, with six patients (10%) relapsing between 6 and 12 years post-transplant. Among the six late relapse patients, all were transplanted within 14 months of diagnosis, 5 had normal karyotypes, and 5 were in CR/PR. Our data provide additional evidence that, while survival may be extended by reduced intensity allogeneic transplant, ultimately, it may not offer a cure.

Keywords

multiple myeloma; reduced intensity; allogeneic; tandem auto-allo; transplantation

Corresponding Author: Dr. Firoozeh Sahebi, Department of Hematology, City of Hope National Medical Center, 1500 E. Duarte Rd., Duarte, CA 91010 Phone: 626-256-4673 ext. 65285, Fax: 626-301-8116, fsahebi@coh.org.

Author Contributions: FS, YS, and SH designed the study, AK, CK, MH, GS and SJF provided advice on study design and execution, FS and AR acquired the data, FS, YS and SH interpreted the data, All authors critically reviewed the manuscript and approved the final draft.

Author Contributions: The authors have no competing financial interests to disclose in relation to the study described.

INTRODUCTION

In the modern era of targeted therapy, autologous haematopoietic cell transplantation (auto-HCT) remains the standard of care for patients with newly diagnosed multiple myeloma, based on randomized studies (Attal, *et al* 1996, Child, *et al* 2003). However, most patients undergoing auto-HCT eventually experience disease recurrence. Randomized comparisons of single versus double auto-HCT demonstrate superior event-free survivals in patients treated with tandem auto-HCT, but most patients eventually relapse despite improvements in disease control (Attal, *et al* 2003, Cavo, *et al* 2007). Additional consolidation and/or maintenance therapy following auto-HCT is also being explored, but cure remains elusive. Allogeneic haematopoietic cell transplantation (allo-HCT) offers the advantage of a tumour-free graft and the potential for a graft-versus-myeloma effect. Standard myeloablative allo-HCT is limited by high transplant-related mortality (TRM), despite reductions in TRM in recent years (Bensinger, *et al* 1996, Bensinger, *et al* 2001, Gahrton, *et al* 2001). Furthermore, standard myeloablative allo-HCT is primarily available to younger patients, excluding the majority of patients with multiple myeloma. Reduced-intensity conditioning (RIC) allo-HCT, either alone as salvage therapy or following auto-HCT, is reported to reduce regimen-related toxicities compared to myeloablative allo-HCT, while maintaining a graft-versus-myeloma effect (Crawley, *et al* 2007, Kroger, *et al* 2004, Maloney, *et al* 2003).

Few studies have reported long-term outcomes in multiple myeloma patients receiving RIC allo-HCT, with the median follow-up typically two to five years. We report long-term follow-up data (median 9.8 years) from a consecutive case-series of 60 multiple myeloma patients who underwent RIC prior to allo-HCT, with the goal of evaluating the impact of RIC allo-HCT on long-term patient outcomes.

PATIENTS AND METHODS

Between August 2000 and March 2008, 60 multiple myeloma patients received reduced intensity transplants using either 1) a uniform conditioning regimen of fludarabine and melphalan prior to allo-HCT (flu-mel group), or 2) auto-HCT followed by non-myeloablative allo-HCT (auto-allo group) in a planned tandem fashion (Maloney, *et al* 2003). Patients in the tandem auto-allo group were transplanted as part of their initial treatment, and patients in the flu-mel group were transplanted either as part of their initial treatment or as salvage therapy for recurrent or progressive disease. The City of Hope Institutional Review Board approved the review and analysis of patient data for this study.

Patient Characteristics

Patient baseline characteristics are detailed in Table I. The median patient age was 51 years (32 – 66). Median time from diagnosis to transplant was 9.5 months (0.8–127.0) with 36 patients (60%) receiving early transplant (< 1 year from diagnosis). In the auto-allo group, 30/39 (76.9%) received early transplant (< 1 year from diagnosis) and in the flu-mel group, 6/21 (28.6%) received early transplant. Thirty-eight (63%) patients had chemo-sensitive disease in complete or partial remission at the time of transplant. Thirty-eight patients had received induction treatment with chemotherapy only, and 22 patients had received newer targeted therapies, (thalidomide, lenalidomide, bortezomib) with or without chemotherapy prior to transplant. All patients (n=39) in the tandem auto-allo group received auto-HCT prior to allo-HCT in a planned tandem fashion as part of prospective studies investigating the role of allograft in patients with available human leucocyte antigen (HLA) donors. The flu-mel patients were selected for allogeneic transplantation based on high-risk features (progressive or recurrent disease or failed autologous transplant) and were ineligible for a fully myeloablative allograft based on age or other comorbidities. In the flu-mel group, 4/21 patients had failed prior single-auto-HCT, 5/21 had failed prior tandem-auto-HCT, and

12/21 received RIC allograft as their first transplant. Fifty-nine patients had documented β_2 -microglobulin levels at the time of evaluation for transplant. Median β_2 -microglobulin was 1.9 mg/l (range 0.8–10 mg/l). Fifty-five patients received allogeneic haematopoietic cells from HLA-matched siblings, and 5 patients, all in the flu-mel group, underwent transplant from a matched unrelated donor.

Cytogenetics

Cytogenetic data were available in 53 patients prior to transplant. Risk stratification in multiple myeloma is based on both conventional cytogenetic and molecular fluorescence in-situ hybridization (FISH) findings. FISH was not performed routinely as many of the patients were treated before it was used in standard practice, so cytogenetic risk assessment for this study was primarily based on conventional cytogenetics. The specific abnormalities considered as high-risk myeloma, based on recommendations from the International Myeloma Workshop Consensus Panel 2 (Munshi *et al* 2011) were: cytogenetically-detected monosomy 13, deletion of the long arm of chromosome 13, t(4;14), or deletion of the short arm of chromosome 17; and FISH-detected *FGFR3/IGH@* or *IGH@/MAF* fusion gene rearrangements corresponding to t(4;14) or t(14;16), or loss of the *TP53* gene locus corresponding to the chromosome 17p13.1 deletion. Hypodiploidy was also considered a high-risk finding (Kapoor, *et al* 2010). Standard-risk was defined as a lack of all specific high-risk abnormalities. Based on these risk criteria, 4 of the 54 patients with available cytogenetic data had high-risk abnormalities prior to allogeneic transplantation (Table I). Complex karyotypes with chromosome 13 abnormalities were detected by chromosome analysis in all 4 and by concurrent FISH in 3 of the 4 patients. Three of the 49 patients with standard-risk had non-specific chromosome abnormalities and the remaining 46 patients had normal karyotypes prior to HCT.

Conditioning Regimens

All patients in the flu-mel group received fludarabine at 25 mg/m² × 5 days on days -6 to -2 and melphalan at 140 mg/m² on day -1 prior to stem cell infusion. Patients in the auto-allo group received melphalan at 200 mg/m² on day -2 of their autologous transplant and within 60–120 days following autologous stem cell infusion, received TBI at 200 cGy on day 0 of their non-myeloablative allogeneic transplant. Graft-versus-host disease (GVHD) prophylaxis in the auto-allo group was cyclosporine and mycophenolate mofetil; in the flu-mel group it was primarily cyclosporine/mycophenolate mofetil or tacrolimus/sirolimus. All patients received allogeneic peripheral haematopoietic cells, except two patients who received bone marrow as the source of haematopoietic cells, one in the auto-allo group and one in the flu-mel group.

Response Assessment

Disease response was assessed according to the European Group for Blood and Marrow Transplantation (EBMT) / International Bone Marrow Registry Criteria (Blade, *et al* 1998). Briefly, complete response (CR) required the disappearance of M protein in serum and urine by immunofixation and less than 5% plasma cells in the bone marrow. Partial response (PR) indicated a 50% reduction in serum M protein and 90% reduction in urinary light chain excretion. Progressive disease (PD) was determined by a 25% increase in serum M protein, urinary light chain excretion, or plasma cells in the bone marrow.

Statistics

Overall survival (OS) was calculated from the date of allogeneic stem cell infusion until death or last contact. Progression-free survival (PFS) was calculated from the date of allogeneic stem cell infusion until the date of relapse, disease progression, or death, which

ever occurred first. Survival estimates were calculated using the Kaplan-Meier product-limit method, and 95% confidence intervals were calculated using the logit transformation of Greenwood's variance estimate. Cumulative incidence of relapse and cumulative incidence of non-relapse mortality were calculated as competing risks. We analysed associations with OS and PFS for the following variables identified from the literature: disease status, time 1 year from diagnosis, disease stage, donor sex match, and conditioning regimen as categorical variables; and age and β -2 microglobulin as continuous variables. Acute GVHD and chronic GVHD were treated as time-dependent variables, using a delayed entry method. We also included prior novel agent therapy, because novel agents came into widespread use during the time of this study. We input these variables into a forward-selection multivariate Cox regression model, forcing disease status into the model, and then forward selected the remaining covariates with the threshold for entry into the model set to $P=0.2$. Statistical significance for covariates in the final model was set to $P=0.05$. Quoted confidence intervals (CI) for survival, cumulative incidence, or hazard ratios (HR) refer to 95% boundaries.

RESULTS

Median follow-up for patients alive at date of analysis was 9.8 years (3.8 – 12.0 years). Outcomes are listed in Table II. Twenty-two (37%) patients experienced acute GVHD grades II–IV. The incidence of severe grade III–IV acute GVHD was 8.3% (5 patients). Two patients died too early to be evaluable for chronic GVHD (day 56, and day 70 after allograft). Extensive chronic GVHD occurred in 43 of 58 evaluable patients (74%), 9 patients had limited cGVHD (16%) and 6 patients had no cGVHD (10%). Best responses achieved post-allogeneic transplant were 41% CR and 7% PR and 37% stable disease (SD). At the time of analysis, 30 patients were alive and 14 of these were in remission.

Overall and Progression-free Survivals

OS was 61% (CI: 0.53, 0.68) at 5 years and 60% (CI: 0.52, 0.67) at 7 years, and PFS was 37% (CI: 0.32, 0.41) at 5 years and 31% (CI: 0.27, 0.34) at 7 years (Figure 1A, B). For auto-allo patients, 7-year OS and PFS were 69% and 30%, and for flu-mel patients OS was 42% and PFS was 21%. Both OS and PFS were superior in patients who were in at least PR at the time of transplant, with 7-year OS rates of 91% (CI: 0.57, 0.98) for CR, 63% (CI: 0.50, 0.73) for PR, and 40% (CI: 0.32, 0.48) in non-responders ($P=0.01$). Seven-year PFS rates of 60% (CI 0.40, 0.76), 29% (CI 0.24, 0.34) and 17% (0.14, 0.20) were seen in patients with CR, PR, and non-responders, respectively ($P=0.01$). Furthermore, 7-year OS and PFS were better in the patients who received allograft within one year from diagnosis: 75% (CI: 0.62, 0.84) and 37% (CI: 0.31, 0.43) compared to 37% (CI: 0.30, 0.44) and 20% (CI: 0.18, 0.24) for those transplanted more than one year from diagnosis ($P=0.002$ for OS, $P=0.034$ for PFS).

In the multivariate analysis (Table III), improved OS was significantly associated with the presence of chronic GVHD [HR: 0.26 (CI: 0.09, 0.74) $P=0.01$], and disease status (SD/PD) was significantly associated with poorer OS [HR: 2.85 (CI: 1.24, 6.58) $P=0.01$]. Likewise, for PFS, disease status (SD/PD) [HR: 2.31 (CI: 1.18, 4.51) $P=0.01$] was independently predictive of a worse outcome.

Relapse and Non-relapse Mortality

Thirty patients died: 23 of disease progression or relapse, and 7 from transplant-related complications. Figure 2 plots the cumulative incidence of relapse and non-relapse mortality. For all 60 patients, 1-year non-relapse mortality (NRM) was 8.3% (CI: 0.03, 0.19) and both 5- and 7-year NRM were 12% (CI: 0.06, 0.23). In the auto-allo group and the flu-mel groups, 1-year incidence of NRM was 8% (CI: 0.02, 0.22) and 10% (CI: 0.02–0.32), respectively. The cumulative incidence of relapse was 53% (CI: 0.4, 0.65) at five years and

59% (CI: 0.46, 0.71) at 7 years for the total group of 60 patients. Relapse incidence at 7 years for auto-allo patients was 54% (CI: 0.38, 0.69) and for flu-mel was 67% (CI: 0.43, 0.84).

Of the 38 patients whose disease relapsed post-allogeneic transplant, 6 had extramedullary (EM) disease. Thirty of the relapsed patients subsequently received salvage therapy with novel agents (bortezomib, lenalidomide, thalidomide). There were six very late relapses, occurring at 6.5, 6.7, 7.0, 7.5, 9.7 and 11.5 years post-allogeneic transplant, none of which were extramedullary. Table IV provides disease and treatment details on the 6 late-relapse patients. Five of these patients received the tandem auto-allo regimen and one received flu-mel. For all 6 late-relapse patients the transplant was performed upfront with a median time from diagnosis of 11 months (range 4.4–14 months). One patient was in CR, 4 in PR and one was in relapse at the time of transplantation. Cytogenetic risk for all patients on whom data is available (5/6) was standard, with normal karyotypes.

DISCUSSION

Despite advances in the treatment of multiple myeloma, including novel agents and autologous HCT, the disease remains largely incurable. Both autologous and allogeneic transplantation have been shown to improve long-term survival (Attal, *et al* 1996, Child, *et al* 2003), with lower relapse rates for allo-HCT compared to auto-HCT (Bjorkstrand, *et al* 2009, Bjorkstrand, *et al* 1996). Molecular remission, which predicts for improved survival, has also been observed more commonly after allogeneic transplant (Corradini, *et al* 2003, Corradini, *et al* 1999). Standard myeloablative allogeneic transplantation is limited by the high transplant-related morbidity and mortality; however, in patients who survive, standard myeloablative allogeneic transplant may offer long-term disease control and, possibly, cure (Barlogie, *et al* 2006, Bensinger, *et al* 1996, Bird, *et al* 1993, Tricot, *et al* 1996).

The rationale for development of reduced intensity or non-myeloablative conditioning regimens was based on reducing transplant-related mortality in an elderly myeloma population via less intense conditioning regimens, while maintaining the immune anti-myeloma effect of the allograft. Although initial reports of RIC allograft have suggested improved outcomes, most studies have short median follow-up of only 2 to 5 years.

An initial retrospective analysis by the EBMT in 229 multiple myeloma patients who underwent reduced intensity allogeneic transplant with heterogeneous conditioning regimens, including the auto-allo graft approach, reported 3-year OS and PFS rates of 41% and 21%, respectively (Crawley, *et al* 2005). Similar to our results, they observed that disease status of CR or PR at transplant is associated with better survival outcomes. They also reported an improvement in OS and PFS with development of chronic GVHD. In our study, the occurrence of chronic GVHD was also significantly associated with improved OS.

A more recent study by the EBMT registry compared RIC to a standard myeloablative conditioning allogeneic transplant (Crawley, *et al* 2007). The two groups differed in prognostic parameters such as age, time from diagnosis and number of previous autologous stem cell transplants. Despite a lower TRM rate in the RIC group (24% in the RIC vs. 37% in the standard) there was no statistically significant difference in OS due to the higher relapse rate in the RIC group (54% in the RIC vs. 27% in the standard).

There are limited long-term follow-up data on RIC allograft for myeloma; three studies have a median follow-up of approximately 6 years. Shimoni *et al.* (2010) retrospectively reported on 50 relapsed or refractory patients undergoing fludarabine and melphalan RIC allo-HCT, showing a plateau in the PFS curve after 3 years, with 34% of patients alive and 26% progression-free at 7 years post-transplantation. Another study included only patients treated

upfront with auto-allo and demonstrated a 5-year OS of 64% and PFS of 36% (Rotta, *et al* 2009). Lokhorst *et al.*(2012) compared upfront auto-allo-HCT to auto-HCT followed by maintenance therapy in patients without available allogeneic donors. The OS was 55% at 6 years in both of the study arms and PFS was 28% for auto-allo-HCT and 22 % for auto-HCT patients, with no plateau in OS or PFS for either group (Lokhorst, *et al* 2012).

In this report with a median follow-up of 9.8 years, we demonstrate an OS of 60% and PFS of 31% at 7 years, for patients undergoing RIC allogeneic transplant. The 3-year OS and PFS for both of the EBMT registry studies (Crawley, *et al* 2007, Crawley, *et al* 2005) is approximately 40% and 20%, respectively. The higher OS and PFS in our study can be explained by the use of T-replete allografts, widespread use of novel agents post-relapse, a patient population with fewer failed prior transplants, and a shorter median time from diagnosis to allograft as compared to the EBMT population. The relapse incidence for our cohort was high, 59% at 7 years, similar to that seen in the EBMT registry study at 3 years (Crawley, *et al* 2007). Furthermore, we saw no plateau in the relapse incidence curve and late relapses continued to occur, even as late as 11.5 years post-transplant. In fact 10% of this cohort experienced a relapse more than 6 years post-allogeneic transplantation. As a result there was also no plateau in OS or PFS. For both OS and PFS, disease status of CR/PR at transplant was significantly associated with better outcomes by multivariate analysis. The presence of chronic GVHD was also independently associated with improved OS.

The six late-relapse patients (>6 years post-transplant) did not have obviously high-risk features pre-transplant; all 6 were transplanted within 14 months of diagnosis, 5 were in CR or PR, and all 5 patients with available cytogenetic data had normal karyotypes. The phenomenon of late relapses in this study may suggest the presence of heterogeneous malignant clones that survived RIC and arose after a long period of dormancy. In paediatric acute lymphoblastic leukaemia, in which late relapses are also reported, multiple genetic subclones of leukaemia-initiating cells have been identified (Anderson, *et al* 2011, Jan and Majeti 2012, Mullighan, *et al* 2008). Recently in multiple myeloma, the Mayo Clinic group has demonstrated the existence of multiple disease clones and alternating clonal dominance in sequential myeloma patient samples (Keats, *et al* 2012).

It is possible that late relapses might be avoided by use of a more intensified conditioning regimen; however, as myeloma patients tend to be elderly, this is impractical. Rather than traditional regimen intensification, incorporation of novel agents, immunotherapy, or targeted radiation technologies as part of conditioning and/or post-transplant maintenance therapy are more logical approaches for the future. A recent report by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) using lenalidomide as maintenance therapy after non-myeloablative allogeneic HCT showed improvement of responses in 37% of patients; however, 47% of patients had to discontinue treatment due to acute GVHD (Kneppers, *et al* 2011). Our group is currently investigating the role of bortezomib and total marrow irradiation as part of the allogeneic conditioning regimen (clinicaltrials.gov # NCT01163357).

Due to the very long follow-up in this study, we have made the novel observation that 10% of patients experienced very late disease relapse after reduced intensity allogeneic transplantation, with no plateau in survival curves. Long-term follow-up of large patient cohorts/registries, as well as analysis of pre-treatment and post-relapse specimens from tissue banks, are needed to determine the incidence of late relapse, factors associated with its occurrence, and its clonality relative to the original disease. In the current era of combination novel agent induction therapy, the relevance of allogeneic HCT as a curative therapy for multiple myeloma is an open question, requiring further investigation.

Acknowledgments

We would like to thank the nurses, research, and administrative staff of City of Hope for their dedication to the patients, and their support of this research.

Funding: This work was supported by grants from the NIH: PO1 CA 30206 and P30 CA33572.

References

- Anderson K, Lutz C, van Delft FW, Bateman CM, Guo Y, Colman SM, Kempinski H, Moorman AV, Titley I, Swansbury J, Kearney L, Enver T, Greaves M. Genetic variegation of clonal architecture and propagating cells in leukaemia. *Nature*. 2011; 469:356–361. [PubMed: 21160474]
- Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, Casassus P, Maisonneuve H, Facon T, Ifrah N, Payen C, Bataille R. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med*. 1996; 335:91–97. [PubMed: 8649495]
- Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, Monconduit M, Hulin C, Caillot D, Bouabdallah R, Voillat L, Sotto JJ, Grosbois B, Bataille R. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2003; 349:2495–2502. [PubMed: 14695409]
- Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, McCoy J, Moore DF Jr, Dakhil SR, Lanier KS, Chapman RA, Cromer JN, Salmon SE, Durie B, Crowley JC. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *Journal of Clinical Oncology*. 2006; 24:929–936. [PubMed: 16432076]
- Bensinger WI, Buckner CD, Anasetti C, Clift R, Storb R, Barnett T, Chauncey T, Shulman H, Appelbaum FR. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood*. 1996; 88:2787–2793. [PubMed: 8839877]
- Bensinger WI, Maloney D, Storb R. Allogeneic hematopoietic cell transplantation for multiple myeloma. *Seminars in Hematology*. 2001; 38:243–249. [PubMed: 11486312]
- Bird JM, Russell NH, Samson D. Minimal residual disease after bone marrow transplantation for multiple myeloma: evidence for cure in long-term survivors. *Bone Marrow Transplantation*. 1993; 12:651–654. [PubMed: 8136748]
- Bjorkstrand BB, Ljungman P, Svensson H, Hermans J, Alegre A, Apperley J, Blade J, Carlson K, Cavo M, Ferrant A, Goldstone AH, de Laurenzi A, Majolino I, Marcus R, Prentice HG, Remes K, Samson D, Sureda A, Verdonck LF, Volin L, Gahrton G. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood*. 1996; 88:4711–4718. [PubMed: 8977265]
- Bjorkstrand B, Iacobelli S, Hegenbart U, Gruber A, Greinix HT, Volin L, Narni F, Musto P, Beksac M, Bosi A, Niederwieser D, Gahrton G. Autologous stem cell transplantation (ASCT) versus ASCT followed by reduced-intensity conditioning (RIC) allogeneic SCT with identical sibling donor in previously untreated multiple myeloma (MM): a prospective controlled trial by the EBMT. *Bone Marrow Transplantation*. 2009; 43:s31.
- Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, Gertz M, Giral S, Jagannath S, Vesole D. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *British Journal of Haematology*. 1998; 102:1115–1123. [PubMed: 9753033]
- Cavo M, Tosi P, Zamagni E, Cellini C, Tacchetti P, Patriarca F, Di Raimondo F, Volpe E, Ronconi S, Cangini D, Narni F, Carubelli A, Masini L, Catalano L, Fiacchini M, de Vivo A, Gozzetti A, Lazzaro A, Tura S, Baccarani M. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *Journal of Clinical Oncology*. 2007; 25:2434–2441. [PubMed: 17485707]

- Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, Brown J, Drayson MT, Selby PJ. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med*. 2003; 348:1875–1883. [PubMed: 12736280]
- Corradini P, Voena C, Tarella C, Astolfi M, Ladetto M, Palumbo A, Van Lint MT, Bacigalupo A, Santoro A, Musso M, Majolino I, Boccadoro M, Pileri A. Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. *Journal of Clinical Oncology*. 1999; 17:208–215. [PubMed: 10458235]
- Corradini P, Cavo M, Lokhorst H, Martinelli G, Terragna C, Majolino I, Valagussa P, Boccadoro M, Samson D, Bacigalupo A, Russell N, Montefusco V, Voena C, Gahrton G. Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. *Blood*. 2003; 102:1927–1929. [PubMed: 12738666]
- Crawley C, Lalancette M, Szydlo R, Gilleece M, Peggs K, Mackinnon S, Juliusson G, Ahlberg L, Nagler A, Shimoni A, Sureda A, Boiron JM, Einsele H, Chopra R, Carella A, Cavenagh J, Gratwohl A, Garban F, Zander A, Bjorkstrand B, Niederwieser D, Gahrton G, Apperley JF. Outcomes for reduced-intensity allogeneic transplantation for multiple myeloma: an analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT. *Blood*. 2005; 105:4532–4539. [PubMed: 15731182]
- Crawley C, Iacobelli S, Bjorkstrand B, Apperley JF, Niederwieser D, Gahrton G. Reduced-intensity conditioning for myeloma: lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. *Blood*. 2007; 109:3588–3594. [PubMed: 17158231]
- Gahrton G, Svensson H, Cavo M, Apperley J, Bacigalupo A, Bjorkstrand B, Blade J, Cornelissen J, de Laurenzi A, Facon T, Ljungman P, Michallet M, Niederwieser D, Powles R, Reiffers J, Russell NH, Samson D, Schaefer UW, Schattenberg A, Tura S, Verdonck LF, Vernant JP, Willemze R, Volin L. Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983–93 and 1994–8 at European Group for Blood and Marrow Transplantation centres. *British Journal of Haematology*. 2001; 113:209–216. [PubMed: 11360893]
- Jan M, Majeti R. Clonal evolution of acute leukemia genomes. *Oncogene*. 2012 Epub ahead of print. 10.1038/onc.2012.48
- Kapoor P, Fonseca R, Rajkumar SV, Sinha S, Gertz MA, Stewart AK, Bergsagel PL, Lacy MQ, Dingli DD, Ketterling RP, Buadi F, Kyle RA, Witzig TE, Greipp PR, Dispenzieri A, Kumar S. Evidence for cytogenetic and fluorescence in situ hybridization risk stratification of newly diagnosed multiple myeloma in the era of novel therapies. *Mayo Clinic Proceedings*. 2010; 85:532–537. [PubMed: 20511484]
- Keats JJ, Chesi M, Egan JB, Garbitt VM, Palmer SE, Braggio E, Van Wier S, Blackburn PR, Baker AS, Dispenzieri A, Kumar S, Rajkumar SV, Carpten JD, Barrett M, Fonseca R, Stewart AK, Bergsagel PL. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012; 120:1067–1076. [PubMed: 22498740]
- Kneppers E, van der Holt B, Kersten MJ, Zweegman S, Meijer E, Huls G, Cornelissen JJ, Janssen JJ, Huisman C, Cornelisse PB, Bruijnen CP, Emmelot M, Sonneveld P, Lokhorst HM, Mutis T, Minnema MC. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. *Blood*. 2011; 118:2413–2419. [PubMed: 21690556]
- Kroger N, Perez-Simon JA, Myint H, Klingemann H, Shimoni A, Nagler A, Martino R, Alegre A, Tomas JF, Schwerdtfeger R, Kiehl M, Fauser A, Sayer HG, Leon A, Beyer J, Zabelina T, Ayuk F, San Miguel JF, Brand R, Zander AR. Relapse to prior autograft and chronic graft-versus-host disease are the strongest prognostic factors for outcome of melphalan/fludarabine-based dose-reduced allogeneic stem cell transplantation in patients with multiple myeloma. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2004; 10:698–708. [PubMed: 15389436]
- Lokhorst HM, van der Holt B, Cornelissen JJ, Kersten MJ, van Oers M, Raymakers R, Minnema MC, Zweegman S, Janssen JJ, Zijlmans M, Bos G, Schaap N, Wittebol S, de Weerd O, Ammerlaan R, Sonneveld P. Donor versus no-donor comparison of newly diagnosed myeloma patients included in the HOVON-50 multiple myeloma study. *Blood*. 2012; 119:6219–6225. [PubMed: 22442350]

- Maloney DG, Molina AJ, Sahebi F, Stockerl-Goldstein KE, Sandmaier BM, Bensinger W, Storer B, Hegenbart U, Somlo G, Chauncey T, Bruno B, Appelbaum FR, Blume KG, Forman SJ, McSweeney P, Storb R. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood*. 2003; 102:3447–3454. [PubMed: 12855572]
- Mullighan CG, Phillips LA, Su X, Ma J, Miller CB, Shurtleff SA, Downing JR. Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. *Science*. 2008; 322:1377–1380. [PubMed: 19039135]
- Munshi NC, Anderson KC, Bergsagel PL, Shaughnessy J, Palumbo A, Durie B, Fonseca R, Stewart AK, Harousseau JL, Dimopoulos M, Jagannath S, Hajek R, Sezer O, Kyle R, Sonneveld P, Cavo M, Rajkumar SV, San Miguel J, Crowley J, Avet-Loiseau H. on behalf of the International Myeloma Workshop Consensus Panel 2. Consensus recommendations for risk stratification in multiple myeloma: report of the International Myeloma Workshop Consensus Panel 2. *Blood*. 2011; 117:4696–4700. [PubMed: 21292777]
- Rotta M, Storer BE, Sahebi F, Shizuru JA, Bruno B, Lange T, Agura ED, McSweeney PA, Pulsipher MA, Hari P, Maziarz RT, Chauncey TR, Appelbaum FR, Sorrow ML, Bensinger W, Sandmaier BM, Storb RF, Maloney DG. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. *Blood*. 2009; 113:3383–3391. [PubMed: 19015394]
- Shimoni A, Hardan I, Ayuk F, Schilling G, Atanackovic D, Zeller W, Yerushalmi R, Zander AR, Kroger N, Nagler A. Allogenic hematopoietic stem-cell transplantation with reduced-intensity conditioning in patients with refractory and recurrent multiple myeloma: long-term follow-up. *Cancer*. 2010; 116:3621–3630. [PubMed: 20564132]
- Tricot G, Vesole DH, Jagannath S, Hilton J, Munshi N, Barlogie B. Graft-versus-myeloma effect: proof of principle. *Blood*. 1996; 87:1196–1198. [PubMed: 8562947]

Figure 1. Survival Probabilities

For both panels survival probability was calculated using the Kaplan-Meier method. Time from transplant is shown in years. Tick-marks indicate censoring. **Panel A** shows overall survival. **Panel B** shows progression-free survival.

Figure 2. Cumulative Incidence of Relapse and Non-relapse Mortality (NRM)

Cumulative incidence of relapse/progression and non-relapse mortality were calculated as competing risks. Time from transplant is shown in years. The cumulative incidence of relapse/progression curve is shown by the solid line and the cumulative incidence of non-relapse mortality curve is indicated by the dashed line.

Table I

Patient characteristics (N = 60)

Variable	N (%) and/or median (range)
Age at transplant (years)	51.0 (32.3, 66.1)
Less than 50 years	27 (45%)
50 years or older	33 (55%)
Time from diagnosis to transplant (months)	9.5 (0.8, 127.0)
Less than one year	36 (60%)
One year or more	24 (40%)
Disease stage at diagnosis (Durie-Salmon)	
Stage I	8 (13%)
Stage II	10 (17%)
Stage III	42 (70%)
Gender	
Female	20 (33%)
Male	40 (67%)
Gender match: donor→recipient	
Other	37 (62%)
Female donor→male recipient	23 (38%)
Stem cell source	
Bone marrow	2 (3%)
Peripheral blood stem cell	58 (97%)
Donor type	
Sibling donor	55 (92%)
Matched unrelated donor	5 (8%)
Disease status at transplant	
Complete remission (CR)	11 (18%)
Partial remission (PR)	27 (45%)
Stable disease/no response (SD)	8 (13%)
Relapse/Progressive disease (PD)	14 (23%)
Beta-2 microglobulin (at transplant), mg/l	1.9 (0.8, 10.0)
> 3.5 mg/l	6 (10%)
3.5 mg/l	53 (90%)
Missing	1
Cytogenetic risk stratification (at transplant)	
Standard-risk *	49 (82%)
High-risk **	4 (7%)

Variable	N (%) and/or median (range)
Unknown	7 (11%)
Prior chemotherapy	
Usual	38 (63%)
Novel	22 (37%)
Treatment Regimen	
Auto-allo tandem	39 (65%)
Flu-mel	21 (35%)

* Standard-risk = lack of all high-risk abnormalities

** High-risk = detection of -13 or del(13q); t(4;14)/*FGFR3/IGH* fusion or t(14;16)/*MAF/IGH* fusion; del(17p)/*TP53* loss by conventional cytogenetic or fluorescence in-situ hybridization analyses.

Table II

Patient outcomes

Outcome	Median (range) or N (%)
Best response to transplant	
Complete remission (CR)	25 (41%)
Partial remission (PR)	4 (7%)
Relapse/Progression (PD)	9 (15%)
Stable disease/No response (SD)	22 (37%)
Relapse	
Yes	38 (63.3%)
No	22 (36.7%)
Relapse location	
Bone marrow (BM)	32
Extramedullary (EM)	6
Vital status	
Dead	30 (50%)
Alive	30 (50%)
Cause of Death	
Disease progression	23
Organ failure	2
aGVHD	1
cGVHD	3
Infection	1
Median survival (years)	
All patients	6.6 (0.3, 12.0)
Alive	9.8 (3.8, 12.0)
Dead	1.4 (0.3, 11.3)

aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease

Table III

Multivariate Cox-regression analysis

Variable	Overall Survival		Progression-Free Survival	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Disease status 1CR/1PR	Baseline		Baseline	
Disease status SD/PD	2.85 (1.24, 6.58)	0.01	2.31 (1.18, 4.51)	0.01
cGVHD no	Baseline		Baseline	
cGVHD yes	0.26 (0.09, 0.74)	0.01	0.42 (0.15, 1.16)	0.09
aGVHD Grade 0, I	Baseline		NA	
aGVHD Grade II, III, IV	2.04 (0.97, 4.30)	0.06	NA	NA
Treatment arm (Auto-allo)	NA		Baseline	
Treatment arm (Flu-mel)	NA	NA	1.78 (0.94, 3.38)	0.08
Disease stage (I,II)	NA		Baseline	
Disease stage (III)	NA	NA	1.72 (0.86, 3.44)	0.13

Cox-regression analysis was carried out by forcing the variable disease status into the model, and allowing all other covariates to be forward selected using $P=0.2$ as the entry criteria.

Auto-allo = tandem autologous allogeneic transplant, Flu-mel = fludaribine and melphalan allogeneic transplant, 1CR = first complete remission, 1PR = first partial remission, SD = stable disease, PD = progression/relapsed disease, NA = not applicable as this variable was not selected by this model. 95% CI, 95% confidence interval.

Table IV

Late Relapses

Pt	Time (years) HCT to Relapse	Conditioning Regimen	Novel Agents Pre-allo or Post-relapse	Time (months) Dx to HCT	Disease Status at HCT	Pre-HCT Karyotype	Outcome
1	6.5	Auto-allo	Post	7.39	CR	Normal	Alive
2	6.8	Auto-allo	None	8.48	PD	Normal	Alive
3	7.0	Auto-allo	Post	13.60	PR	Normal	Alive
4	7.5	Flu-mel	Pre and Post	4.47	PR	NA	Alive
5	9.7	Auto-allo	Post	14.09	PR	Normal	Alive
6	11.5	Auto-allo	None	13.54	PR	Normal	Alive

Pt = patient, allo = allograft, Auto-allo = tandem autologous allogeneic transplant, Flu-mel = fludarabine and melphalan allogeneic transplant, NA=not available, HCT=haematopoietic cell transplant, Dx=diagnosis, CR=complete response, PD=relapse/progression, PR=partial response