Biol Blood Marrow Transplant 25 (2019) 335–342

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Alternative Donors

Outcomes of Haploidentical Transplantation in Patients with Relapsed Multiple Myeloma: An EBMT/CIBMTR Report

Firoozeh Sahebi[1,2,*], Laurent Garderet[3], Abraham S. Kanate[4], Diderik-Jan Eikema[5], Nina Simone Knelange[6], Omar F. Dávila Alvelo[7], Yener Koc[8], Didier Blaise[9], Qaiser Bashir[10], José M. Moraleda[11], Peter Dreger[12], James F. Sanchez[1], Stefan Ciurea[10], Harry Schouten[13], Nirav N. Shah[14], Mareike Verbeek[15], Wolf Rösler[16], Jose L. Diez-Martin[17], Stefan Schoenland[12], Anita D'Souza[14], Nicolaus Kröger[18], Parameswaran Hari[14]

[1] *Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Medical Center, Duarte, California*
[2] *Southern California Kaiser Permanente Medical Group, Los Angeles, California*
[3] *Department of Hematology and Cellular Therapy, Hospital Saint Antoine, Paris, France*
[4] *Department of Medicine, West Virginia University, Morgantown, West Virginia*
[5] *European Society for Blood and Marrow Transplantation Statistical Unit, Leiden, The Netherlands*
[6] *European Society for Blood and Marrow Transplantation Data Office, Leiden, The Netherlands*
[7] *Center for International Blood and Marrow Transplant Research, Milwaukee Campus, Milwaukee, Wisconsin*
[8] *Stem Cell Transplantation Unit, Medical Park Hospitals, Antalya, Turkey*
[9] *Department of Hematology, Centre de Recherche en Cancérologie de Marseille, Marseille, France*
[10] *Department of Stem Cell Transplantation and Cellular, Therapy The University of Texas MD Anderson Cancer Center, Houston, Texas*
[11] *Unidad de Terapia Celular, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain*
[12] *Department of Medicine, University of Heidelberg, Heidelberg, Germany*
[13] *Department of Hematology, University Hospital Maastricht, Maastricht, The Netherlands*
[14] *Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[15] *Allogene und autologe Stammzelltransplantation, Klinikum Rechts der Isar, Munich, Germany*
[16] *Department of Hematology and Oncology, University Hospital Erlangen, Erlangen, Germany*
[17] *Department of Hematology, Hospital Gregorio Marañón, Madrid, Spain*
[18] *Department of Stem Cell Transplantation, University Hospital, Eppendorf, Germany*

Article history:
Received 31 July 2018
Accepted 13 September 2018

Key Words:
Multiple myeloma
Haploidentical
Allogeneic hematopoietic cell transplantation

A B S T R A C T

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 patients with multiple myeloma (MM); 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 haploidentical allo-HCT within European Society for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplant Research centers. A total of 96 patients underwent haploidentical allo-HCT between 2008 and 2016. With a median follow-up of 24.0 months (range, 13.2 to 24.9 months), 97% (95% confidence interval [CI], 93% to 100%) of patients had neutrophil engraftment by day 28, and 75% (95% CI, 66% to 84%) achieved platelet recovery by day 60. Two-year progression-free survival (PFS) was 17% (95% CI, 8% to 26%), and overall survival (OS) was 48% (95% CI, 36% to 59%). At 2 years, the cumulative risk of relapse/progression was 56% (95% CI, 45% to 67%), and 1-year nonrelapse mortality (NRM) was 21% (95% CI, 13% to 29%). The incidences of acute graft-versus-host-disease (GVHD) grades II-IV by 100 days and chronic GVHD at 2 years were 39% (95% CI, 28% to 49%) and 46% (95% CI, 34% to 59%), respectively. On univariate analysis, use of post-transplantation cyclophosphamide (PT-Cy) (54% [95% CI, 41% to 68%] versus 25% [95% CI, 1% to 48%]; P =.009) and use of bone marrow as source of stem cells (72% [95% CI, 55% to 89%] versus 31% [95% CI, 17% to 46%]; P = .001) were associated with improved OS at 2 years. Disease status, patient sex,

Financial disclosure: See Acknowledgments on page 341.

* Correspondence and reprint requests: Firoozeh Sahebi, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, 1500 Duarte Road, Duarte, CA 91010

E-mail address: fsahebi@coh.org (F. Sahebi).

https://doi.org/10.1016/j.bbmt.2018.09.018

intensity of conditioning regimen, recipient/donor sex mismatch, and cytomegalovirus serostatus 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 of 21% at 1 year, supporting further investigation of haploidentical allo-HCT in suitable candidates with MM.

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 overall survival (OS) 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, the European Society for Blood and Marrow Transplantation (EBMT), the American Society of Blood and Marrow Transplantation, and the Blood and Marrow Transplant Clinical Trials Network, allo-HCT should be considered appropriate therapy for eligible patients with relapse occurring <24 months after a primary therapy that included autologous HCT (auto-HCT), those with high-risk features (eg, cytogenetics, extramedullary disease, plasma cell leukemia) or both, preferably in the context of a clinical trial [6]. In hematologic malignancies overall, allo-HCT is traditionally performed with use of HLA-identical sibling donors or unrelated donors, although it may be underutilized in high-risk MM. Because such donors are frequently unavailable, especially for non-Caucasian patients, allo-HCT from haploidentical related donors is being increasingly used, with decreased nonrelapse mortality (NRM) and favorable outcomes in disease control reported [7-9]. Data on the use of haploidentical transplantation in MM remain limited, although 2 small retrospective studies of haploidentical allo-HCT have 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 were to evaluate OS, PFS, NRM, relapse rates, cumulative incidence of acute and chronic graft-versus-host disease (GVHD), and engraftment rates in patients with MM.

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 more than half-matched and have common alleles on the unshared haplotype (mismatched related donor). The most recent EBMT report defined a haploidentical donor as a family member with 2 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 Declaration of Helsinki.

Statistical Analysis

Pretransplantation patient characteristics were expressed as median and range for continuous variables and as frequency and proportion for categorical variables. Primary endpoints were OS, PFS, cumulative incidence of relapse/progression, and NRM, evaluated at 12 and 24 months after transplantation. Outcomes were analyzed only for patients with complete relapse information (n = 93). The median duration of follow-up was determined using the reverse Kaplan-Meier method. The cumulative incidences of grade II-IV and III-IV acute GVHD (aGVHD) and limited/extensive chronic GVHD (cGVHD) were estimated at 100 days and at 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 using a log-rank test. The cumulative incidences of relapse and NRM were analyzed together in a competing-risks framework. Competing-risks analyses were also separately applied to estimate the incidences of 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 (CIs). Statistical analyses were performed using R version 3.0.3 with the survival, prodlim, and cmprsk packages (R Institute for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

Our cohort comprised 96 patients with MM who underwent haploidentical allo-HCT in an EBMT or CIBMTR center between 2008 and 2016. All haploidentical transplantations in this study were performed as salvage treatment after recurrent disease and were the first allograft for each patient. None of these transplantations was performed as first-line treatment. Patient characteristics are displayed in Table 1. The median age was 54.9 years (range, 36.6 to 73.3 years). Sixty-three patients (65.6%) were male, and 33 (34.4%) were female. Forty-three patients (53.8%) were stage I and II and 37 (46.2%) were stage III by the International Staging System classification. All patients had undergone previous auto-HCT, including 66 patients (68.8%) with 1 previous auto-HCT, 26 patients (27.1%) with 2 previous auto-HCTs, and 4 patients (4.2%) with 3 previous auto-HCTs. At the time of conditioning, 36 patients (37.5%) were in very good partial response or better, 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 and proteasome inhibitors given before haploidentical allo-HCT. Cytogenetic data were not available in all patients.

Characteristics of the haploidentical allo-HCT regimens are listed in Table 2. A myeloablative conditioning regimen was used in 17 patients (18.4%), and a reduced-intensity or nonmyeloablative conditioning regimen was used in 75 patients (81.5%) (Table 3). The graft donor was the patient's own child in 32 patients (50.8%), a sibling in 27 patients (42.9%), a parent in 2 patients (3.2%), and a further removed relative in 2 patients (3.2%). As GVHD prophylaxis, post-transplantation cyclophosphamide (PT-Cy) was administered to 73 patients (81.1%), and 17 patients (18.9%) received non-PT-Cy-based prophylaxis. The stem cell source was bone marrow (BM) in 33 patients (34.7%) and peripheral blood (PB) in 62 patients (65.2%). The sex match was female donor to male recipient in 31 patients (32.6%) and male donor to female recipient in 17 patients (17.9%). Cytomegalovirus (CMV)-seronegative donor to seropositive recipient was reported in 8 cases (12.1%), and

Table 1
Patient Characteristics

Characteristic	Value
Age, yr, median (range)	54.9 (36.6-73.3)
Sex, n (%)	
Male	63 (65.6)
Female	33 (34.4)
ISS, n (%)	
Stage I-II	43 (53.8)
Stage III	37 (46.2)
Missing	16
Subtype, n (%)	
IgG	41 (43.6)
IgA	15 (16)
LCD	34 (36.2)
Others	4 (4.3)
Missing	2
KPS score, n (%)	
90%-100%	52 (57.1)
<90%	39 (42.9)
Missing	5
HCT-CI, n (%)	
0	13 (13.7)
1	44 (46.3)
2	14 (14.7)
3	24 (25.3)
Missing	1
Pre-haploidentical allo-HCT treatment, n (%)	
VTD	3 (8.6)
VRD	10 (28.6)
VCD	12 (34.3)
VD	4 (11.4)
RD	6 (17.1)
Missing	61
Disease status, n (%)	
CR/sCR/VGPR	36 (37.5)
PR	30 (31.2)
SD	13 (13.5)
PD/relapse	17 (17.7)
Previous autologous HCT, n (%)	
1	66 (68.8)
2	30 (27.1)
3	4 (4.2)
Time from diagnosis, n (%)	
>24 mo	79 (82.3)
18-24 mo	8 (8.3)
<18 mo	9 (9.4)

ISS indicates International Staging System; LCD, light chain disease; VTD, Velcade/thalidomide/ dexamethasone; VRD, Velcade/Revlimid/dexamethasone; VCD, Velcade/cyclophosphamide/ dexamethasone; VD, Velcade/dexamethasone; CR, complete response; sCR, stringent complete response; PR, partial response; RD, Revlimid/dexamethasone; SD, stable disease; PD, progressive disease.

CMV-seropositive donor to seronegative recipient in 6 cases (9.1%). Anti-thymocyte globulin was used in 11 patients (11.7%). The median interval from diagnosis to transplantation was 39 months (range, 6.7 to 178.9 months). Seventy-nine patients (82.3%) underwent allo-HCT at >24 months after diagnosis, 8 (8.3%) did so at 18 to 24 months after diagnosis, and 9 (9.4%) did so at <18 months from diagnosis (Table 1). The Karnofsky Performance Scale (KPS) score was 90% to 100% in 52 patients (57.1%) and <90% in 39 patients (42.9%). The HCT comorbidity index (HCT-CI) [13] score was 0 in 13 patients (13.7%), 1 in 44 (46.3%), 2 in 14 (14.7%), and 3+ in 24 (25.3%). 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 another Ig subtype, and data were missing in 2 patients. Post-transplantation maintenance or consolidation was not planned.

Table 2
Transplantation Characteristics

Characteristic	Value, 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/NMAC	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
Recipient/donor sex	
Male/male	31 (32.6)
Male/female	31 (32.6)
Female/male	17 (17.9)
Female/female	16 (16.9)
Missing	1
GVHD prophylaxis	
PT-Cy	73 (81.1)
No PT-Cy	17 (18.9)
Missing	6
CMV serostatus, 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

MAC indicates myeloablative conditioning; TBI, total body irradiation; RIC, reduced-intensity conditioning; NMAC, non-myeloablative conditioning; ATG, anti-thymocyte globulin.

Engraftment

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

PFS/OS/NRM/Relapse

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

The intensity of the conditioning regimen (myeloablative conditioning versus reduced-intensity/nonmyeloablative conditioning) was not associated with significant differences in OS, PFS, NRM, or relapse rate (Supplementary Figure S3). In contrast, the stem cell source was linked with a strong

Table 3
Conditioning Regimens from the EBMT and CIBMTR

Regimen	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

Flu indicates fludarabine; Mel, melphalan; Thio, thiotepa; Bu, busulfan; Treo, treosulfan.

difference in OS at 2 years favoring the of use of BM over PB (72% [95% CI, 55% to 89%] versus 31% [95% CI, 17% to 46%]; P = .001), although there was no significant difference in PFS. Two-year NRM was lower with the use of BM compared with PB (11% [95% CI, 0% to 23%] versus 35% [95% CI, 22% to 48%]; P = .016). There was a trend toward a higher relapse rate with use of BM (75% [95% CI, 58% to 92%] versus 45% [95% CI, 32% to 58%]; P = .083) (Figure 3).

The use of PT-Cy was associated with improved OS, with a 2-year OS of 54% (95% CI, 41% to 68%) vs 25% (95% CI, 1% to 48%) using no PT-Cy (P = .009); however, use of PT-Cy had no effect on PFS, relapse incidence, or NRM (Figure 4). There was a trend toward inferior OS with the use of anti-thymocyte globulin (P = .07) but with no statistically significant difference in PFS, relapse rate, or NRM (Supplementary Figure S4); however, only a small number of patients received this therapy.

We examined the association of PT-Cy and source of stem cells on OS. OS at 24 months was 69% (95% CI, 51% to 87%) for patients who received a BM graft and PT-Cy, compared with 38% (95% CI, 19% to 58%) for those who received a PB graft and PT-Cy (Supplementary Figure S5), indicating that the difference in OS by stem cell source may be independent of the use of PT-Cy.

aGVHD and cGVHD

The cumulative incidences of grade II-IV and III-IV aGVHD at day 100 were 39% (95% CI, 28% to 49%) and 12% (95% CI, 5% to 19%), respectively (Figure 5A and B). cGVHD occurred in 31 patients, with a 1-year cumulative incidence of 41% (95% CI, 30% to 53%) and a 2-year cumulative incidence of 46% (95% CI, 34% to 59%) (Figure 5C).

KPS score, HCT-CI score, donor-recipient sex mismatch, patient and donor age, remission status at transplantation, time from autologous HCT to relapse (<6 months, 6 to 12 months, >12 months), and donor/recipient CMV status did not have any statistically significant impact on OS, NRM, or relapse rate (Supplementary Figures S6 and 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], its use in patients 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, based on a recent report from the EBMT [19]. Given the limited availability of matched donors and the encouraging results of haploidentical allo-HCT for other malignancies, we conducted this retrospective analysis to investigate the outcomes of patients in the EBMT and CIBMTR registries with MM who underwent haploidentical allo-HCT. Our results demonstrate that haploidentical allo-HCT can be safely performed in appropriate patients with MM who lack an HLA-matched sibling or unrelated donor. All patients had failed at least 1 previous auto-HCT, and one-third had failed 2 auto-HCTs, a reflection of more advanced refractory disease. The 2-year OS of 48% in these patients compares favorably with that in allo-HCT using matched related or unrelated donors in patients with relapsed MM [20-23].

In a study reported by Castagna et al [10] of 30 patients with relapsed MM who underwent haploidentical allo-HCT using PT-Cy, 87% had neutrophil recovery and 60% had platelet recovery by day 30. In our present cohort, 97% of the patients had neutrophil recovery by day 28, and 75% had platelet recovery by day 60. The 1-year NRM of 21% in our study is somewhat higher than that reported by Castagna et al (10% at 18 months); however, it is in line with present observations of haploidentical allo-HCT in patients with myelodysplastic syndrome, a disease of older age similar to MM [9]. As supportive care

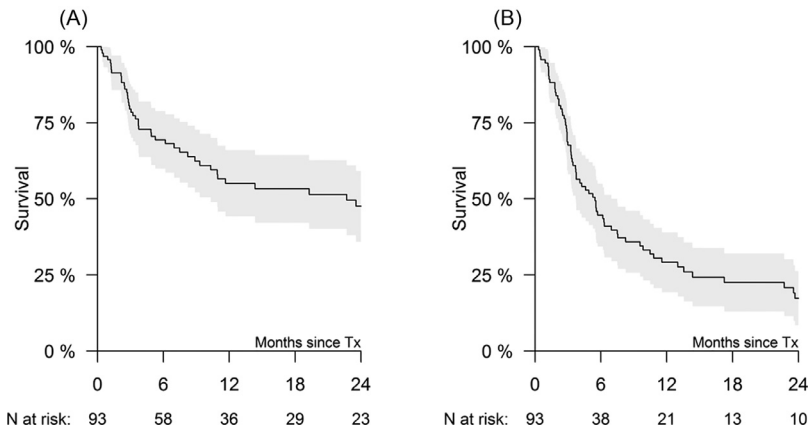

Figure 1. OS (A) and PFS (B).

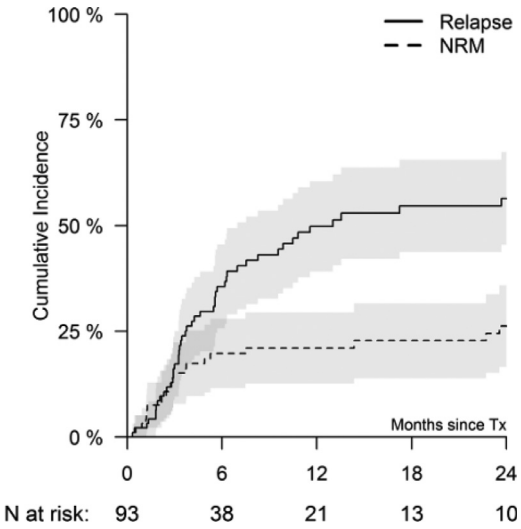

Figure 2. NRM and relapse rate.

continues to improve and new preparative regimens are developed, it is anticipated that the NRM rate will continue to decline. Our 2-year OS of 48% is close to that reported by Castagna et al [10]. In contrast to their observation, however, we noted an improved OS with BM as the stem cell source. The PFS of 17% and relapse rate of 56% in our study, although suboptimal, are similar to the results of salvage allo-HCT using matched donors in patients with relapsed/refractory MM as reported by the EBMT and other groups [24,25].

PT-Cy has been used to selectively deplete alloreactive T cells in haploidentical allo-HCT and can be extended to matched donor transplantation as a means of reducing 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 BM compared to PB as the stem cell source, mainly because of lower NRM. This observation requires validation by future studies. A recent retrospective comparison of BM and PB as the graft source in

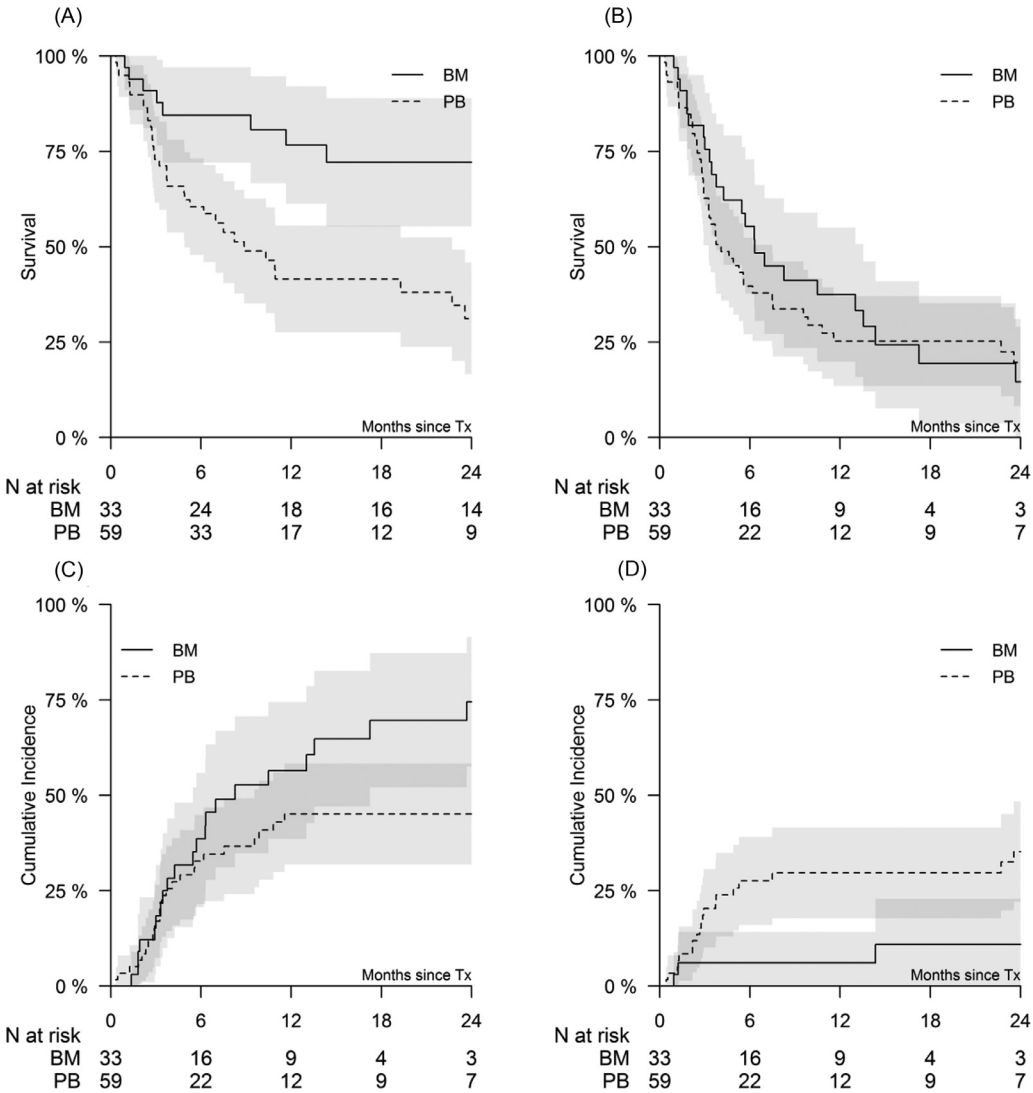

Figure 3. Effect of stem cell source on OS (A), PFS (B), relapse (C), and NRM (D).

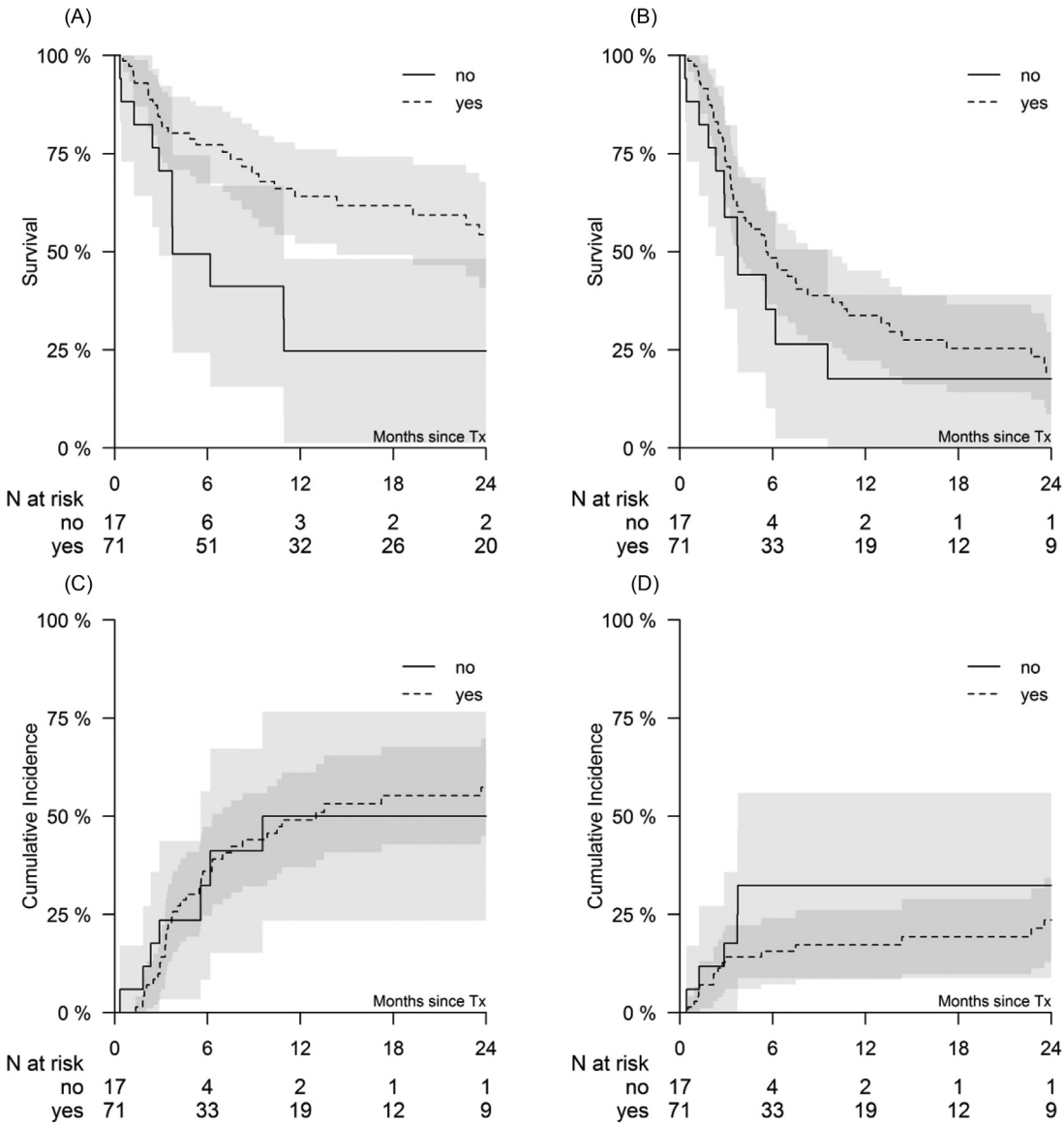

Figure 4. Effect of PT-Cy on OS (A), PFS (B), relapse (C), and NRM (D).

haploidentical allo-HCT recipients with various hematologic malignancies and receiving PT-Cy reported no significant differences in nonrelapse mortality risk, but a greater relapse risk with the use of BM [26].

Another study of 10 patients with MM who underwent haploidentical allo-HCT with a conditioning regimen of cytarabine, busulfan, cyclophosphamide, and simustine reported a 2-year OS of 46%, comparable to our experience [11]. In addition, our OS of 48% despite a high relapse rate indicates improved outcomes using salvage interventions, as well as possible synergism between a graft-versus-myeloma effect and retreatment after haploidentical allo-HCT [27]. This finding has been previously observed in the setting of allo-HCT [14,28].

The incidences of aGVHD and cGVHD in our present study are somewhat higher than those reported after haploidentical allo-HCT in patients with other malignancies. This finding may be explained in part by the older and more heterogeneous patient population in the registry data. We did not observe any associations between outcome and disease status, recipient and donor age, CMV serostatus, patient and donor sex mismatch, KPS score, or HCT-CI 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 rate; however, the allo-HCT platform can be used in the context of other post-transplantation immune-based strategies, such as donor-derived chimeric antigen receptor T cells and natural killer cell infusions, newer immunomodulatory drugs or proteasome inhibitors, bispecific T cell engagers, and bispecific killer cell engagers, to further enhance antitumor effects and ultimately improve survival in an appropriate patient population [29-31].

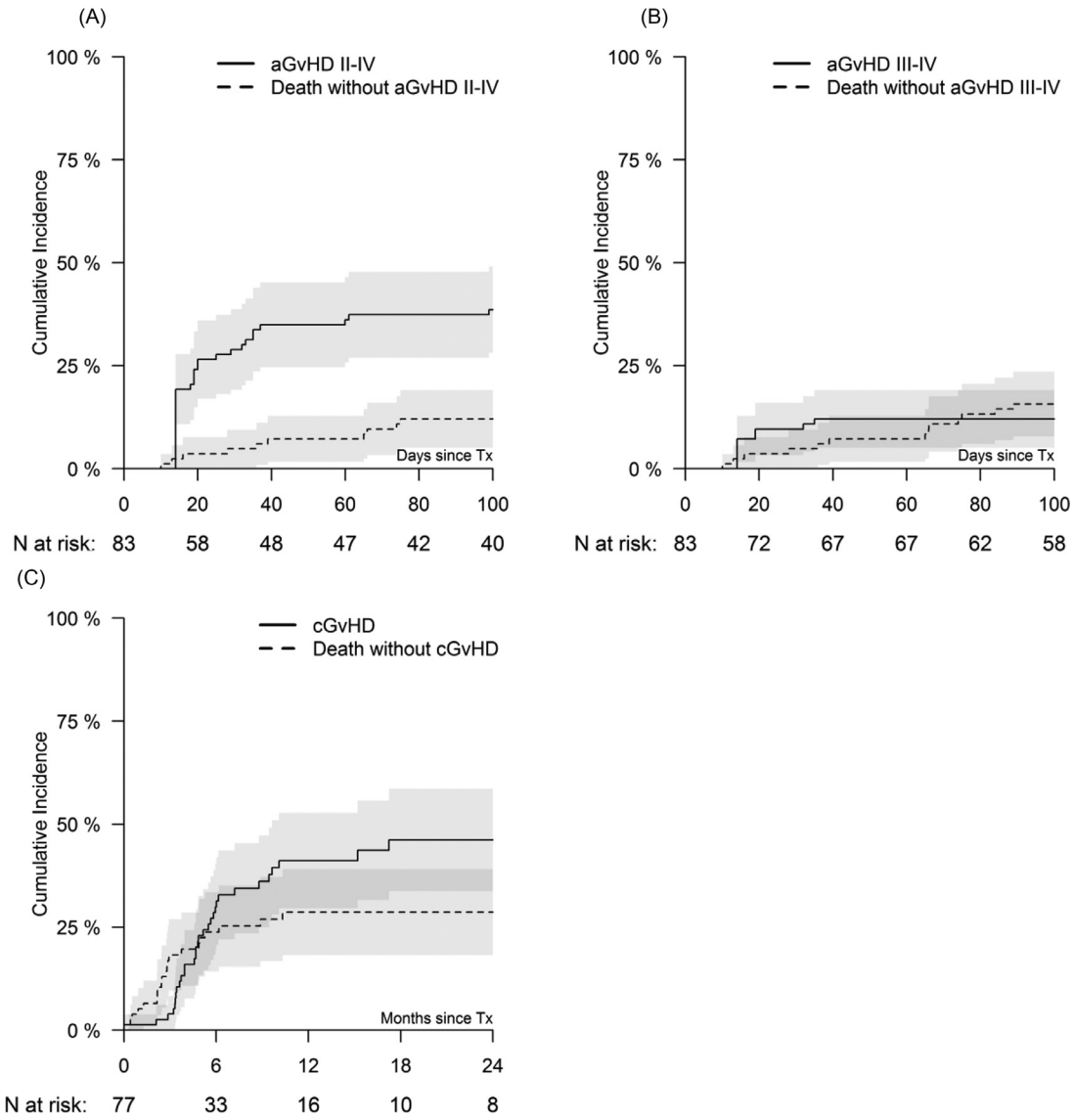

Figure 5. Cumulative incidence of aGVHD grade II-IV and death without aGVHD II-grade IV (A), aGVHD grade III-IV and death without aGVHD grade III-IV (B), and cGVHD and death without cGVHD (C).

ACKNOWLEDGMENTS

The authors thank the bone marrow transplant coordinator's office, the physicians and nurses, and members of the bone marrow transplant service for providing outstanding care. This work was presented in part at the 44th annual meeting of the European Society for Blood and Marrow Transplantation, Lisbon, Portugal, March 18-21, 2018.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: F.S., L.G., A.D., N.K., and P.H. designed the study; D.-G.E. performed the statistical analysis; all authors analyzed the data; F.S. and J.F.S. wrote the manuscript; and all authors reviewed the manuscript.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.bbmt.2018.09.018.

REFERENCES

1. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood*. 2007;109:3489–3495.
2. Wirk B, Byrne M, Dai Y, Moreb JS. Outcomes of salvage autologous versus allogeneic hematopoietic cell transplantation for relapsed multiple myeloma after initial autologous hematopoietic cell transplantation. *J Clin Med Res*. 2013;5:174–184.
3. Rosiñol L, Pérez-Simón JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*. 2008;112:3591–3593.
4. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;356:1110–1120.
5. Rotta M, Storer BE, Sahebi F, et al. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. *Blood*. 2009;113:3383–3391.
6. 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.

7. Devillier R, Legrand F, Rey J, et al. HLA-matched sibling versus unrelated versus haploidentical related donor allogeneic hematopoietic stem cell transplantation for patients aged over 60 years with acute myeloid leukemia: a single-center donor comparison. *Biol Blood Marrow Transplant*. 2018;24:1449–1454.
8. Salvatore D, Labopin M, Ruggeri A, et al. Outcomes of hematopoietic stem cell transplantation from unmanipulated haploidentical versus matched sibling donor in patients with acute myeloid leukemia in first complete remission with intermediate or high-risk cytogenetics: a study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*. 2018;103:1317–1328.
9. Robin M, Porcher R, Ciceri F, et al. Haploidentical transplant in patients with myelodysplastic syndrome. *Blood Adv*. 2017;1:1876–1883.
10. Castagna L, Mussetti A, Devillier R, et al. Haploidentical allogeneic hematopoietic cell transplantation for multiple myeloma using post-transplantation cyclophosphamide graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant*. 2017;23:1549–1554.
11. Chen Y, Lu J, Xu LP, et al. Safety and efficacy of haploidentical stem cell transplantation for multiple myeloma. *Bone Marrow Transplant*. 2018;53:507–510.
12. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant*. 2017;52:811–817.
13. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912–2919.
14. Gahrton G, Iacobelli S, Björkstrand B, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. *Blood*. 2013;121:5055–5063.
15. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol*. 2011;12:1195–1203.
16. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood*. 2006;107:3474–3480.
17. Lokhorst HM, van der Holt B, Cornelissen JJ, et al. Donor versus no-donor comparison of newly diagnosed myeloma patients included in the HOVON-50 multiple myeloma study. *Blood*. 2012;119:6219–6225.
18. Björkstrand B, Iacobelli S, Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. *J Clin Oncol*. 2011;29:3016–3022.
19. 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.
20. Auner HW, Szydlo R, van Biezen A, et al. 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;48:1395–1400.
21. Shimoni A, Hardan I, Ayuk F, et al. 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.
22. Kröger N. Unrelated stem cell transplantation for patients with multiple myeloma. *Curr Opin Hematol*. 2010;17:538–543.
23. Kröger N, Shimoni A, Schilling G, et al. Unrelated stem cell transplantation after reduced-intensity conditioning for patients with multiple myeloma relapsing after autologous transplantation. *Br J Haematol*. 2010;148:323–331.
24. Crawley C, Iacobelli S, Björkstrand 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.
25. Freytes CO, Vesole DH, LeRademacher J, et al. Second transplants for multiple myeloma relapsing after a previous autotransplant-reduced-intensity allogeneic vs autologous transplantation. *Bone Marrow Transplant*. 2014;49:416–421.
26. Bashey A, Zhang MJ, McCurdy SR, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T cell-replete haploidentical donor transplantation using post-transplant cyclophosphamide. *J Clin Oncol*. 2017;35:3002–3009.
27. Htut M, D'Souza A, Krishnan A, et al. Autologous/allogeneic hematopoietic cell transplantation versus tandem autologous transplantation for multiple myeloma: comparison of long-term postrelapse survival. *Biol Blood Marrow Transplant*. 2018;24:478–485.
28. 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*. 2011;117:6721–6727.
29. Shi J, Tricot G, Szmania S, et al. Infusion of haplo-identical killer immunoglobulin-like receptor ligand mismatched NK cells for relapsed myeloma in the setting of autologous stem cell transplantation. *Br J Haematol*. 2008;143:641–653.
30. Khan MW, Gul Z. Blinatumomab may induce graft-versus-host leukemia in patients with pre-B ALL relapsing after hematopoietic stem cell transplant. *Clin Case Rep*. 2016;4:743–746.
31. Ruggeri L, Capanni M, Mancusi A, et al. Alloreactive natural killer cells in mismatched hematopoietic stem cell transplantation. *Blood Cells Mol Dis*. 2004;33:216–221.