Long-Term Follow-Up of a Donor versus No-Donor Comparison in Patients with Multiple Myeloma in First Relapse after Failing Autologous Transplantation

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Abstract

We report the long-term clinical outcomes of a retrospective multicentre study that enrolled 169 multiple myeloma (MM) patients at first relapse after failing autologous stem cell transplantation (SCT). After HLA-typing at relapse, 79 patients with a suitable donor, 72 (91%) of whom eventually underwent salvage allogeneic SCT, were compared with 90 patients without a donor who were treated with multiple lines of salvage treatment with bortezomib and/or immune modulating agents. At a median follow-up of 30 months (range 1-280) for all patients and 110 months (range 3-280) for surviving patients, 7-year progression free survival (PFS) was 18% in the donor group and 0% in the no-donor group (hazard ratio [HR] 2.495; 95% CI, 1.707-3.517; p<0.0001). Seven-year overall survival (OS) was 31% in the donor group and 9% in the no-donor group (HR 1.835; 95% CI, 1.302-2.577; p<0.0001). By multivariate analysis, chemosensitivity to salvage treatments and presence of a suitable donor significantly associated with better PFS and OS. The long term follow-up of this study confirms the significant PFS benefit and provides new evidence of an OS advantage for MM patients who have a suitable donor and undergo allogeneic SCT. Allogeneic SCT should be considered as a treatment option in young relapsed patients with high-risk disease features after first-line treatment.

Highlights:

- These are the long-term results of a donor vs no donor comparison in multiple myeloma patients at first relapse after autologous stem cell transplantation (SCT).
- A significant benefit of progression free survival and overall survival was shown in the donor group at a median follow-up of 110 months.
- This study suggests that allogeneic SCT could be an option in young patients with high-risk relapse after first-line treatment.

Median follow-up after the beginning of salvage treatment was 30 months (range 2-180) in all patients and 110 months (range 13-180) in surviving patients. Seven-year PFS was 18% in the “donor” group and in the “no donor” group (hazard ratio [HR] 0.517; p<0.0001). Seven-year OS was in the “donor” group and “no donor” group (HR 1.835; 95% CI, 1.306-2.577; p<0.0001). Significant variables (p≤0.10) which were associated with PFS by univariate proportional hazards model were absence of a suitable donor, high-risk karyotype, duration of salvage treatment and failure to achieve at least PR before allo-SCT. Those associated with OS were older age, absence of a suitable donor, high-risk karyotype and resistance to salvage treatment before allo-SCT. By multivariate analysis, resistance to salvage treatment and absence of a donor significantly reduced both PFS and OS (PFS: HR 2.243; 95% CI, 1.182-4.200; p=0.011; HR 2.311; 95% CI, 1.278-4.178; p=0.006, respectively. OS: HR 2.007; 95% CI, 1.098-3.668; p=0.024; HR 1.891; 95% CI, 1.087-3.289; p=0.024, respectively).

A total of 72 out of 79 patients (91%) with a donor eventually underwent allo-SCT. Cumulative incidence of NRM at 5 years was 27%. Grade II-IV acute GVHD developed in 24 patients (33%) and chronic GVHD was seen in 43 out of 66 evaluable patients (65%). Chronic GVHD was graded (NIH criteria) as follows: limited in 20 patients, moderate and severe in 16 and 7 patients, respectively. Estimated 7-year PFS and OS were 20% and 35%, respectively. At last follow-up, 12 patients (17%) are alive and in persistent clinical remission, 4 (33%) of them with limited chronic GVHD but off immunosuppression and good quality of life. Six other patients are long-term survivors though relapse occurred at a median of 77 months (range 8-129) and were rescued with new drugs with the addition of donor lymphocyte infusions in 2 patients.

By univariate analysis, failure to obtain at least PR before allo-SCT was the only significant variable associated with worse PFS (HR 2.976; 95% CI, 1.304-6.792; p=0.010), while bone marrow as stem cell source was associated with worse OS (HR 2.470; 95% CI, 1.51-2.126; p=0.010). Donor type and development of acute and chronic GVHD had no significant impact on either PFS or OS.

Discussion

The first analysis of the present study was performed at a median follow-up of 29 months. Though the donor group showed a significantly longer PFS as compared with the no donor group, 2-year OS were similar (54% vs 53%, respectively). In the current updated analysis, at a median follow-up of 110 months for surviving patients, not only PFS but also OS were significantly better in the donor group. Other studies previously suggested that a long-follow up might be necessary to

observe a potential survival advantage of allo-SCT over other treatments in MM, mainly due to a prolonged graft-vs.-myeloma (GvM) effect and/or a synergy with salvage treatments. The EBMT study (10) comparing outcomes between donor and no donor groups in newly diagnosed MM showed that a follow-up longer than 5 years was required to highlight the superior outcome of the donor group given that early NRM related to allo-SCT could initially cancel the effects of GvM. Moreover, the EBMT trial along with the GITMO study (11, 12) reported a significantly longer OS from the time of first relapse in allo-SCT patients as compared with auto-SCT patients. These findings may mostly be due to a synergy between GvM and new drugs in long-term survivors after allo-SCT. In our study, rates of continuous complete remissions were low in both donor group and allo-SCT patients (18% and 20% at 7 years after SCT, respectively) and PFS curves did not show a clear plateau indicating late MM relapses. Nonetheless, it is important to point out that these clinical outcomes were achieved with drugs and treatment strategies used longer than 10 years ago and mostly considered presently outdated. In fact, most patients underwent first auto-SCT before 2004; thus they could not benefit from bortezomib-based induction and maintenance after transplant. At that time, salvage treatment of first relapse was thalidomide-based for 44% of patients and lenalidomide-based in only 16% of patients and its use was protracted for a short period (median 5 months). Our study confirmed that the achievement of at least a partial response to first-line second treatment was the most important factor influencing PFS and OS; therefore, it can hypothesized that novel combinations of drugs including second-generation proteosoma inhibitors or monoclonal antibodies could improve quality of response after salvage and outcome after subsequent allo-SCT (13).

Some investigators suggest that the current role of allo-SCT should prospectively be evaluated at first relapse in young fit MM patients with high-risk clinical features, including early relapse, and/or poor prognosis cytogenetic abnormalities (14-16). In our analysis, we could not evaluate the impact of cytogenetics as data were incomplete in half of our patients mainly due to the fact that at the time of this study cytogenetic abnormalities were not routinely tested at all centers. Of note, time from auto-SCT to first relapse did not have a significant impact on clinical outcomes after allo-SCT, suggesting that GvM may overcome the unfavorable prognostic significance of early relapse. Most previous studies, that included reduced intensity conditioning and peripheral blood as stem cell source, reported significant mortality and morbidity due to chronic GVHD (17-18). In our case series overall and moderate-severe chronic GVHD rates were 65% and 32%, respectively, suggesting that this complication could contribute to increasing late NRM and impairing the survival benefit. However, the achievement of immunotolerance can be hypothesized in long-term survivors, since all our 12 surviving patients were off immunosuppression with good

quality of life though a persistent limited chronic GVHD in 4 of them.

We conclude that the long term follow-up of the study confirms the significant PFS benefit and provides evidence of an OS advantage of RIC-allo-SCT in relapsed MM patients who have a suitable donor, suggesting that allo-SCT could be an option in young patients with high-risk relapse after first-line treatment. However, allo-SCT allowed long-term MM control only in a small fraction of patients, indicating the need of achieving a deep response before the procedure and administering consolidation and maintenance after transplant. The availability of new immune modulatory agents and monoclonal antibodies targeting both myeloma and immune cells could help to design prospective trials in the near future.

LEGEND TO TABLES AND FIGURES

Table 1. Clinical characteristic of the 167 patients included in the study (*SCT: stem cell transplantation; high risk karyotype included either t (4:14), 17p deletion, or 13q deletion; CR: complete remission; VGPR: very good partial remission; PR: partial remission).*

Table 2. Characteristic of 72 allogeneic transplants (*TBI: total body irradiation; SCT: stem cell transplantation)*

Figure 1. Comparison of progression free survival (PFS) between donor- and no-donor groups ($p<0.0001$) by intent-to-treat analysis.

Figure 2. Comparison of overall survival (OS) between donor and no-donor groups ($p<0.0001$) by intent-to-treat analysis.

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***Table 1**

	Donor group	No donor group	p
N° pts	79	90	
Age at auto-SCT	55 (34-69)	59 (31-73)	**0.0001**
Kariotype Standard risk High-risk missing	 23/36 (64%) 13/36 (36%) 43	 17/32 (53%) 15/32 (47%) 58	 0.368
Time diagnosis-autoSCT, months median (range)	8 (3-115)	8 (2-119)	0.182
Auto-SCT year 2001-2003	 23/79 (29%) 22/79 (28%) 34/79 (43%)	 14/90 (16%) 39/90 (43%) 37/94 (41%)	 0.430
Tandem auto-SCT	48/79 (60%)	62/90 (69%)	0.215
Time auto-SCT-relapse, months median (range)	16 (2-88)	16 (2-54)	0.668
Treatment of relapse Thalidomide-based Bortezomib-based Lenalidomide-based Other drugs	 39/79 (52%) 25/79 (33%) 11/79 (9%) 4/79 (6%)	 35/90 (39%) 30/90 (33%) 16/90 (18%) 9/90 (10%)	 0.290
Treatment duration , months median (range)	5 (1-52)	5 (1-55)	0.278
Response to relapse treatmen CR+VGPR PR Resistance Progression missing	 24/64 (38%) 28/64 (43%) 7/64 (11%) 5/64 (8%) 15	 21/81 (26%) 27/81 (33%) 16/81 (20%) 17/81 (21%) 9	 **0.039**

***Table 2**

N° pts	72
Time diagnosis-alloSCT, months medina(range)	51 (9-204)
Donor HLA matched sibling Unrelated	 25 /72 (35%) 47/72 (65%)
Source Bone marrow Peripheral blood	 18/72 (24%) 54/72 (76%)
Conditioning regimen Fludarabine, melphalan ±thiotepa Fludarabine + 2 Gy TBI ± melphalan Fludarabine + other alkylating agents	 28/72 (39%) 27/72 (37%) 17/72 (24%)
Anti-thymoglobulin	24/72 (33%)

Figure 1

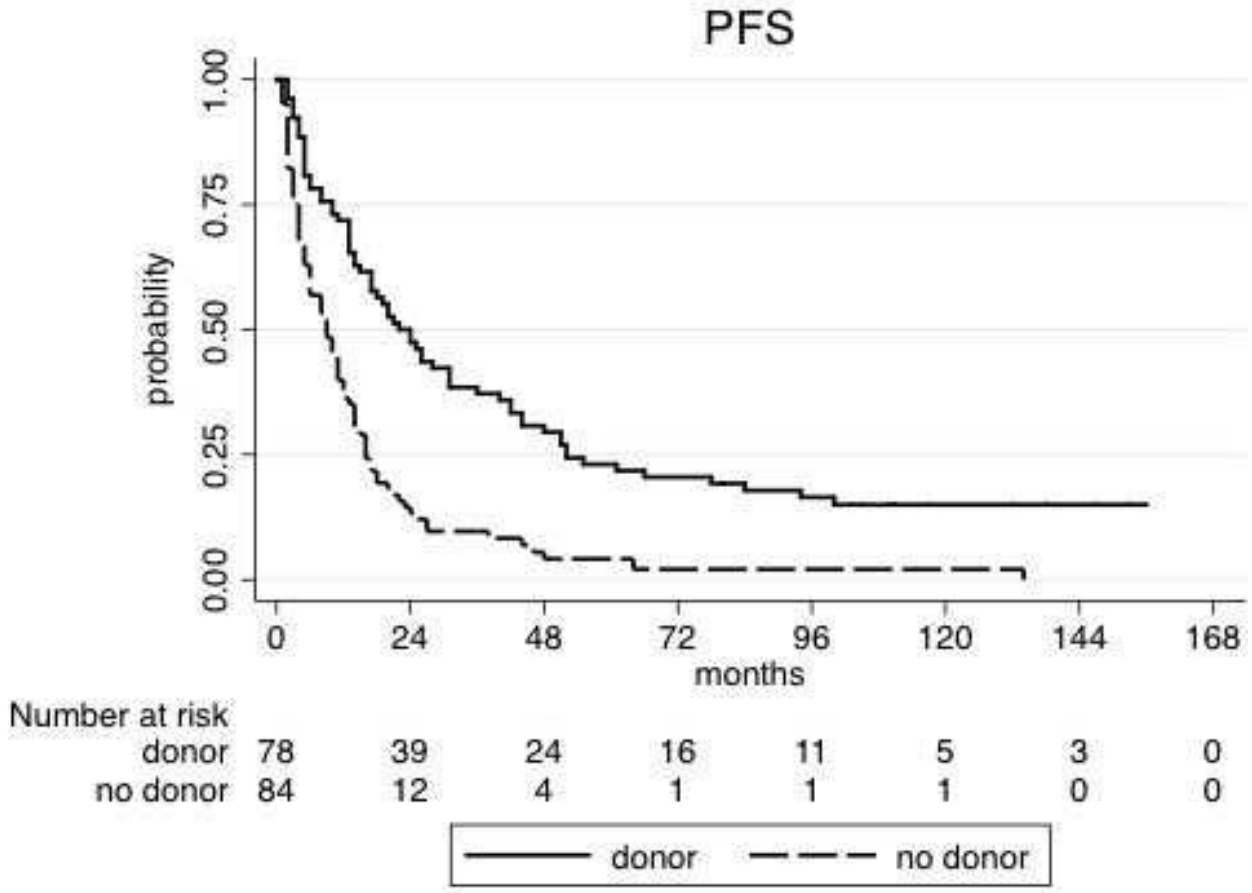

Figure 1

Figure 2

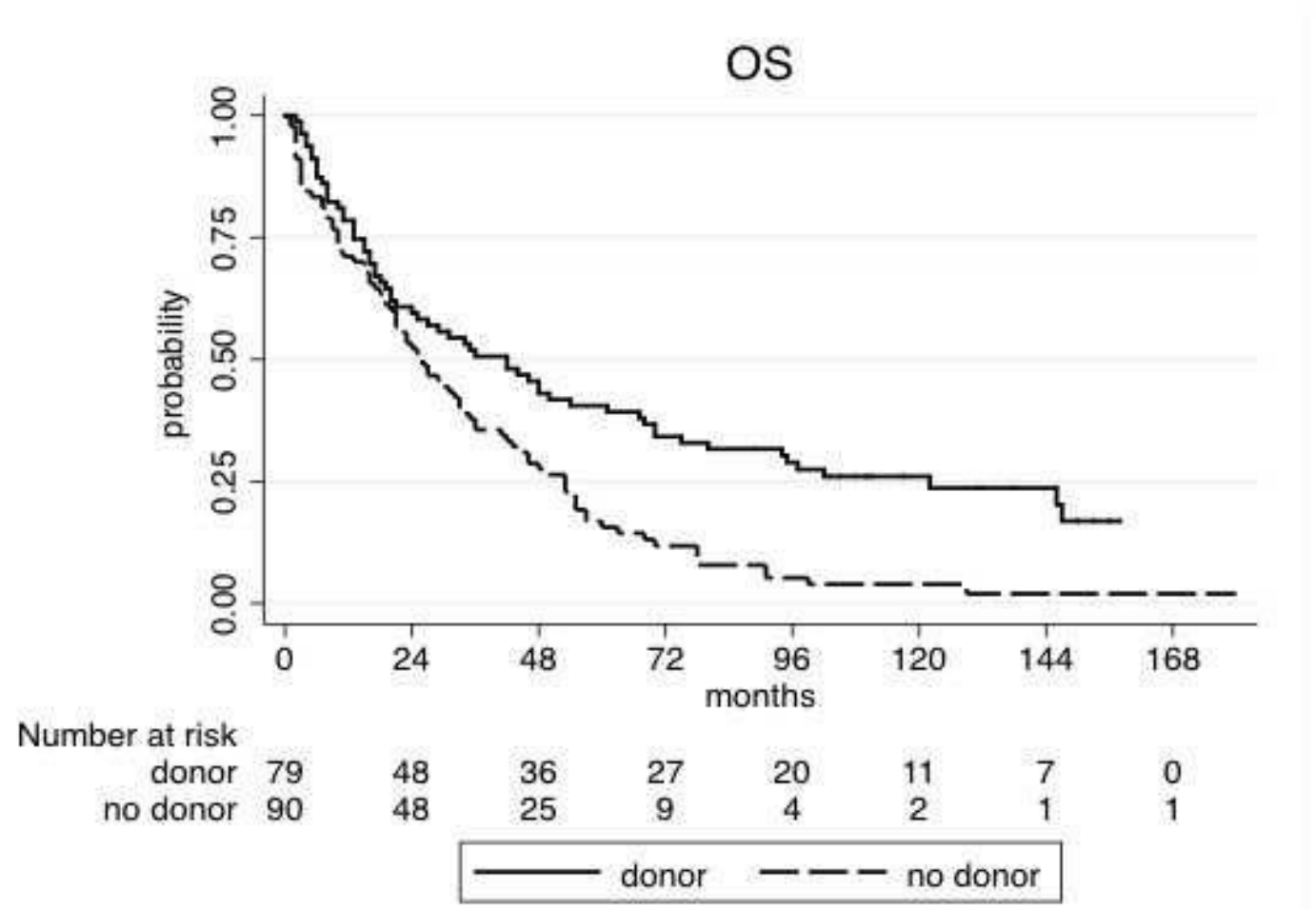

Figure 2