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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Long-term follow-up of a "donor" versus "no donor" comparison in multiple myeloma patients at first relapse after failing autologous transplantation

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long-term follow-up after allo-SCT in multiple myeloma

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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 2-180) for all patients and 110 months (range 38-180) 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, 1.770-3.517; 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, 1.306-2.577; p<0.0001). By multivariate analysis, chemo-sensitivity to salvage treatments and presence of a suitable donor were 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.

Introduction

Despite a tremendous expansion of the drug armamentarium for multiple myeloma (MM) in the past two decades, MM patients invariably relapse and mainly die of disease progression. Allogeneic hematopoietic stem cell transplantation (allo-SCT) from related and unrelated donors was mostly applied to young patients with relapsed MM in the early 2000'. Major limits of this approach were the high relapse rate, significant morbidity due to chronic GVHD and very low rates of long-term disease control, if any. These limitations led to a progressive reduction of the number of allo-SCT performed in relapsed MM patients in Europe (1). However, clinical results on allo-SCT in relapsed patients were biased by the retrospective nature of the analyses and the heterogeneity of patient cohorts including patients in different disease stages, with the predominance of heavily pre-treated patients. Moreover, most studies enrolled patients who had not been treated with "new drugs" or had incomplete data on salvage treatments (2-5). In 2011, we initially reported the clinical findings of a multicentre retrospective study (6) with an original design for the following points: a) all patients included were at first relapse after failing autologous stem cell transplantation (auto-SCT); b) patients received salvage treatment with "new drugs" 3) clinical outcomes between patients with and without a suitable HLA-matched donor were compared. Here, we present the long-term follow-up of the study showing a survival advantage for the transplanted patients.

Patients and methods

A multicentre retrospective study was conducted in 7 Haematology Centres between 2002 and 2008 and included patients who relapsed after first-line auto-SCT and were then treated with salvage therapy based on bortezomib and/or immune-modulating agents (thalidomide and lenalidomide). The study was designed by an intention-to-treat analysis and included only those patients who underwent HLA typing immediately after the relapse. One-hundred sixty-nine patients were enrolled. Overall, a total of 79 patients (47%) had a suitable donor and 90 (53%) did not. Seventy-two of the 79 patients with a donor (91%) underwent allo-SCT while 7 (9%) did not undergo the planned allo-SCT because of disease progression or severe comorbidities (table 1). In comparison with our first report (6), 4 additional patients found a donor and underwent allo-SCT. Donors were HLA-identical sibling (no. 25) or HLA-matched or single class I allele/antigen mismatched unrelated donors (no. 47). Fifty-four out of 72 patients (76%) received peripheral blood stem cells.

All conditioning regimens were fludarabine-based, with the addition of 2 Gy total body irradiation (TBI) (no. 27) or melphalan (no. 28) or other alkylating agents (no. 17). Anti-thymocyte globulin (ATG) was administered in 24 out of 47 (51%) unrelated donors (table 2). MM response and acute and chronic GVHD were evaluated according standard criteria (7-9).

Statistical analysis

The close-out date was December 2010 for the first analysis (6) and February 2017 for the present update. Patient status (alive/dead) was updated for all 169 patients while disease status (remission/progression) was collected for 162 as data were incomplete in 7 out of 169. Two analyses were performed: "donor" versus "no donor" group by intent-to-treat analysis; and patients who eventually completed the allo-SCT program versus those who received other treatments as by protocol. Non-relapse mortality (NRM), overall survival (OS), progression-free-survival (PFS) were defined as previously published (6). Comparison between groups were performed using the t test or Chi test, as required. OS and PFS curves were compared using Cox proportional hazard models. Multivariate stepwise analyses included all variables found to be significant at $P \leq .10$ by univariate analysis. Retention in the stepwise model required the variable be significant at $P \leq .05$ by multivariate analysis.

Results

Patient median age at the time of auto-SCT was 57 years (range 31-73). Karyotype was evaluated at diagnosis by FISH analysis in 68 out of 169 patients (40%). Twenty-eight out of 68 (41%) carried either t (4:14), 17p deletion, or 13q deletion. Ninety-eight patients (58%) performed auto-SCT before 2004 and 110 (65%) underwent tandem auto-SCT. Median time to first relapse from auto-SCT was 16 months (range 2-88). Salvage treatments included thalidomide-based regimens in 74 patients (44%), bortezomib-based in 55 patients (32%), lenalidomide-based in 27 patients (16%) and included other drugs in the remaining 13 patients (8%), without significant differences between the 2 groups. Median duration of salvage treatment was 5 months (range 1-55), response was observed in 100 patients (59%), 45 achieved complete remission (CR) or very good partial remission (VGPR) and 65 partial remission (PR). Clinical characteristics were well balanced between the "donor" versus the "no-donor groups" with the exception of younger median age and higher response rate to salvage treatment for the donor group (55 years versus 59, p=0.0001; CR+VGPR, PR and resistance rates of 38%, 43% and 19% versus vs 26%, 33%, 31%, p=0.039 respectively) (table2).

Median follow-up after the beginning of salvage treatment was 30 months (range 2-180) in all patients and 110 months (range 38-180) in surviving patients. Seven-year PFS was 18% in the "donor" group and 0% in the "no-donor" group (hazard ratio [HR] 2.495; 95% CI, 1.770-3.517; p<0.0001). Seven-year OS was 31% in the "donor" group and 9% in the "no-donor group" (HR 1.835; 95% CI, 1.306-2.577; p<0.0001). Significant variables ($p \leq .10$) 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, 1.200-4.189; 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, 1.156-5.262; 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 (10-12) 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 allo-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-line 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 it was protracted for a short period (median 5 months). Our study confirmed that the achievement of at least a partial response to second-line 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 deeper 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.

References

1. Sobh M, Michallet M, Gahrton G et al. Allogeneic hematopoietic cell transplantation for multiple myeloma in Europe: trends and outcomes over 25 years. A study by the EBMT Chronic Malignancies Working Party. Leukemia. 2016;30:2047-2054.
2. Kroger N, Shimoni A, Schilling G et al. Unrelated stem cell transplantation after a reduced intensity conditioning for patients with multiple myeloma relapsing after autologous tarnsplanattion. Br J Hemat 2010; 148: 323-331
3. Osman K, Elliott B, Mandeli J, et al. Non-myeloablative condi- tioning and allogeneic transplantation for multiple myeloma. Am J Hematol. 2010;85:249-254.
4. Efebera YA, Qureshi SR, Cole SM, et al. Reduced-intensity he- matopoietic stem cell transplantation for relapsed multiple my- eloma. Biol Blood Marrow Transplant. 2010;16:1122-1129.
5. Auner HW, Szydlo R, van Biezen A et alk Reduced intensity-conditioned allogeneic stem cell transplantation for multiple myeloma relapsing or progressing after autologous transplantation: a study by the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2013;48:1395-400
6. Patriarca F, Heisele H, Spina F et al. Allogeneic stem cell transplantation in multiple myeloma relapsed after autograft: amulticenter retrospective study based on donor availability Biol Blood Marrow Transplant. 2012 ; 18: 617-626
7. Durie BG, Harousseau JL, Miguel JS, et al., for the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467-1473.
8. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15:825-828.
9. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11:945-956.
10. Gahrton G[1], Iacobelli S, Björkstrand B et al EBMT Chronic Malignancies Working Party Plasma Cell Disorders Subcommittee. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood. 2013;121:5055-63.
11. Giaccone L, Storer B, Patriarca F, et al.: Long-term follow-up of a comparison of nonmyeloablative allografting with autografting for newly diagnosed myeloma. Blood 117:6721-6727, 2011
12. Giaccone L, Evangelista A, Patriarca F. et al. Upfront Tandem Auto-Allo Transplant in Multiple Myeloma: long-term follow-up and impact of “new drugs” at relapse. 16th International Myeloma Workshop New Delhi, India March 1-4, 2017 . PS 118
13. Patriarca F, Giaccone L, Onida F New drugs and allogeneic hematopoietic stem cell transplantation for hematological malignancies: do they have a role in bridging, consolidating or conditioning transplantation treatment? Expert Opin Biol Ther. 2017 Jul;17(7):821-836.

14. Giralt S, Garderet L, Durie B et al. American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma Biol Blood Marrow Transplant. 2015; 21: 2039–2051.

15. Laubach J, Garderet L, Mahindra A et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia. 2016;30:1005-17

16. Blade , Rosinol L, and de Larrea CF How I treat relapsed myeloma Blood 2015; 125: 1532-1540.

17. Arora M, Cutler CS, Jagasia MH et al. Late Acute and Chronic Graft-versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. 2016 Mar;22:449-55

18. Arai S, Arora M, Wang T, Spellman SR, He W, Couriel DR, et al. Increasing Incidence of Chronic Graft-versus-Host Disease in Allogeneic Transplantation - A Report from CIBMTR. Biol Blood Marrow Transplantation. 2015 ; 21 (266-274).

***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 ≤ 2000 2001-2003 ≥2004	 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 treatment 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

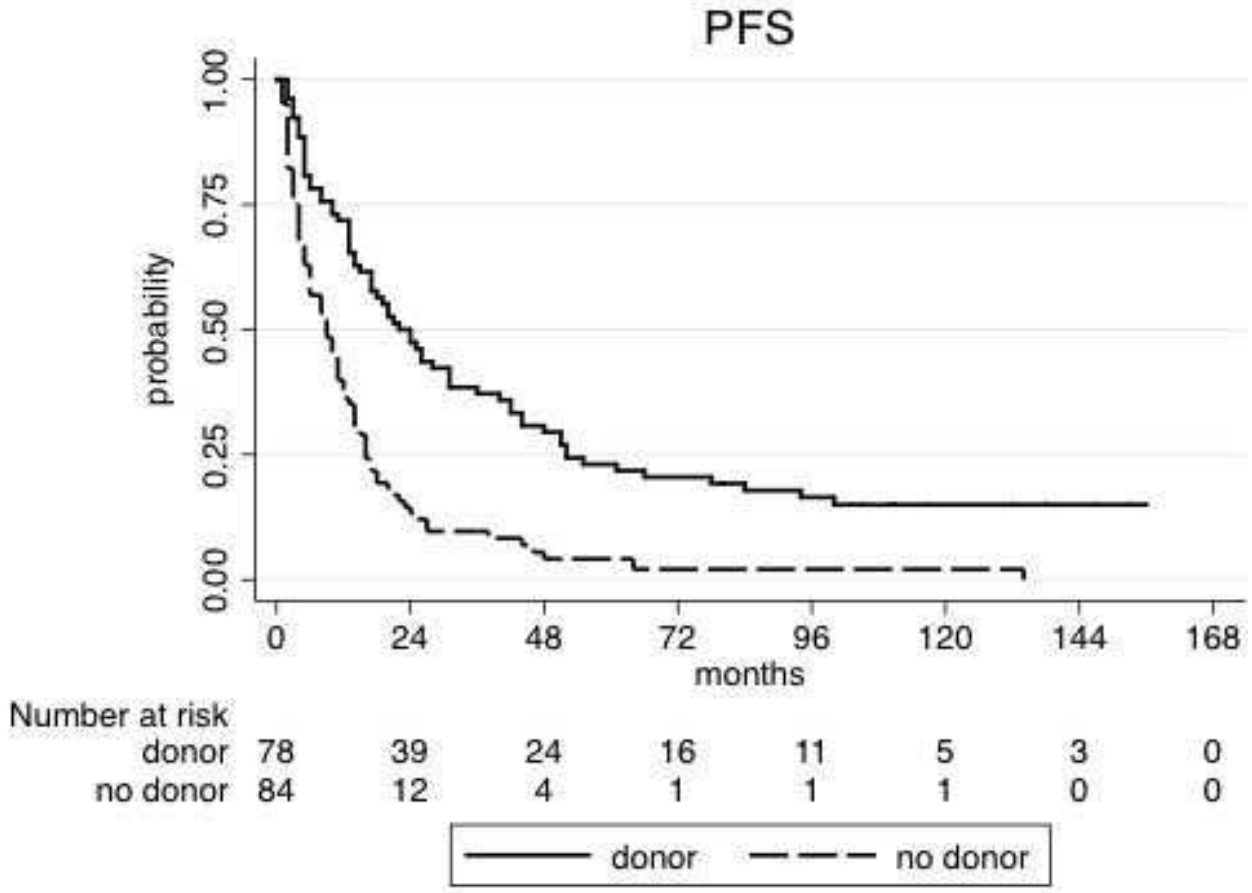

Figure 1

Figure 2

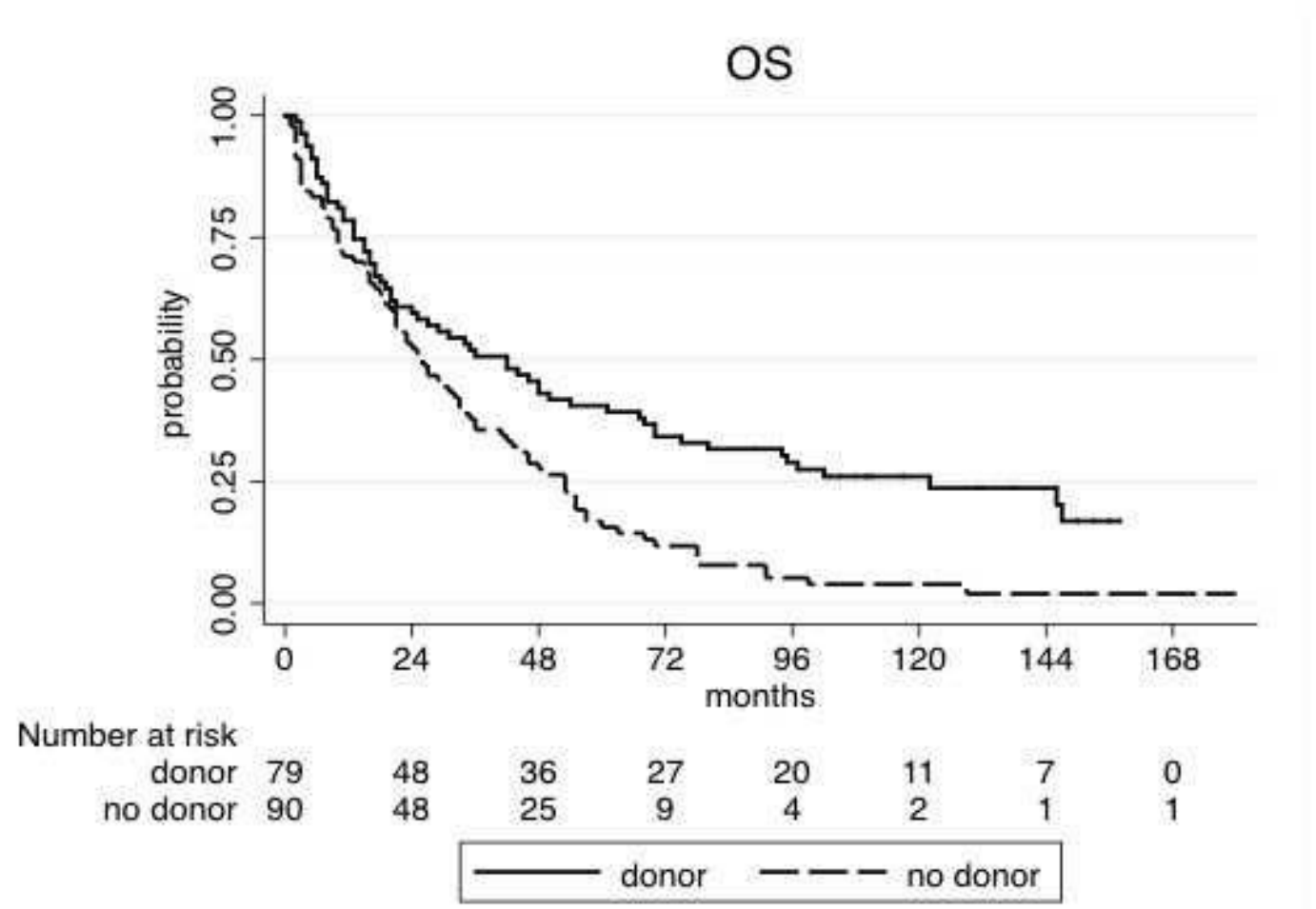

Figure 2