Alternative Donors

HLA-Mismatched Donors in Patients with Myelodysplastic Syndrome: An EBMT Registry Analysis

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A B S T R A C T

Recently, haploidentical transplantation (haplo) using post-transplant cyclophosphamide (PTCy) has been reported to give very encouraging results in patients with hematological malignancies. Patients who have no HLA-matched donor currently have the choice between a mismatched unrelated donor, an unrelated cord blood (CB) donor, and a haploidentical related donor. The aim of our study is to compare the outcome of patients with myelodysplastic syndrome (MDS) who have been transplanted from a haploidentical donor using PTCy, an HLA-mismatched unrelated donor (marrow or peripheral blood stem cells), or an unrelated mismatched CB donor. A total of 833 MDS patients from the European Group for Blood and Marrow Transplantation (EBMT) registry, transplanted between 2011 and 2016, were identified. The potential benefit of haplo was compared with mismatched unrelated and CB donors in an adjusted and weighted model taking into account potential confounders and other prognostic variables. Haplo was at lower risk of acute graft-versus-host disease (GVHD) than mismatched unrelated donor (P = .010) but at similar risk than CB. Progression-free survival was better after haplo (versus

mismatched unrelated, *P* = .056; versus CB, *P* = .003) and overall survival tended to be superior after haplo (versus mismatched unrelated, *P* = .082; versus CB, *P* = .002). Nonrelapse mortality was not significantly different between haplo and mismatched unrelated donors. Relapse risk was not influenced by the type of donor. In conclusion, patients with MDS from the EBMT registry receiving hematopoietic stem cell transplantation from a haplo donor have significantly better outcome than those receiving hematopoietic stem cell transplantation from a CB donor and at least similar or better outcome than with a mismatched unrelated donor. Prospective studies comparing the type of donors will be needed to confirm this assumption.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation remains the only curative treatment in patients with myelodysplastic syndrome (MDS). The reduction in transplant-related mortality in recent years has expanded the applicability of transplant to older patients and those with comorbidities. This is particularly relevant for patients with MDS who have a median age at diagnosis of 72 years. The introduction of reduced-intensity conditioning (RIC) regimens and the improvement in donor availability has further contributed to an increase transplant numbers globally. Lack of donor availability is less a significant problem given improvements in HLA typing methodology allowing better choices among unrelated donors, the development of cord blood banking, and finally the recent impressive improvements in haploidentical transplantation [1–8]. Indeed, patients lacking an HLA-matched donor could benefit from a mismatched unrelated donor (MisUD), haploidentical donor (haplo), or unrelated cord blood (CB) donor. Lee et al. [9] recently gave an European Group for Blood and Marrow Transplantation (EBMT) position regarding the place of haplo in patients with acute leukemia, stating that it is a valid option for patients without an HLA-matched donor or in patients needed an urgent transplant but fewer data are available in MDS. The EBMT group has previously reported that haplo performed before 2014 in MDS patients was complicated by a relatively high nonrelapse mortality (NRM); however, patients who received post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis had a better outcomes [10]. Given these significant improvements the question arises whether haploidentical transplantation using PTCy may be a better option for patients with MDS when fully matched HLA donors are unavailable. Herein we report a recent EBMT analysis comparing transplant outcomes among haplo with PTCy, MisUD, and CB.

METHODS

Patients with a primary diagnosis of MDS transplanted between 2011 and 2016 and registered in the European ProMise database were included if they had information regarding the type of donor: unrelated CB, MisUD (1 HLA mismatch of 10), or mismatched HLA-related donor (at least 2 mismatches). All time-to-event outcomes were counted from the date of transplant to the date of event or date of last follow-up. Grade II to IV acute GVHD was analyzed as a binary variable, as information was available for all patients with follow-up shorter than 3 months. NRM was considered as death by any cause occurring before disease relapse/progression. Death and second transplant were considered as a competing event for chronic GVHD. NRM and relapse/progression were considered to be mutually competing risks. The primary objective was to compare outcomes between the 3 donor groups, namely mismatched related donor (haplo), MisUD, and unrelated CB. To account for potential confounding, several strategies were used. First we used regression adjustment, by adjusting the analyses on potential confounders using Cox proportional hazards (overall survival [OS], progression-free survival [PFS]), proportional cause-specific hazards (competing risk outcomes), and logistic (grade II to IV acute GVHD) regression models. Variables used for adjustment were period of transplantation, age, patient sex, disease classification, time to transplant, blast count at transplantation, status at transplant, female donor to male recipient, cytomegalovirus recipient/donor matching, and conditioning regimen. Then we used inverse probability of treatment weighting [11,12]. This approach aims at reconstructing by weighting pseudopopulations where patients in the different groups have similar characteristics (pipeline is available in the Supplementary Methods). Inverse probability weights were obtained by modeling the group as a response variable in a multinomial model with the same variables as those used for regression adjustment as predictors. To avoid unstable results due to extreme weights, weights were trimmed at their first and 99th percentile (ie, the lowest and highest 1% weights were set equal to the first and 99th percentile, respectively). Last regression adjustment and inverse probability of treatment weighting were combined. For logistic and Cox models in the weighted sample, we used a robust variance estimator. Adjusted survival curves and cumulative incidence curves were obtained using the weighting approach [13]. The proportional hazards assumption was checked by examination of Schoenfeld residuals and Grambsch and Therneau's lack-of-fit test [14]. Missing data were handled through multiple imputations by chained equations methods [15,16]. Because International Prognostic Scoring System (IPSS) score and cytogenetics were missing for most patients, they were neither imputed nor used for imputation. With other predictors, 19% of patients had missing potential prognostic factors, so that 20 independent imputed datasets were generated and analyzed separately [17]. Variables used for multiple imputations were factors used for adjustment. Estimates of model parameters and discrimination indexes were then pooled over the imputations according to Rubin's rule [15]. All tests were 2-sided. Analyses were performed using the R statistical software version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient and Transplant Characteristics

A total of 833 patients undergoing a first hematopoietic stem cell transplantation for MDS between January 2011 and January 2016 were included in the study. Median follow-up was 30 (interquartile range, 18 to 47) months. Follow-up was shorter in the haplo group (median 24 months) than in the CB (median 37 months) and MisUD (median 33 months) groups (*P* = .002). Main characteristics of patients and transplant are given in Table 1. Characteristics did not differ according to donor type for patient and donor sex, disease classification, median time from diagnosis to transplant, and cytogenetics. Haplo transplanted patients were older (61 years of age), have been transplanted more recently (71% in 2014 to 2016), were less frequently in complete remission (CR) at time of transplant (29%). MisUD transplanted patients were characterized by a higher proportion of CR at time of transplant (38%), the more frequent use of peripheral blood as source of stem cells as compared with haplo (90% versus 54%), a high proportion of RIC (70%), and in vivo T cell depletion (86%). Patients transplanted from unrelated cord blood received RIC in a similar proportion to MisUD (69%) but more frequently received total body irradiation (TBI) (24%) and were younger.

Transplant Outcome

During follow-up, 447 patients died. Relapse was the cause of death for approximately one third of patients (33% in MisUD, 34% in haplo, and 31% in CB). Among nonrelapse causes of mortality, infection was the most frequent for the 3 groups: 45% for MisUD, 68% for haplo, and 56% for CB (among known causes of death, missing in 20 MisUD, 21 haplo, and 3 CB) followed by GVHD: 41%, 30%, and 25% for MisUD, haplo, and CB, respectively.

Weighted estimations for probability and incidences are reported in Table 2. Briefly, the probability of neutrophil engraftment was lower using CB (76% versus ≥84%) and grade II to IV acute GVHD was lower with haplo (23% versus ≥32%). Three-year adjusted cumulative incidence of chronic GVHD was higher using MisUD (39%) or haplo (36%) than using CB

Table 1
Characteristics of the Patients

	Haplo	MisUD	CB	*P* Value
Patient number	222	443	168	
Transplant period				
2011-2013	64 (29)	259 (59)	120 (71)	
2014-2016	158 (71)	184 (41)	48 (29)	<.0001
Sex				
Female	97 (44)	166 (37)	71 (42)	
Male	125 (56)	277 (62)	97 (58)	.25
Age at transplant, yr	61 (51-66)	59 (52-65)	57 (45-64)	.004
Disease classification				
RA/RARS/del5q	11 (5)	20 (4.5)	7 (4)	
RCMD	25 (11)	52 (12)	7 (4)	
RAEB	97 (44)	186 (42)	78 (46)	
Secondary AML	74 (33)	161 (36)	64 (38)	
Unclassifiable/other	15 (7)	24 (5.5)	12 (7)	.30
Time from diagnosis to transplant, mo	13 (8-26)	11 (7-21)	11 (6-22)	.12
Marrow blasts				
<5%	97 (45)	225 (53)	91 (56)	
≥5%	119 (55)	202 (47)	70 (43)	.061
Missing	6	16	7	
Status at transplant				
Untreated	33 (16)	91 (22)	23 (14)	
CR	60 (29)	159 (38)	78 (49)	
Non CR	115 (55)	170 (40.5)	59 (37)	
Missing	14	23	8	.0002
Cytogenetics*				
Good	56 (54)	106 (48)	35 (40	
Intermediate	28 (27)	56 (25.5)	33 (38)	
Poor	20 (19)	58 (26.5)	20 (23)	
Missing	118	223	80	.15
Donor/recipient sex match				
Female/male	37 (17)	91 (20.5)	34 (20)	
Other	185 (83)	352 (79.5)	134 (80)	.48
Donor/recipient cytomegalovirus match				
Negative/negative	36 (17)	102 (24)		
Positive/negative	9 (4)	39 (9)		
Negative/positive	41 (24)	133 (31)		
Positive/positive	118 (55)	152 (36)		
Missing	8	17		<.0001
Stem cell source				
Marrow	101 (45.5)	43 (10)		
PB	121 (54.5)	400 (90)		
Regimen				
RIC	123 (55.5)	308 (70)	116 (69)	
Myeloablative	99 (45)	134 (30)	52 (31)	.0009
Missing	0	1	0	
TBI ≥4 Gy	9 (4)	19 (4)	40 (24)	<.0001
In vivo T cell depletion	9 (4)	381 (86)	74 (44)	<.0001
Missing	0	11	3	
Post-transplant cyclophosphamide	222 (100)	28 (6.5)	5 (3)	
Missing	0	11	3	<.0001

Values are n (%) or median (interquartile range).
AML indicates acute myelogenous leukemia; RA, refractory anemia; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage cytopenia; RAEB, refractory anemia with excess blasts.
 * The cytogenetics group is defined as described in IPSS [38].

(29%). Three-year adjusted OS was 47%, 38%, and 31% with haplo, MisUD, and CB, respectively, while 3-year adjusted PFS was 43%, 33%, and 29%, respectively (Figure 1). Three-year NRM and 3-year relapse incidence were 36%, 40%, and 48% and 21%, 27%, and 23%, with haplo, MisUD, and CB, respectively (Figure 1). Comparison significance (*P* value) of haplo versus MisUD or CB of the weighted model is given in Table 3. Of note, in haplo, the use of marrow instead of peripheral blood (PB) was not a significant protector (hazard ratio [HR], 1.56; 95% confidence interval, .95 to 2.56; *P* = .077) while the source of stem cells had no impact on chronic GVHD incidence (HR, 1.08; 95% confidence interval, .66 to 1.76; *P* = .75).

Effect of the Type of Donor

To test the potential advantage of 1 type of donor over the others, 3 kinds of analyses were done: weighted; adjusted Cox analysis on period of transplantation, age, patient sex, disease classification, time to transplant, blast count at transplantation, status at transplant, female donor to male recipient, cytomegalovirus recipient/donor matching, and conditioning regimen; and a combined adjusted and weighted analysis. The complete adjusted analysis is available in **Supplementary Table S1**. The effect of the type of donor is shown in Table 3. Looking at the 3 models, the engraftment was generally better with haplo as compared with CB (HR between .55 and .59, *P* value between .057 and .094) but it was worse with haplo as compared with MisUD (HR between 1.47 to 1.67, *P* value between .066 and .14) without reaching significance. Grade II to IV acute GVHD was significantly reduced in haplo as compared with MisUD (HR between 1.68 and 1.79, *P* value between .011 and .006), but not significantly different as compared with CB even if there was a trend (HR between 1.52 and 1.56, *P* value between .071 and .10). Chronic GVHD was not influenced by the type of donor. Relapse risk was not influence by the type of donor. All 3 models were in favor of a significantly better outcome for NRM, PFS, and OS with haplo as compared with CB (*P* value always ≤.01 for the 3 models and 3 endpoints) (Table 3). When haplo was compared with MisUD, NRM was not significantly reduced (HR between 1.18 and 1.29, *P* value between .096 and .31) while there was a trend to a better PFS (*P* value between .034 and .056) and OS (*P* value between .027 and .082) with haplo.

Discussion

This study from the EBMT registry compared outcomes of patients who received transplant from a haploidentical donor, a MisUD or an unrelated CB donor in patients with MDS. The aim was to determine the best alternate donor in patients without a fully HLA-matched donor. Given the inherent limitations of the retrospective studies, we used 2 different methods to correct clinical disparities when testing the impact of donor type. In details, we used both regression adjustment and inverse probability weighting [18,19]. Formally regression adjustment and inverse probability weighting estimate a different treatment effect (conditional versus marginal) and rely on different assumption. Using several approaches is often used to strengthen the analysis of observational data as we and other have previously reported [20−22]. There remained differences in patients and transplant characteristics inherent to the transplant procedures and linked to donor type, for example, the use of post-transplant cyclophosphamide in haplo, the use of marrow or peripheral blood stem cells in haplo or MisUD, or the frequent use of TBI, which characterized the CB procedure. This could be explained by the different "packages," related with each procedure and type of graft (ie, PCT used with haplo, peripheral blood and in vivo T cell depletion used with MisUD, a TBI-based regimen with CB). Adjusted models take into account potential other risk factors, especially if they are unequally balanced between groups. The weighted model is done to correct differences between populations in each group and to create populations which are comparable. Hence adjusted and weighted models are probably most reflective of the real effect of type of donor.

In our study, NRM was the highest after CB consistent with other studies in acute myelogenous leukemia [4,23] and previous EBMT report comparing CB with PB [24]. Of note, NRM was relatively high after all types of HLA-mismatched transplant. While NRM is usually reported at <20% after haplo [5,25−27],

Table 2
Probabilities and Incidence for Outcome

Outcome at 3 yr	Haplo (95% CI) (%)	MisUD PB or marrow (%)	Unrelated CB (%)
Engraftment	84 (79-89)	90 (87-93)	76 (69-82)
Grade II-IV acute GVHD	23 (17-28)	35 (31-40)	32 (25-40)
Chronic GVHD	36 (28-44)	39 (33-44)	29 (21-37)
OS	47 (40-56)	38 (33-43)	31 (25-40)
PFS	43 (36-51)	33 (28-38)	29 (22-37)
NRM	36 (27-44)	40 (35-45)	48 (39-57)
Relapse	21 (15-28)	27 (22-32)	23 (16-31)

it was 36% in the current study, which was slightly lower with the previous MDS EBMT report on haplo (41%) [10]. The use of PTCy instead of ex vivo T cell depletion reduces the immunological defect; however, infections remained the first cause of death in haplo using PTCy, as it is after CB transplant. Regarding the role of source of stem cells in haplo, NRM was not significantly higher using PB, even if there was a trend. The

reason why MDS patients are more susceptible to die from NRM than patients with other diseases remains unclear but hypotheses could include the relatively older age of this group, potential treatment for previous malignancies, which make patients more sensitive to toxicity, and possibly more comorbidities. GVHD and death related to GVHD were more frequent after MisUD in this series. Taken with caution the registry data
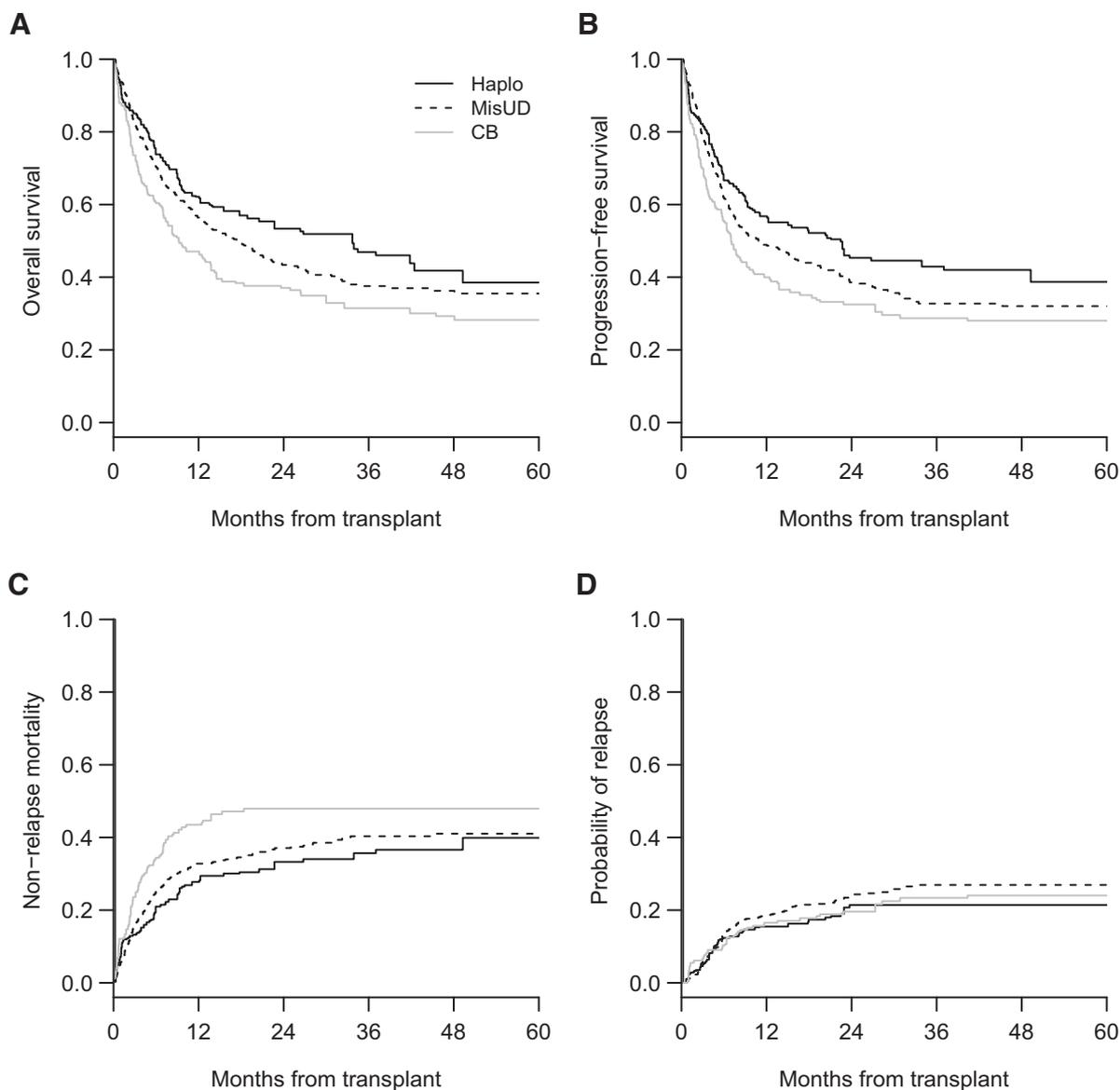

Figure 1. Outcome of patients according to the type of donor: (A) OS, (B) PFS, (C) NRM, and (D) relapse incidences. Potential significance between haplo and MisUD or haplo and CB are given in Table 3.

Table 3
Effect of the Type of Donor on Outcome

	Adjusted		Weighted		Adjusted and weighted	
	OR/HR (95% CI)	P Value	OR/HR (95% CI)	P Value	OR/HR (95% CI)	P Value
Engraftment						
Haplo	1		1		1	
MisUD	1.47 (.88-2.46)	.14	1.67 (.97-2.88)	.066	1.60 (.93-2.76)	.091
CB	.57 (.32-1.02)	.060	.59 (.32-1.09)	.094	.55 (.30-1.02)	.057
Grade II-IV acute GVHD						
Haplo	1		1		1	
MisUD	1.68 (1.13-2.49)	.011	1.83 (1.19-2.81)	.006	1.79 (1.15-2.78)	.010
CB	1.52 (.93-2.49)	.092	1.62 (.96-2.74)	.071	1.56 (.91-2.66)	.10
Chronic GVHD						
Haplo	1		1		1	
MisUD	1.17 (.85-1.60)	.35	1.15 (.83-1.61)	.39	1.11 (.78-1.59)	.57
CB	1.07 (.72-1.61)	.74	1.00 (.65-1.54)	.99	.95 (.60-1.50)	.82
Relapse/progression						
Haplo	1		1		1	
MisUD	1.27 (.88-1.83)	.21	1.35 (.91-2.02)	.14	1.36 (.90-2.05)	.14
CB	1.25 (.78-2.01)	.35	1.37 (.83-2.25)	.22	1.38 (.83-2.31)	.21
NRM						
Haplo	1		1		1	
MisUD	1.29 (.96-1.74)	.096	1.18 (.86-1.63)	.31	1.23(.88-1.72)	.22
CB	1.68 (1.17-2.41)	.005	1.66 (1.13-2.45)	.010	1.76 (1.16-2.65)	.007
PFS						
Haplo	1		1		1	
MisUD	1.29 (1.02-1.62)	.034	1.24 (.97-1.60)	.090	1.29 (.99-1.67)	.056
CB	1.51 (1.14-2.02)	.005	1.56 (1.14-2.13)	.005	1.64 (1.18-2.27)	.003
OS						
Haplo	1		1		1	
MisUD	1.32 (1.03-1.69)	.027	1.22 (.94-1.59)	.13	1.27 (.97-1.67)	.082
CB	1.65 (1.23-2.23)	.001	1.61 (1.17-2.22)	.003	1.73 (1.23-2.42)	.002

Haplo is the reference in this analysis.
OR indicates odds ratio.

which do not always distinguish primary or secondary cause of death (ie; GVHD versus infection), haplo appears to be followed by a higher rate of mortality due to infection, while MisUD was followed by higher rate of mortality due to GVHD leading to similar NRM haplo and MisUD.

Alternatively, it is uncertain that patients have received optimal GVHD prophylaxis. While prospective studies have reported the benefit of in vivo T cell depletion [28–31], this was not consistently used in all MisUD patients potentially contributing to higher rates of GVHD. Additionally the use of PTCy in the setting of unrelated transplant is challenging with interesting results reported so far [32,33]. In our study only 6.5% of patients in the MisUD received PTCy preventing any conclusions. For inferior outcomes with CB, similar observations can be done. Indeed, in a recent joint study from EBMT-EUROCORD, RIC was followed by the best outcome however 31% of patients in this cohort received a myeloablative approach [34]. In addition, the benefit of in vivo T cell depletion in CB transplant is highly debated however 44% of patients received it. Furthermore, high number of nucleated cells at CB collection is an important risk factor for outcome, but CB patients were all included regardless of the number of cells due to insufficient data on cell number. Other characteristics known to influence success in mismatched transplantation such as presence of donor directed HLA antibodies, CD34 count, and potency metrics such as CFU assay results were also not available. Results in patients transplanted from CB may have been better if we had excluded those with poor graft characteristics.

Given the possibility that haplo donors could have been selected based on a strategy believed to be better (the use of PTCy) but MisUD and CB have not been selected on donor availability, and comparison between groups should be interpreted with caution.

It is important to note that as in all studies, the current analysis reflects past results (2011 to 2016) and we cannot extrapolate to future years because 1 or several procedures and management strategies continue to improve. In 2017, we reported quite disappointing OS (38%) after haplo using PTCy performed previously (2006 to 2014), which has now increased to 47% (2011 to 2016), even if NRM remains relatively high (36%) [10]. The increased numbers of haplo transplant and substantial improvement in supportive care have probably contributed to improved expertise of centers transplanting into a decrease in mortality [1].

Regarding relapse risk, it is noteworthy that there was no difference between the 3 donor types. While it has been supposed that relapse risk may be increased after haplo, we failed to find it in this study confirming that graft-versus-MDS effects may be as strong as after HLA-MisUD. Relapse risk excess in haplo was initially reported after nonmyeloablative protocols using marrow as source of stem cells but not been confirmed recently and is not reported in more recent series [7,35,36]. One explanation may be that even if haplo is followed by lower risk of acute GVHD, the risk of chronic GVHD is as high as after unrelated donor transplant, possibly maintaining the graft-versus-MDS effect. The source of stem cells in haplo or MisUD might have an impact on chronic GVHD and relapse risk. In this study, the vast majority of MisUD transplant was PB, which prevented any supplemental statistical analysis. Regarding haplo, it has previously been demonstrated by the EBMT in MDS patients that the source of stem cells did not matter for outcome (OS, PFS, NRM, chronic GVHD) [6]. Two recent registry studies have also reported in patients with mixed malignancies that outcomes appear similar using PB or marrow [36,37].

In conclusion, the results of this large EBMT analysis show that the outcome from haplo using PTCy in MDS is a valid

option, possibly better than CB. As previously suggested in the setting of acute leukemia, in patients without an HLA-matched donor, haplo should be considered [9]. Furthermore, the cost effectiveness may in in favor haplo over an unrelated transplant. Prospective studies comparing the type of donor (haplo versus MisUD), especially using the same platform (PTCy) are required answer to this dilemma.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.08.026.

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