### Title

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# The Outcome of Haplo-Identical Transplantation in Patients with Relapsed Multiple Myeloma: An EBMT/CIBMTR Report

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## Abstract

Allogeneic hematopoietic cell transplantation (allo-HCT) using siblings and matched donors has the potential for long-term disease control in a subset of high-risk multiple myeloma (MM) patients. However, the data on using haploidentical donors in this disease are limited. We conducted a retrospective analysis to examine the outcomes of patients with MM who underwent

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Author contributions

FS, LG, AD, NK, and PH designed the study. D-GE performed the statistical analysis. All authors analyzed data. FS and JFS wrote the manuscript. All authors reviewed the manuscript.

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Conflicts of Interest

All authors declare no relevant competing conflicts of interest.

haploidentical allo-HCT within EBMT/CIBMTR centers. A total of 96 patients underwent haploidentical transplantation between 2008 and 2016. With a median follow up of 24.0 months (range, 13.2–24.9 months), 97% (95%CI, 93%−100%) of patients had neutrophil engraftment by day 28, and 75% (95%CI, 66%−84%) achieved platelet recovery by day 60. Two-year progression-free survival (PFS) was 17% (95%CI, 8%−26%), and overall survival (OS) was 48% (95%CI, 36%−59%). At 2 years, the cumulative risk of relapse/progression was 56% (95%CI, 45%−67%), and 1-year non-relapse mortality (NRM) was 21% (95%CI, 13%−29%). The incidence of acute graft-versus-host -disease (GVHD) grades II-IV by 100 days and chronic GVHD at 2 years were 39% (95%CI, 28%−49%) and 46% (95%CI, 34%−59%), respectively. On univariate analysis, use of post-transplant cyclophosphamide (PT-Cy) (54% [95%CI, 41%−68%] vs 25% [95%CI, 1%−48%], p=0.009), and use of bone marrow as source of stem cells (72% [95%CI, 55%−89%] vs 31% [95%CI, 17%−46%], p=0.001), were associated with improved OS at 2 years. Disease status, patient gender, intensity of conditioning regimen, recipient/donor gender mismatch, and CMV status had no impact on OS, PFS, or NRM. Haploidentical transplantation is feasible for patients with multiply relapsed or high-risk MM, with an encouraging 2-year OS of 48% and an NRM rate of 21% at 1 year, supporting further investigation of haploidentical transplantation in suitable candidates with MM.

**Keywords**

multiple myeloma; haploidentical; allogeneic hematopoietic cell transplantation

## INTRODUCTION

Despite tremendous strides in the treatment of multiple myeloma (MM), the disease remains incurable and is defined by multiple series of responses and relapses. In the relapsed/refractory setting, outcomes for patients may be particularly discouraging. Moreover, patients with adverse cytogenetics and other high-risk features may experience particularly short progression-free survival (PFS) and inferior survival rates.[1] Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially effective by virtue of a graft-versus-myeloma effect.[2–5] According to consensus recommendations by the International Myeloma Working Group (IMWG), the European Society of Blood and Marrow Transplantation (EBMT), the American Society of Blood and Marrow Transplantation (ASBMT), and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), allo-HCT should be considered appropriate therapy for eligible patients with relapse <24 months after a primary therapy that included an autologous HCT, those with high risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia) or both, preferably in the context of a clinical trials.[6] In hematologic malignancies overall, allo-HCT is traditionally performed with use of HLA-identical siblings or unrelated donors, although it may be under-utilized in high risk MM. Because such donors are frequently unavailable, especially for non-Caucasian patients, allo-HCT from haploidentical related donors has been developed and increasingly used as non-relapse mortality (NRM) rates have diminished and favorable outcomes in disease control have been reported.[7–9]

Data on the use of haploidentical transplantation in MM, however, remain limited. Two small retrospective studies of haploidentical allo-HCT reported encouraging results in patients with MM.[10, 11]

We conducted a retrospective analysis to examine the outcome of patients with MM who underwent haploidentical allo-HCT using the EBMT and Center for International Blood and Marrow Transplant Research (CIBMTR) databases. The objectives of this retrospective analysis are to evaluate overall survival (OS), NRM, PFS, relapse rates, cumulative incidence of acute and chronic graft versus host disease (GVHD), and engraftment rates in MM patients.

## PATIENTS AND METHODS

Patients with a diagnosis of MM who underwent haploidentical allo-HCT in EBMT and CIBMTR centers were selected. A haploidentical related donor is defined by the sharing of one haplotype (or a single identical copy of chromosome 6) with the patient, containing the HLA region, which encompasses class I and class II histocompatibility genes. However, a haploidentical family donor may be greater than half-matched and have common alleles on the unshared haplotype (mismatched related donor). The most recent EBMT report described haploidentical donors as a family member with two or more loci mismatch within the loci HLA-A, -B, -C, -DRB1 and -DQB1.[12]

Informed consent for transplantation and data collection was obtained by the local centers in accordance with the Helsinki Declaration.

### Statistical analysis

Pre-transplant patient characteristics were expressed as the median and range for continuous variables and frequencies and proportions for categorical variables. Primary endpoints were OS, PFS, cumulative incidence of relapse/progression and NRM, evaluated at 12 and 24 months after transplant. Outcomes are only analyzed for patients with complete relapse information (n=93). Median follow-up was determined using the reverse Kaplan-Meier method. The cumulative incidence of grade II-IV and III-IV acute GvHD (aGvHD) and limited/extensive chronic GvHD (cGvHD) were estimated at 100 days and 12 and 24 months, respectively. The cumulative incidences of neutrophil and platelet engraftment were estimated at 28 days and 60 days, respectively. OS and PFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. Cumulative incidences of relapse and NRM were analyzed together in a competing risks framework. Competing risks analyses were also separately applied to estimate aGvHD with the competing event of death before aGvHD and cGvHD with the competing event of death before cGvHD. For neutrophil engraftment and platelet engraftment, the competing events were graft loss, relapse, and death before any of these events. Subgroup differences in cumulative incidences were assessed using Gray's test. All estimates are reported with 95% confidence intervals. Statistical analyses were performed using R version 3.0.3 using packages '*survival,*' '*prodlim,*' and '*cmprsk*'.

# RESULTS

## Patient characteristics

A total of 96 patients with multiple myeloma underwent haploidentical allo-HCT between 2008 and 2016. All haploidentical transplantations in this study were performed as salvage treatment after recurrent disease and were the first allograft. None of these haploidentical transplantations were given as first-line treatment. Patient characteristics are displayed in Table 1. The median age was 54.9 (range, 36.6–73.3). Sixty-three (65.6%) were male, and 33 (34.4%) were female. Forty-three (53.8%) were stage I and II, and 37 (46.2%) were stage III by ISS classification. All patients had prior autologous stem cell transplantation, with 66 patients (68.8%) having one prior autologous transplant, and 26 patients (27.1%) having two, and 4 patients (4.2%) having three. At the time of conditioning, 36 patients (37.5%) were in ≥very good partial response (VGPR), 30 (31.2%) were in partial response, 13 (13.5%) had stable disease, and 17 (17.7%) had progressive disease. Table 1 lists the immunomodulatory drugs or proteasome inhibitors given prior to haplo alloHCT. Cytogenetic data were not available in all patients.

Characteristics of the haploidentical transplant regimens are listed in Table 2. A myeloablative conditioning regimen was used in 17 patients (18.4%), and reduced intensity or non-myeloablative (NMA) conditioning was performed in 75 patients (81.5%) (see Table 3 for more details). Thirty-two patients received a transplant from their child (50.8%), whereas a sibling was the donor for 27 patients (42.9%), a parent for 2 patients (3.2%), and a further removed relative for another 2 patients. As GVHD prophylaxis, post-transplant cyclophosphamide (PT-Cy) was administered to 73 patients (81.1%), and 17 patients (18.9%) received non-PT-Cy-based GVHD prophylaxis. The source of stem cells was bone marrow (BM) in 33 (34.7%) patients and peripheral blood (PB) in 62 (65.2%) patients. Female donor to male recipient was noted in 31 (32.6%); male donor to female recipient was 17 (17.9%). Cytomegalovirus (CMV) seronegative donor to seropositive recipient was reported in 8 (12.1%) and CMV seropositive donor to seronegative recipient was observed in 6 (9.1%) patients. Anti-thymocyte globulin (ATG) was used in 11 (11.7%) patients. The median interval from diagnosis to transplant was 39 months (range, 6.7–178.9 months). Seventy-nine (82.3%) patients received their transplant more than 24 months after diagnosis, 8 (8.3%) receiving their transplant in 18–24 months, and 9 (9.4%) receiving their transplant <18 months from diagnosis (Table 1). Karnofsky performance status was 90–100% in 52 (57.1%) patients and <90% in 39 (42.9%) patients. Transplant comorbidity index[13] was 0 in 13 (13.7%), 1 in 44 (46.3%), 2 in 14 (14.7%), and 3+ in 24 (25.3%) patients. Forty-one patients (43.6%) had the IgG subtype, 15 (16.0%) had IgA, 34 (36.2%) had light chain myeloma, 4 (4.3%) had other Ig subtypes, and data were missing in 2 patients. Post-transplant maintenance or consolidation was not planned.

## Engraftment

At a median follow up of 24.0 months (range, 13.2–24.9 months), the cumulative incidence of neutrophil recovery by 28 days was 97% (95%CI, 93%−100%), at a median of 16 days (95%CI, 15%−17%) (Fig. S1). The cumulative incidence of platelet recovery by 60 days was 75% (95%CI, 66%−84%), at a median of 25 days (95%CI, 23%−29%) (Fig. S2).

### Progression-free survival/Overall survival/Non-relapse mortality/Relapse

The OS for the entire cohort at 2 years was 48% (95%CI, 36%−59%), with a median OS of 22.7 months (95%CI, 10.3–39.1 months) (Fig 1a). PFS at 2 years was 17% (95%CI, 8% −26%), at a median of 5.5 months (95%CI, 3.7–7.5 months) (Fig 1b). The cumulative risk of relapse at 1 and 2 years was 50% (95%CI, 39%−61%) and 56% (95%CI, 45%−67%), respectively. The NRM was 21% (95%CI, 13%−29%) at 1 year and 26% (95%CI, 17% −36%) at 2 years (Fig 2).

The intensity of the conditioning regimen (myeloablative vs reduced intensity/non-myeloablative) was not associated with significantly different OS or PFS rates, nor was there a significant difference in NRM or relapse rate (Fig S3). By contrast, the source of stem cells was linked with a strong difference in OS at 2 years in favor of use of BM (72% [95%CI, 55%−89%] vs. 31% [95%CI, 17%−46%], p=0.001), although there was no significant difference in PFS. Two-year NRM using BM was lower compared with that of PB (11% [95%CI, 0%−23%] vs. 35% [95%CI, 22%−48%]) (p=0.016). There was a trend for higher relapse rate with use of BM (75% [95%CI, 58%−92%] vs. 45% [95%CI, 32%−58%]) (p=0.083) (Fig 3).

Use of PT-Cy was associated with improved OS, with a 2-year OS of 54% (95%CI, 41% −68%) vs 25% (95%CI, 1%−48%) using no PT-Cy (p=0.009); however, PT-Cy did not affect PFS, relapse incidence, or NRM (Fig 4). There was a trend toward inferior OS using ATG (p=0.07) but with no statistically significant difference in PFS, relapse rate, or NRM (Fig. S4); it should be noted that the number of patients in this instance was small.

We examined the association of PT-Cy and source of stem cells on overall survival. For patients who received BM graft and PT-Cy, overall survival at 24 months was 69% (95% CI, 51–87%) as compared to 38% (95% CI, 19–58%) in those who received peripheral stem cells and PT-Cy (Fig. S5), indicating that the difference in OS from use of stem cell source may be independent of use of PT-Cy.

### Acute GVHD and Chronic GVHD

The cumulative incidences of grade II-IV and III-IV aGVHD at day 100 were 39% (95%CI, 28%−49%) and 12% (95%CI, 5%−19%), respectively (Fig. 5a-b). Chronic GvHD occurred in 31 patients (1 year cumulative incidence of 41% [95%CI, 30%−53%], 2-year cumulative incidence of 46% [95%CI, 34%−59%]) (Fig. 5c).

Karnofsky Performance Score, HCT comorbidity index, donor-recipient sex mismatch, patient and donor age, remission status at transplant, time from autologous transplantation to relapse (<6 months, 6–12 months, >12 months), and donor/recipient CMV status did not have any statistically significant impact on OS, NRM, and relapse rate (Fig S6-S7).

## DISCUSSION

Although the role of allo-HCT in MM is often refuted in the upfront setting on the basis of conflicting results from randomized clinical trials,[3, 4, 14–18] use in those with early relapsed or high risk MM is considered an appropriate option.[6] Indeed, the use of allo-HCT continues

to rise in relapsed patients on the basis of a recent report by the EBMT group.[19] Given the limited availability of matched donors and the encouraging results of haploidentical allo-HCT in other malignancies, we conducted this retrospective analysis to investigate the outcomes of patients with MM who underwent haploidentical allo-HCT within the EBMT and CIBMTR registries. Our results demonstrate that haploidentical HCT can be safely performed in appropriate MM patients who lack HLA-matched siblings or unrelated donors. All patients had failed one prior auto-HCT, and one third had failed two auto-transplants, a reflection of more advanced refractory disease. The 2-year overall survival of 48% in these patients compares favorably to allogeneic HCT results using matched related or unrelated donors in relapsed MM.[20–23]

A report by Castagna et al. included 30 patients with relapsed MM who underwent haploidentical allo-HCT using PT-Cy.[10] Eighty-seven percent of patients had neutrophil recovery, and 60% had platelet recovery by day 30. In our study, 97% had neutrophil recovery by day 28, and 75% had platelet recovery by day 60. The one-year NRM of 21% in our study is somewhat higher than those reported by Castagna et al. (10% at 18 months);[10] however, it is in line with present observations of haplo-HCT in myelodysplastic syndrome, a disease of older age similar to MM.[9] As supportive care is improved and new preparative regimens are developed, it is anticipated that the NRM rate will continue to decline. The OS of 48% at 2 years is close to the results from Castagna et al.[10] Contrary to their observation, we noted an improved overall survival using BM as a source of stem cells. The PFS of 17% with relapse rate of 56% in our study, although suboptimal, are similar to results of salvage allo-HCT using matched donors in patients with relapsed/refractory MM patients as reported by the EBMT and other groups.[24, 25] PT-Cy has been used to selectively deplete allo-reactive T cells in haploidentical-HCT and now extends to matched donor transplantation as a means of lowering GVHD and NRM in an effort to improve OS. Similarly, we observed an association between the use of PT-Cy and substantially improved OS, supporting the use of PT-Cy for GVHD prophylaxis in future studies of haploidentical allo-HCT in patients with MM. We also observed superior OS using bone marrow as compared to peripheral stem cells, mainly because of lower NRM. This observation needs to be validated by future studies. One recent retrospective comparison of bone marrow and peripheral stem cells as the source of graft in haploidentical transplant patients with various hematologic malignancies and receiving PT-Cy reported no significant differences in nonrelapse mortality risks, but relapse risks were higher using bone marrow.[26]

In another study of 10 patients with MM who received haploidentical allo-HCT with a conditioning regimen of cytarabine, busulfan, cyclophosphamide, and simustine, the 2-year survival was reported to be 46%, comparable to our experience.[11] Additionally, an OS of 48% herein despite a high relapse rate indicates improved outcomes using salvage interventions and possible synergism between a graft-versus-myeloma effect and re-treatment after haploidentical allo-HCT.[27] This finding has been previously observed in the setting of allogeneic transplant.[14, 28]

The incidences of acute and chronic GVHD in our study are somewhat higher than those reported using haploidentical allo-HCT in other malignancies. This finding may partially be explained by older patient age and a more heterogeneous patient population in the registry

data. We did not observe any association between outcome and disease status, patient and donor age, CMV sero-status, patient and donor gender mismatch, KPS, or transplant comorbidity score.

In conclusion, haploidentical allo-HCT as a salvage treatment in patients with MM who lack a matched donor is feasible with acceptable NRM with reference to traditional donor-based transplants. Widespread application of this procedure is limited by the high relapse rates; however, the allo-HCT platform can be utilized in the context of other post-transplant immune-based strategies, such as donor-derived CAR T-cells and NK cell infusions, newer immunomodulatory drugs or proteasome inhibitors, bispecific T cell engagers, and bispecific killer cell engagers to further enhance anti-tumor effects and ultimately survival in an appropriate patient population.[29–31]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Highlights

- Haploidentical allogeneic hematopoietic cell transplantation is feasible as salvage in myeloma.
- Two-year progression-free survival was 17%, and overall survival was 48%.
- At 2 years, the cumulative risk of relapse/progression was 56%, and 1-year non-relapse mortality was 21%.
- Use of post-transplant cyclophosphamide and bone marrow as source of stem cells were associated with improved OS at 2 years.

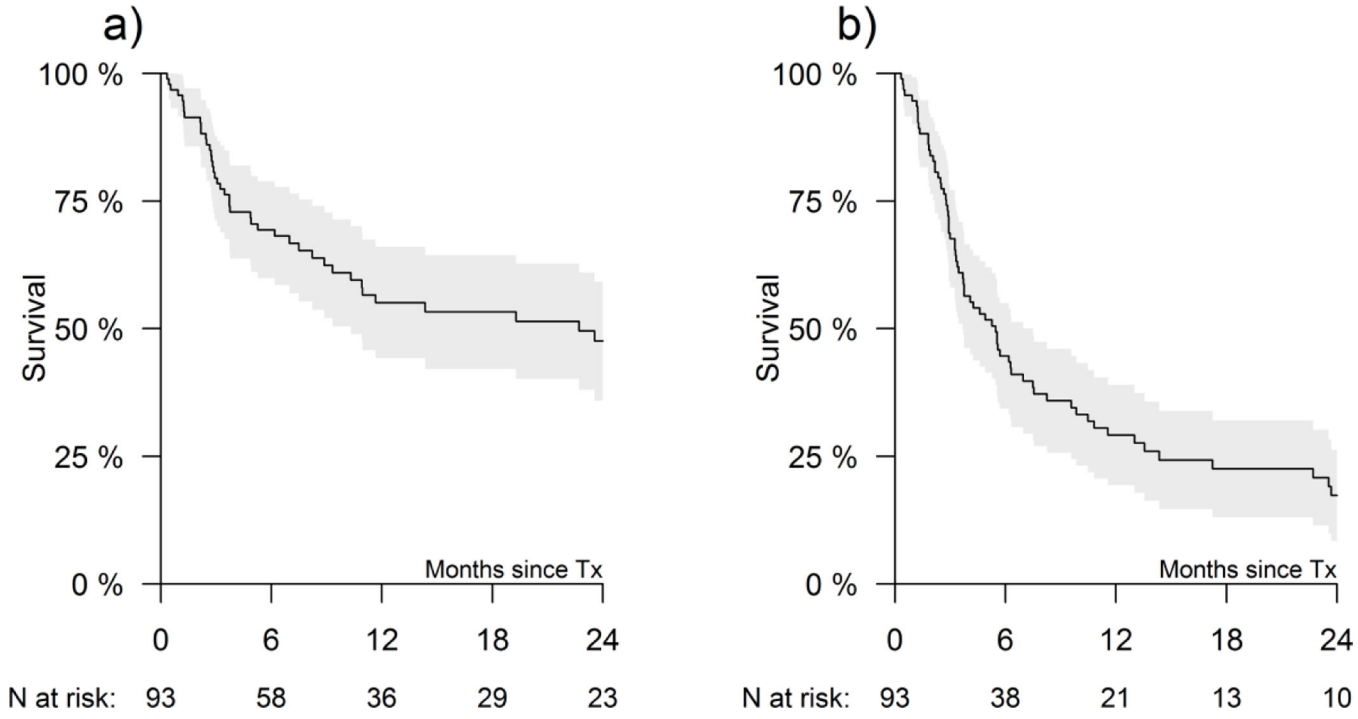


**Figure 1.**

a) Overall survival, b) Progression-free survival

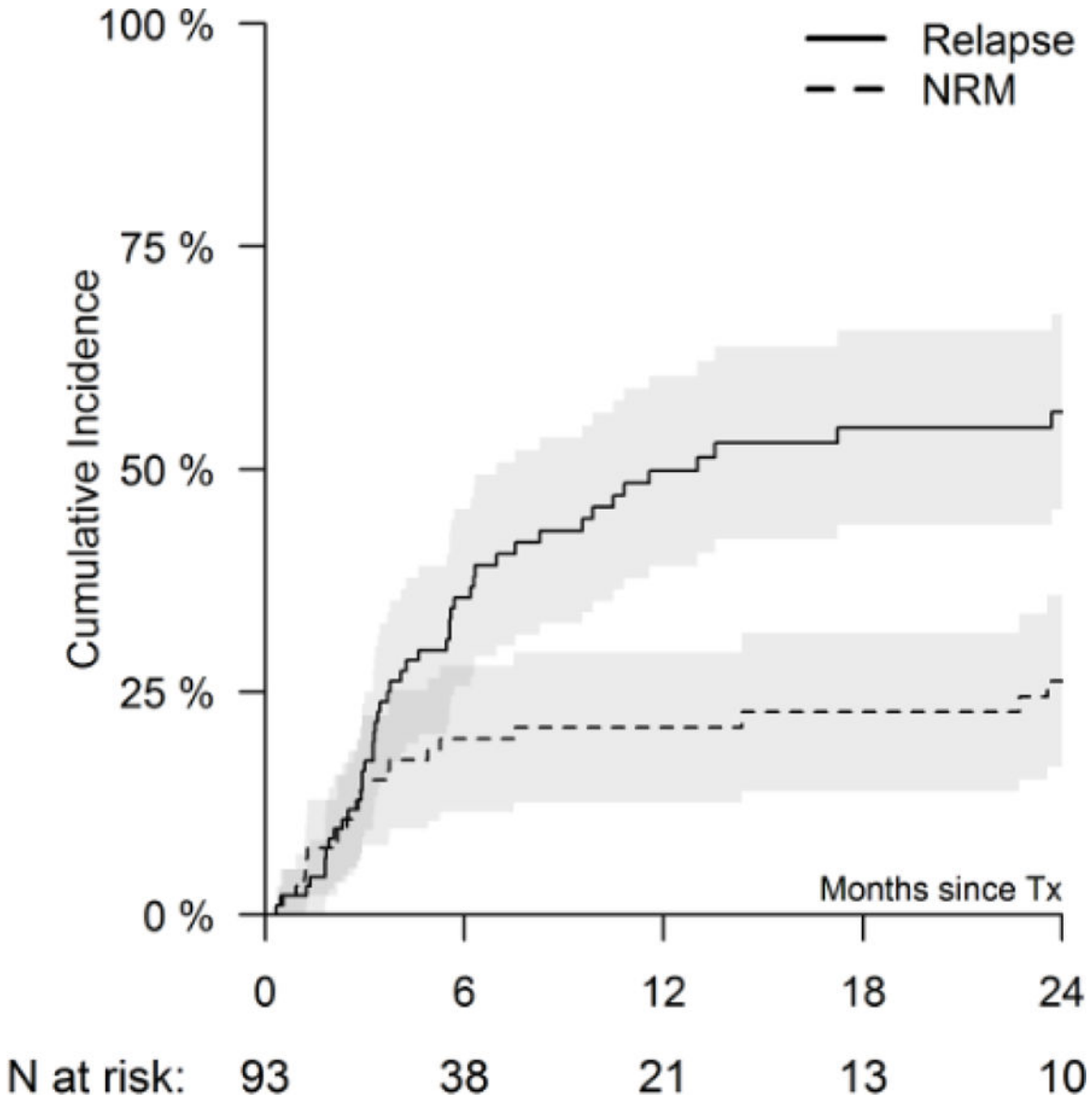


**Figure 2.**
NRM and relapse rate.

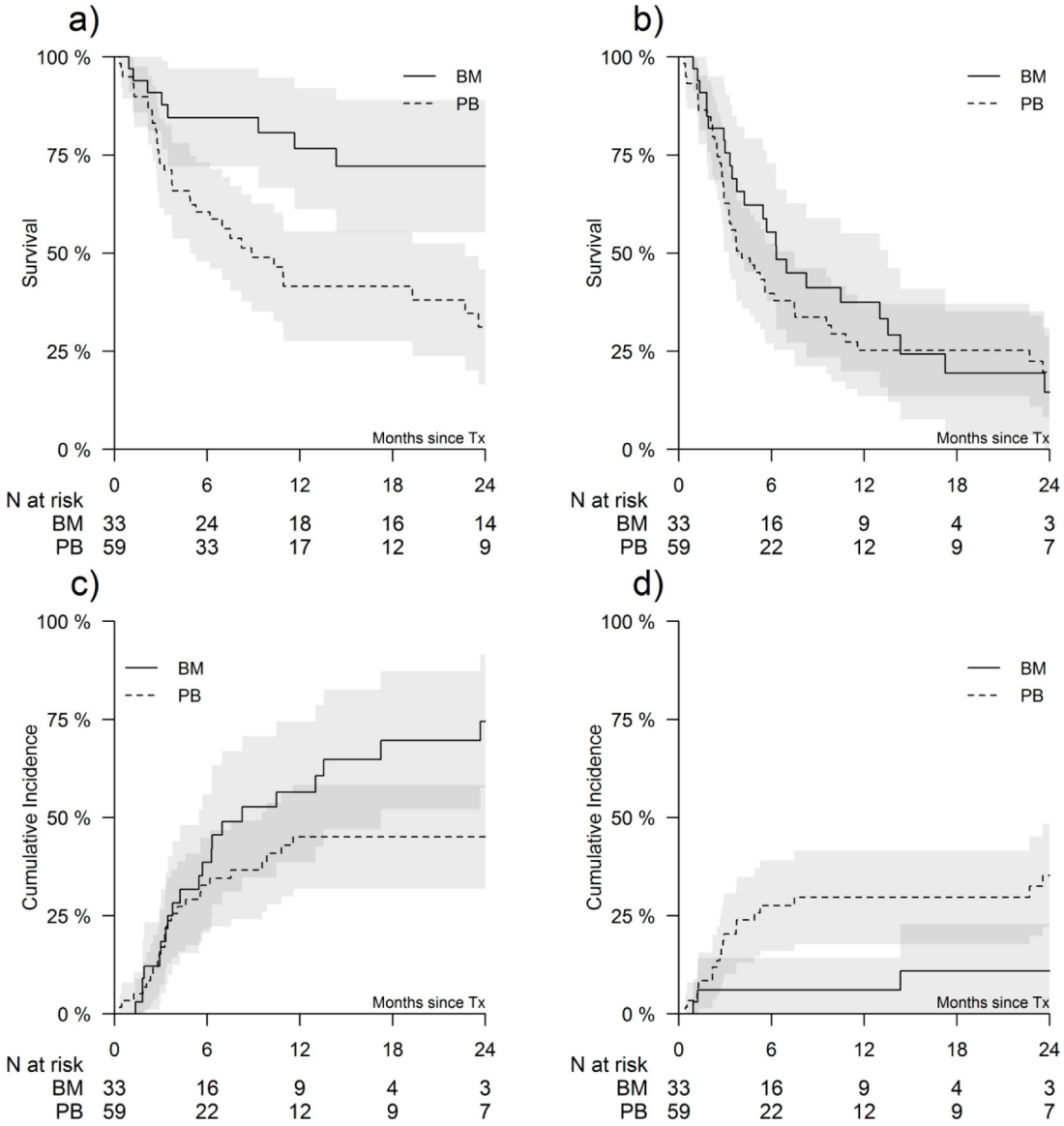


**Figure 3.**
Effect of stem cell source on a) OS, b) PFS, c) relapse, and d) NRM.

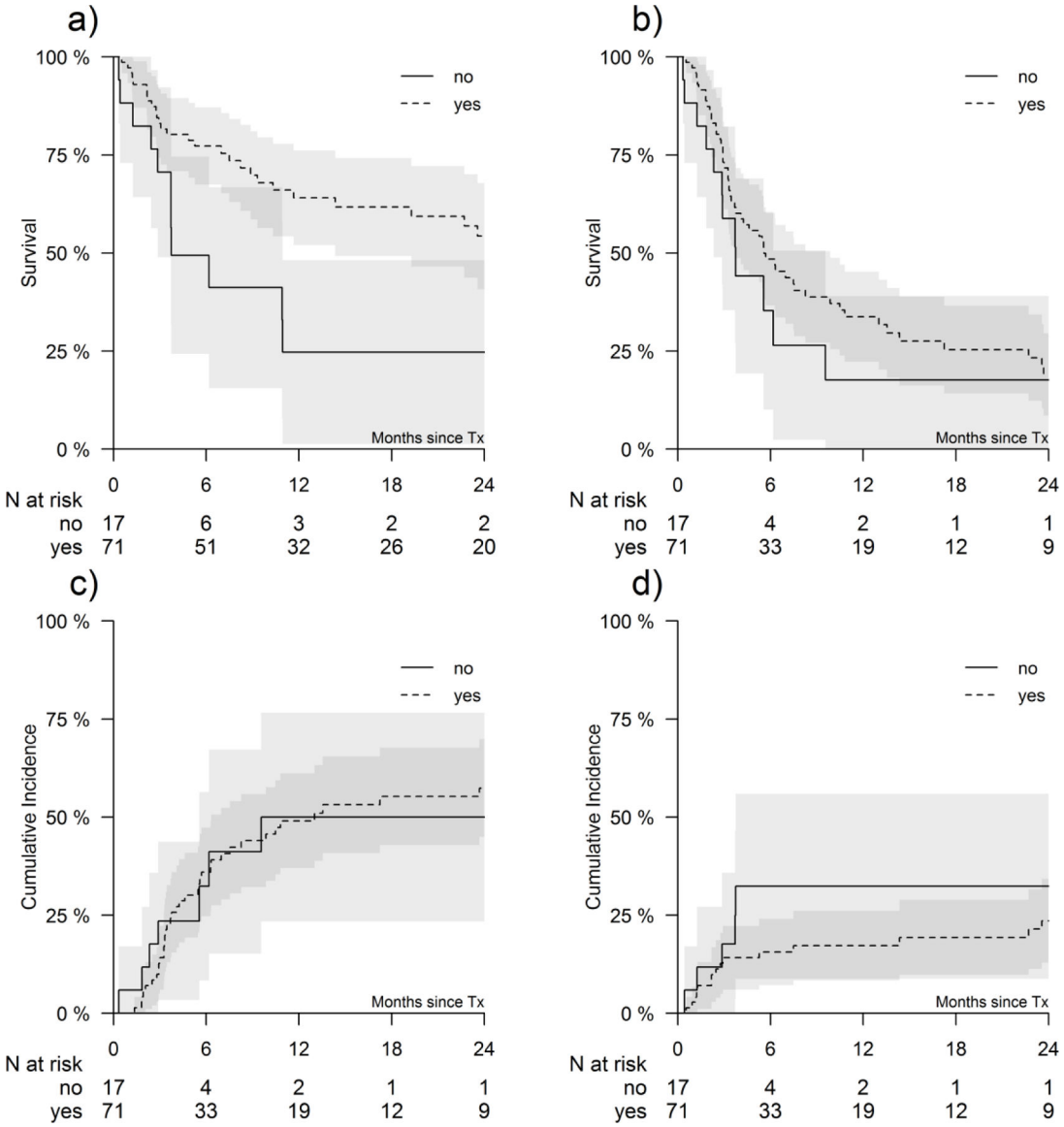


**Figure 4.**
Effect of PT-Cy on a) OS, b) PFS, c) relapse, and d) NRM.

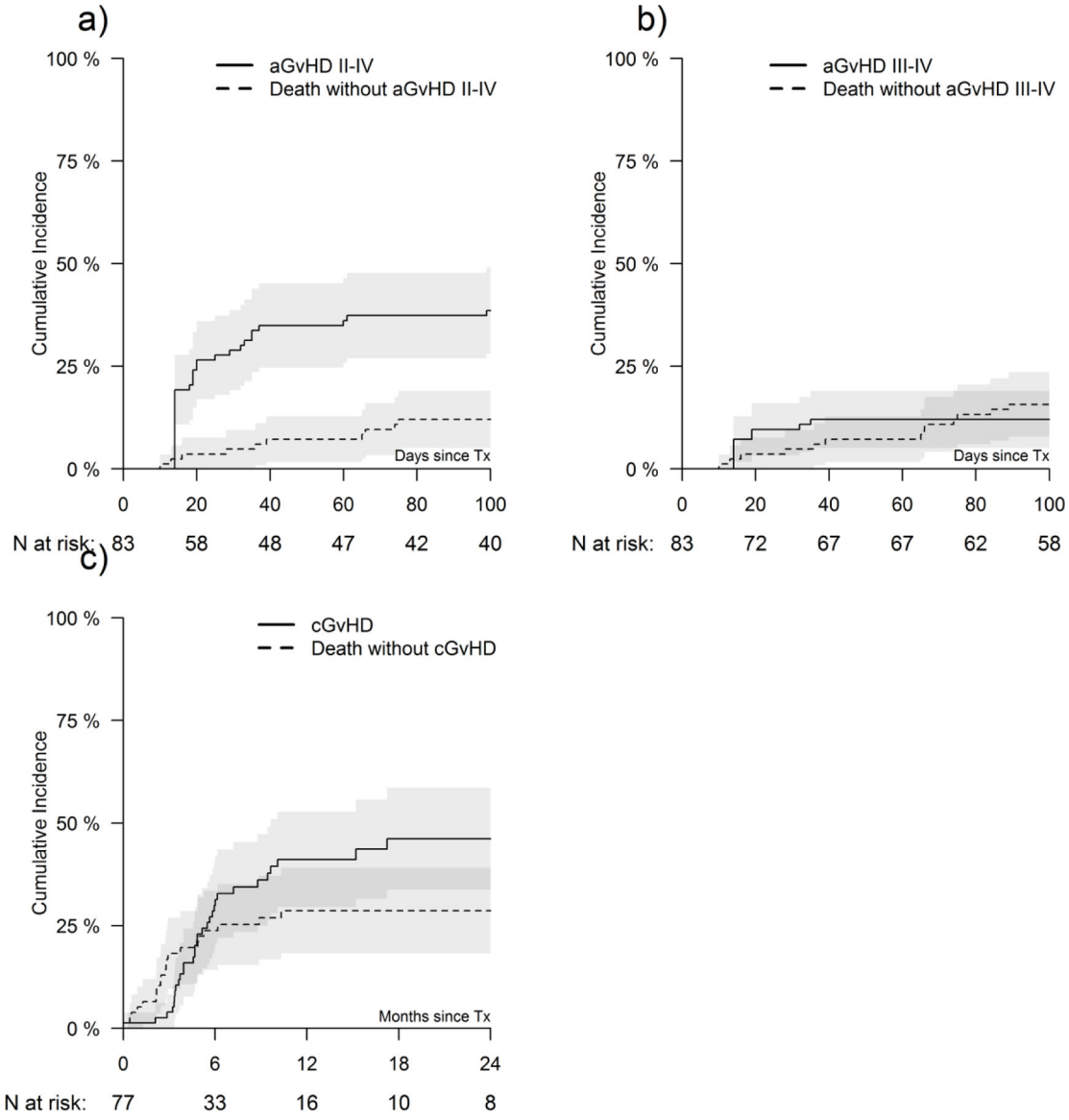


**Figure 5.**

a) cumulative incidence of aGvHD II-IV and death without aGvHD II-IV, b) a GVHD III-IV and death without aGvHD III-IV, c) and cGvHD and death without cGvHD.

**Table 1.**

Patient characteristics.

| | N, range or (%) |
|---|---|
| Age (median) | 54.9 years (36.6–73.3) |
| Gender | |
| Male | 63 (65.6%) |
| Female | 33 (34.4%) |
| ISS | |
| stage I-II | 43 (53.8%) |
| stage III | 37 (46.2%) |
| missing | 16 |
| Subtype | |
| IgG | 41 (43.6%) |
| IgA | 15 (16%) |
| LCD | 34 (36.2%) |
| others | 4 (4.3%) |
| missing | 2 |
| KPS | |
| 90–100% | 52 (57.1%) |
| <90% | 39 (42.9%) |
| missing | 5 |
| HCT Comorbidity Index | |
| 0 | 13 (13.7%) |
| 1 | 44 (46.3%) |
| 2 | 14 (14.7%) |
| 3 | 24 (25.3%) |
| Missing | 1 |
| Pre-haplo treatment | |
| VTD | 3 (8.6%) |
| VRD | 10 (28.6%) |
| VCD | 12 (34.3%) |
| VD | 4 (11.4%) |
| RD | 6 (17.1%) |
| Missing | 61 |
| Disease status | |
| CR/sCR/VGPR | 36 (37.5%) |
| PR | 30 (31.2%) |
| SD | 13 (13.5%) |
| PD/relapse | 17 (17.7%) |
| Prior autologous HCT | |
| 1 | 66 (68.8%) |
| 2 | 30 (27.1%) |

| | N, range or (%) |
|---|---|
| 3 | 4 (4.2%) |
| Time from diagnosis | |
| >24 mo | 79 (82.3%) |
| 18–24 mo | 8 (8.3%) |
| <18 mo | 9 (9.4%) |

Abbreviations: ISS, International Staging System; Ig, immunoglobulin; LCD, light chain disease; KPS, Karnofsky Performance Score; HCT, hematopoietic cell transplantation; CR, complete response; sCR, stringent complete response; PR, partial response; RD, Revlimid/Dexamethasone; SD, stable disease; PD, progressive disease; VCD, Velcade/Cyclophosphamide/Dexamethasone; VD, Velcade/Dexamethasone; VRD, Velcade/Revlimid/Dexamethasone; VTD, Velcade/Thalidomide/Dexamethasone.

**Table 2.**

Transplant characteristics.

| | N (%) |
|---|---|
| Stem cell source | |
| BM | 33 (34.7%) |
| PB | 62 (65.2%) |
| Missing | 1 |
| Conditioning regimen | |
| MAC | 17 (18.4%) |
| TBI based | 4 (23.5%) |
| Non-TBI based | 13 (76.5%) |
| RIC/NMA | 75 (81.5%) |
| TBI based | 50 (66.7%) |
| Non-TBI based | 25 (33.3%) |
| Missing | 4 |
| Donor relationship | |
| Child | 32 (50.8%) |
| Sibling | 27 (42.9%) |
| Parent | 2 (3.2%) |
| Further removed | 2 (3.2%) |
| Missing | 33 |
| Gender recipient/donor | |
| M/M | 31 (32.6%) |
| M/F | 31 (32.6%) |
| F/M | 17 (17.9%) |
| F/F | 16 (16.9%) |
| Missing | 1 |
| GVHD prophylaxis | |
| PT-Cy | 73 (81.1%) |
| No PT-Cy | 17 (18.9%) |
| Missing | 6 |
| CMV recipient/donor | |
| −/− | 13 (19.7%) |
| +/− | 8 (12.1%) |
| +/+ | 39 (59.1%) |
| −/+ | 6 (9.1%) |
| Missing | 30 |
| ATG | 11 (11.7%) |
| No ATG | 80 (83.3%) |
| missing | 2 |

Abbreviations: BM, bone marrow; PB, peripheral blood; MAC, myeloablative conditioning; TBI, total body irradiation; RIC, reduced intensity conditioning; NMAC, non-myeloablative conditioning; GVHD, graft versus host disease; PT-Cy, post-transplant cyclophosphamide; CMV, cytomegalovirus; ATG, anti-thymocyte globulin.

**Table 3.**

Conditioning regimens from EBMT and CIBMTR.

| | N (%) |
|---|---|
| **EBMT, N=56** | |
| Flu+Mel+TBI 2 Gy | 5 |
| Flu + Cy + TBI 2 Gy | 16 |
| Thio + Flu + Mel | 2 |
| Thio + Bu + Flu | 5 |
| Treo + Flu + TBI 2 Gy | 2 |
| Treo + Flu + Mel | 1 |
| **CIBMTR, N=40** | |
| TBI 10 Gy/Cy/others | 1 |
| Bu + TBI 2 Gy | 1 |
| Cy + TBI 2 Gy | 33 |
| Mel + TBI 2 Gy | 3 |
| Bu + Cy | 1 |
| Flu + Mel | 1 |