Biol Blood Marrow Transplant 25 (2019) 522–528

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Alternative Donors

Family Mismatched Allogeneic Stem Cell Transplantation for Myelofibrosis: Report from the Chronic Malignancies Working Party of European Society for Blood and Marrow Transplantation

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Article history:
Received 19 December 2017
Accepted 19 October 2018

Key Words:
Myelofibrosis
Haploidentical
Mismatched related donor

A B S T R A C T

This analysis included 56 myelofibrosis (MF) patients transplanted from family mismatched donor between 2009 and 2015 enrolled in the European Society for Blood and Marrow Transplantation database. The median age was 57 years (range, 38 to 72); 75% had primary MF and 25% had secondary MF. *JAK2* V617F was mutated in 61%. Donors were HLA mismatched at 2 or more loci. Stem cells were sourced from bone marrow in 66% and peripheral blood in 34%. The median $CD34^+$ cell dose was 4.8×10^6/kg (range, 1.7 to 22.9; n = 43). Conditioning was predominantly myeloablative in 70% and reduced intensity in the remainder. Regimens were heterogeneous with thiotepa, busulfan, fludarabine, and post-transplant cyclophosphamide used in 59%. The incidence of neutrophil engraftment by 28 days was 82% (range, 70% to 93%), at a median of 21 days (range, 19 to 23). At 2 years the cumulative incidence of primary graft failure was 9% (95% CI 1% to 16%) and secondary graft failure was 13% (95% CI 4% to 22%). The cumulative incidence of acute graft-versus-host disease (GVHD) grades II to IV and III to IV was 28% (95% CI 16% to 40%) and 9% (95% CI 2% to 17%) at 100 days. The cumulative incidence of chronic GVHD at 1 year was 45% (95% CI 32% to 58%), but the cumulative incidence of death without chronic GVHD by 1 year was 20% (95% CI 10% to 31%). With a median follow-up of 32 months, the 1- and 2-year overall survival was 61% (95% CI 48% to 74%) and 56% (95% CI 41% to 70%), respectively. The 1- and 2- year progression-free survival was 58% (95% CI 45% to 71%) and 43% (95% CI 28% to 58%), respectively, with a 2-year cumulative incidence of relapse of 19%

Financial disclosure: See Acknowledgments on page 528.

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https://doi.org/10.1016/j.bbmt.2018.10.017

(95% CI 7% to 31%). The 2-year nonrelapse mortality was 38% (95% CI 24% to 51%). This retrospective study of MF allo-SCT using family mismatched donors demonstrated feasibility of the approach, timely neutrophil engraftment in over 80% of cases, and acceptable overall and progression-free survival rates with relapse rates not dissimilar to the unrelated donor setting. However, strategies to minimize the risk of graft failure and the relatively high nonrelapse mortality need to be used, ideally in a multicenter prospective fashion.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-SCT) for primary myelofibrosis (MF) and secondary MF (post–polycythemia vera or post–essential thrombocythemia MF) remains the only established curative therapy. Current consensus European LeukemiaNet–European Society for Blood and Marrow Transplantation (EBMT) guidelines recommend that all patients with intermediate-2 or high-risk disease based on International Prognostic Scoring System (IPSS), Dynamic (D)-IPSS, or DIPSS-plus score up to age 70 years should be considered candidates for allo-SCT [1]. Those with intermediate-1 risk disease up to age 65 years should also be considered candidates for allo-SCT if they have either refractory or transfusion-dependent anemia, a percentage of blasts > 2% in the peripheral blood, or adverse cytogenetics [1].

The outcomes from such allo-SCT demonstrate survival rates of 40% to 60% at 4 to 5 years, yet there remains a significant transplant-related mortality of between 10% and 40% [2–4]. Data from the Center for International Blood and Marrow Transplant Research in the past decade indicate that approximately 1440 patients with MF underwent either a sibling or matched unrelated (MUD) donor transplant [5]. Within this period, although the numbers of haploidentical donor transplants increased relative to other donor sources, which remained stable in other disease types, this increase was not seen for MF [5].

Few transplants using mismatched related donors (MMRDs) in MF have been performed because of the risk of nonengraftment, augmented graft-versus-host disease (GVHD) rates, and historical exclusion of these patients from national clinical trials, leading to a paucity of data. Current donor selection strategies in the absence of a matched related or unrelated donor would consist of a mismatched unrelated donor (MMUD) or double umbilical cord blood transplants. Historically, umbilical cord blood transplants were associated with a higher graft failure rate that was abrogated by alterations to the conditioning regimen but achieved 2-year overall survival (OS) and disease-free survival rates of only 44% and 30%, respectively [6].

Recently, a single center compared its contemporaneous sibling (n = 11), unrelated (n = 6), and haploidentical (n = 20) transplants for MF, predominantly using myeloablative conditioning (MAC), demonstrating a 3-year transplant-related mortality of 16%, relapse rate of 16%, and actuarial OS of 70%, whereby survival of patients with an alternative donor was 69%—similar to the 72% obtained with matched sibling donors (MSDs) [7]. Given the need for alternative donors we retrospectively studied the outcomes of MMRD transplants recorded in the EBMT database between 2009 and 2015.

METHODS

All patients provided informed consent for data registration, according to the Declaration of Helsinki. This study was approved by the Chronic Malignancies Working Party of the EBMT. Data were retrieved from the EBMT registry for MMRD transplants performed between 2009 and 2015. Because this is a registry-based study, albeit very probable, it cannot be confirmed that all consecutive patients from each center were submitted to the EBMT.

A MED-C questionnaire was sent to centers to complete missing data and for diagnosis confirmation. Patients were included if the family donor was ≥2 Ag mismatch and at least haplotype (3/6) matched.

Neutrophil engraftment was defined as the time at which the absolute neutrophil count was $\geq .5 \times 10^9$/L for 3 consecutive days and platelet engraftment as a platelet count $> 20 \times 10^9$/L for 7 consecutive days without transfusion support. Primary graft failure was defined as failing to reach a neutrophil count $> .5 \times 10^9$/L in the first 28 days after SCT or documentation of autologous reconstitution by chimerism analysis in the absence of relapse [8]. Secondary graft failure was defined by the treating physician: Standard criteria across Europe would be loss of a functioning graft demonstrated by cytopenia in at least 2 lineages and loss of donor chimerism.

Complete remission was conventionally defined if all the following were achieved: resolution of disease-related symptoms and signs including palpable hepatosplenomegaly, hemoglobin > 11 g/dL, platelets $> 100 \times 10^9$/L, and neutrophils $> 1 \times 10^9$/L with normal bone marrow histology and fibrosis grade no higher than 1. Relapse was defined as loss of complete remission. For this study both complete remission and relapse were designated by the treating physician.

Conditioning regimes were defined as MAC if they contained either total body irradiation (TBI) with a dose > 6 Gy, oral busulfan dose > 8 mg/kg, or i.v. busulfan > 6.4 mg/kg. Additional variables included remission status, stem cell source, donor gender, donor–recipient gender match, and recipient age.

Pretransplant patient characteristics were expressed as the median and range for continuous variables and frequencies and proportions for categorical variables. Primary endpoints were OS, progression-free survival (PFS), cumulative incidence of relapse/progression (CIR), and nonrelapse mortality (NRM), evaluated at 24 months after transplant. Median follow-up was determined using the reverse Kaplan-Meier method. The cumulative incidences of grades II to IV and III to IV acute GVHD (aGVHD) and limited/extensive chronic GVHD (cGVHD) were also estimated at 100 days and 12 and 24 months, respectively. The cumulative incidences of neutrophil and platelet engraftment were estimated at 28 days and 100 days, respectively. OS and PFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups before 12 months 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 death before aGVHD and cGVHD with the competing event 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 were assessed using Gray's test. All estimates were reported with (95% CI) confidence intervals. All P values were 2-sided, and $P < .05$ was considered significant. Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL) and R version 3.0.3 (R core team, Vienna, Austria) using packages "prodlim" and "cmprsk."

RESULTS

Patient Characteristics

From the EBMT registry 56 patients were identified with primary MF or secondary MF who underwent allo-SCT from ≥2 antigen MMRDs. The median patient age at the time of transplant was 57 years (range, 38 to 72). Recipients were predominantly men (57%), with 43% women. Disease type at diagnosis was primary MF (75%) and post–polycythemia vera/post–essential thrombocythemia MF (25%). Patient, disease, and transplant characteristics are shown in Table 1. The median interval from diagnosis to allo-SCT was 48 months (range, 4 to 213). IPSS score was not complete and hence not analyzed. Karnofsky performance status was 90 to 100 in 64% and <90% in 36% of patients; data were missing for 6 patients. Cytogenetic data were unfortunately largely unavailable and hence not analyzed. Regarding mutational profile, *JAK2* V617F was mutated in 61% of patients for whom the status was known (n = 33). Data for *MPL* and *CALR* mutations was not

Table 1
Patient Characteristics

Characteristic	Value
Patient age, yr, median (range) (n = 56)	57 (38-72)
Sex (n = 56)	
Male	32 (57)
Female	24 (43)
MPS subclassification (n = 56)	
Primary MF	42 (75)
Secondary MF	14 (25)
Risk profile according to Lille score (n = 41)	
Low	8 (20)
Intermediate	21 (51)
High	12 (29)
Splenomegaly (n = 41)	
Enlarged	27 (66)
Not enlarged	14 (34)
JAK2V617F mutation status (n = 33)	
Positive	20 (61)
Negative	13 (39)
Disease status at transplant (n = 49)	
No prior treatment/stable disease	33 (67)
Relapse/progression	16 (33)
Relationship HLA mismatch relative (n = 39)	
Child	34 (87)
Sibling	4 (10)
Further removed	1 (3)
Donor gender (n = 56)	
Female	15 (27)
Male	41 (73)
Donor–recipient (n = 56)	
F–M	8 (14)
F–F	7 (13)
M–F	17 (30)
M–M	24 (43)
Stem cell source (n = 56)	
Bone marrow	37 (66)
PBSCs	19 (34)
Median $CD34^+$ infused stem cells, $\times 10^6$/kg body weight (range) (n = 43)	4.8 (1.7-22.9)
Cytomegalovirus serostatus of recipient and donor (n = 51)	
Negative–negative	5 (10)
Negative–positive	3 (6)
Positive–negative	17 (33)
Positive–positive	26 (51)
Conditioning intensity (n = 56)	
MAC	39 (70)
RIC	17 (30)
GVHD prophylaxis	
PTCy	44 (79)
Other	12 (21)
Karnofsky performance score (n = 50)	
≥90	32 (64)
<90	18 (36)

Values are n (%) unless otherwise defined. MPS indicates myeloproliferative syndrome.

available. Because this is a registry-based study, albeit very probable, it cannot be confirmed that all consecutive patients from each center were submitted to the EBMT.

Donor and Transplant Characteristics

All 56 mismatched donors were relatives with ≥2 Ag HLA mismatch with the recipient. Among 39 donors, for whom the relationship was available in registry data, offspring accounted for 87%, sibling 10%, and a donor from a further removed relative in 3%. Regarding donors, 41 (73%) were men and 15 (27%) were women, with a median age of 32 years (range, 20 to 53). Cytomegalovirus recipient–donor serology was −/− in 10%, −/+ in 6%, +/− in 33%, and +/+ in 51%; data were missing in 5 cases. As regards hematopoietic stem cell source, bone marrow was used in 66% and peripheral blood in 34%. The median total nucleated cell count was 7.5×10^8/kg (range, 2.4 to 17.6; n = 11). The median $CD34^+$ cell dose was 4.8×10^6/kg (range, 1.7 to 22.9), with available data in 43 recipients. Conditioning was MAC in 70% of patients and reduced-intensity conditioning (RIC) in 30%. Post-transplant cyclophosphamide (PTCy) was used as GVHD prophylaxis in 79%, and hence 21% used alternative GVHD prophylaxis. Conditioning regimens were heterogeneous and are shown in Supplementary Table 1. The most common regimen (n = 33; 59%) was thiotepa 10 mg/kg, busulfan 6.4 or 9.6 mg/kg, and fludarabine 150 mg/m^2 with PTCy and cyclosporine A/mycophenolate mofetil.

Table 2
Outcomes

Outcome	Value
Neutrophil engraftment (ANC > $.5 \times 10^9$/L)	
Days to ANC engraftment, median (95% CI)	21 (19-23)
Incidence at 28 days post-HSCT, %	82 (70-93)
Platelet engraftment (platelets > 20×10^9/L)	
Days to platelet engraftment, median (95% CI)	35 (27-81)
Incidence at 100 days post-HSCT, %	70 (53-88)
2-Year cumulative incidence of primary graft failure, % (95% CI)	9 (1-16)
Secondary graft failure, % (95% CI)	13 (4-22)
Cumulative incidence of aGVHD at 100 days, % (95% CI)	
Grades II-IV	28 (16-40)
Grades III-IV	9 (2-17)
Cumulative incidence of limited/extensive cGVHD at 1 year, % (95% CI)	
Death without cGVHD	45 (32-58)
cGVHD at 2 years	20 (10-31)
Death without cGVHD	48 (34-61)
	25 (12-38)
OS, %	
12 months (95% CI)	61 (48-74)
24 months (95% CI)	56 (41-70)
PFS, %	
12 months (95% CI)	58 (45-71)
24 months (95% CI)	43 (28-58)
CIR, %	
12 months (95% CI)	7 (0-14)
24 months (95% CI)	19 (7-31)
GVHD relapse-free survival, %	
12 months (95% CI)	32 (19-45)
24 months (95% CI)	21 (8-35)
NRM, %	
12 months (95% CI)	35 (22-48)
24 months (95% CI)	38 (24-51)

ANC indicates absolute neutrophil count; CI, confidence interval.

Engraftment

Primary engraftment data (Table 2) were available for 56 patients. The incidence of neutrophil engraftment at 28 days was 82% (95% CI 70% to 93%), at a median time of 21 days (range, 19 to 23).

The cumulative incidence of primary graft failure at 2 years was 9% (95% CI 1% to 16%) and secondary graft failure was 13% (95% CI 4% to 22%). Secondary graft loss occurred at a median of 4.2 months (range, 3.5 to 12.1) after allo-SCT. The incidence of platelet engraftment at 100 days was 70% (95% CI 53% to 88%), at a median time of 35 days (range, 27 to 81). Three patients did not nadir platelets to below 20×10^9/L. Subanalyses did not demonstrate any significant differences in engraftment times for neutrophils or platelets between peripheral blood stem cell (PBSC) and bone marrow stem cell source, MAC versus RIC, sex mismatch or age of donor or recipient, GHVD prophylaxis with PTCy, or CD34 dose > or $<5 \times 10^6$/kg.

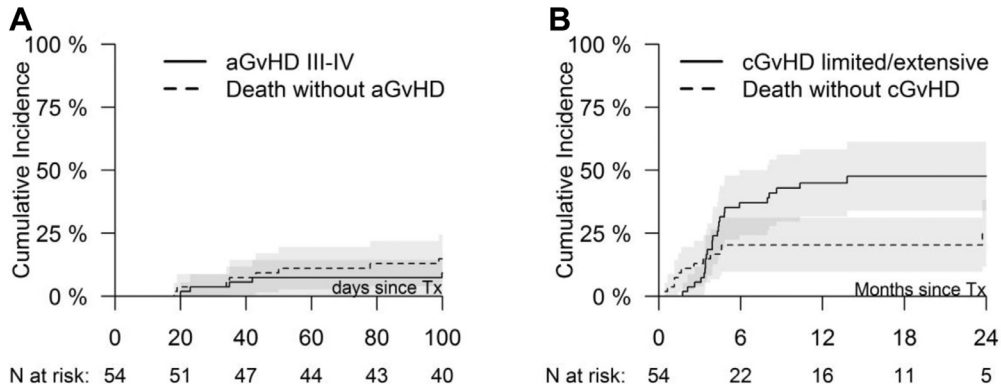

Figure 1. (A) Cumulative incidence of aGVHD grades III to IV. (B) Cumulative incidence of cGVHD until 2 years after transplant.

Graft-versus-Host Disease

The cumulative incidence of grades II to IV aGVHD at 100 days was 28% (95% CI 16% to 40%), whereas the cumulative incidence of grades III to IV aGVHD at 100 days in surviving patients was 9% (95% CI 2% to 17%) (Figure 1 A). The cumulative incidence of cGVHD at 1 year was 45% (95% CI 32% to 58%); the cumulative incidence of limited cGHVD at 1 year was 39% (95% CI 26% to 52%), extensive 6% (95% CI 0% to 12%), and mortality without 20% (95% CI 10% to 31%). The cumulative incidence of limited cGVHD at 2 years was 42% (95% CI 28% to 56%) (Figure 1B), extensive 6% (95% CI 0% to 12%), and mortality without 25% (95% CI 12% to 38%). Those who died before engraftment (n = 2) and failed primary engraftment (n = 5) were not assessable for aGVHD or cGHVD.

Survival and Relapse

The median follow-up was 32 months (range, 18 to 37), and all patients had complete survival and relapse information. A total of 33 patients were alive at last follow-up. Disease relapse/progression caused death in 2 patients (9%). OS at 12 months was 61% (95% CI 48% to 74%) and at 24 months was 56% (95% CI 41% to 70%). PFS at 12 months was 58% (95% CI 45% to 71%) and at 24 months was 43% (95% CI 28% to 58%) Figure 2. Univariate analysis for factors affecting OS and PFS are shown in Table 3. No factor was statistically significant in affecting OS or PFS. The CIR at 1 year was 7% (95% CI 0% to 14%), whereas the 2-year CIR was 19% (95% CI 7% to 31%). Of the patients who relapsed, 8 had engrafted previously and 1 patient was reported as secondary graft failure with disease progression. The NRM was 35% (95% CI 22% to 48%) at 1 year and 38% (95% CI 24% to 51%) at 2 years. The causes of NRM were infection (14 patients, 61%), GVHD (4 patients, 17%), and organ damage or failure (3 patients, 13%). Finally, GVHD relapse-free survival at 1 year was 32% (95% CI 19% to 45%) and at 2 years was 21% (95% CI 8% to 35%), although we recognize the caveats of using this endpoint from registry data.

Donor Lymphocyte Infusions and Second Stem Cell "Infusions"

Two patients had a donor lymphocyte infusion (DLI), and both were censored (1 was lost to follow-up at approximately 1 year and 1 at 2.5 years and so was administratively censored at 2 years.). With regard to second stem cell "top-ups," full details were unavailable.

Comparison between Conditioning Regimens

No significant differences in OS, PFS, CIR, NRM, or aGVHD and cGVHD rates between thiotepa/busulfan/fludarabine–PTCy and other MMRD conditioning regimens were evident, although it must be acknowledged that this is a small cohort. No difference in OS, PFS, or GVHD-free relapse-free survival was evident between patients transplanted with PTCY as GVHD prophylaxis (n = 44) versus those who had other GVHD prophylaxis (n = 12).

DISCUSSION

It is well established that allo-SCT for MF can be curative and is normally reserved for those with IPSS/DIPSS intermediate-II or high-risk disease who have a suitable donor and no contraindication to allo-SCT [3,9]. Although MSDs appear to consistently provide better outcomes, MUDs have been reported to result in inferior outcomes in some reports [9–14] but equivalent in others [3]. Current donor algorithms, although under review, would place an MMRD as an alternative to cord blood transplantation for MF cases lacking an MSD or MUD/MMUD. Collectively, however, outcomes from MMUDs in MF tend to suggest adverse outcomes as regards both relapse-free and OS with NRM approaching 38% at 1 year in some published cohorts; hence, it is important to understand the role of MMRDs [3,4]. In this retrospective registry analysis we demonstrate, in the largest cohort published to date, that patients with MF undergoing a family mismatched/haploidentical allo-SCT can achieve engraftment with acceptable levels of both aGVHD or cGVHD and encouraging PFS and OS rates.

In the current series failure of sustained engraftment occurred in up to 22% of patients. Although these rates of graft failure appear to be comparable with previous reports from unrelated donors [9–11], they contrast with the 95% engraftment rate reported by Bregante et al. [7] for MMRDs using a myeloablative, dual alkylator thiotepa, busulfan, and PTCy conditioning with bone marrow as the stem cell source. Factors that may have affected engraftment in that series were anticipated and preemptive interventions planned such as splenectomy if splenic dimensions were ≥22 cm (in 24% of recipients), aiming for a higher CD34 cell dose of $>3.3 \times 10^6$/kg recipient body weight and managing primary engraftment with a $CD34^+$ selected PBSC infusion if chimerism was >99% but in the presence of poor counts. If chimerism was less than 100% a fludarabine/Cy/TBI PBSC haploidentical allo-SCT was performed. Each of these strategies would be of potential value to enhance engraftment with MMRDs, and these data suggest that their timely deployment yields good results. It must also be noted

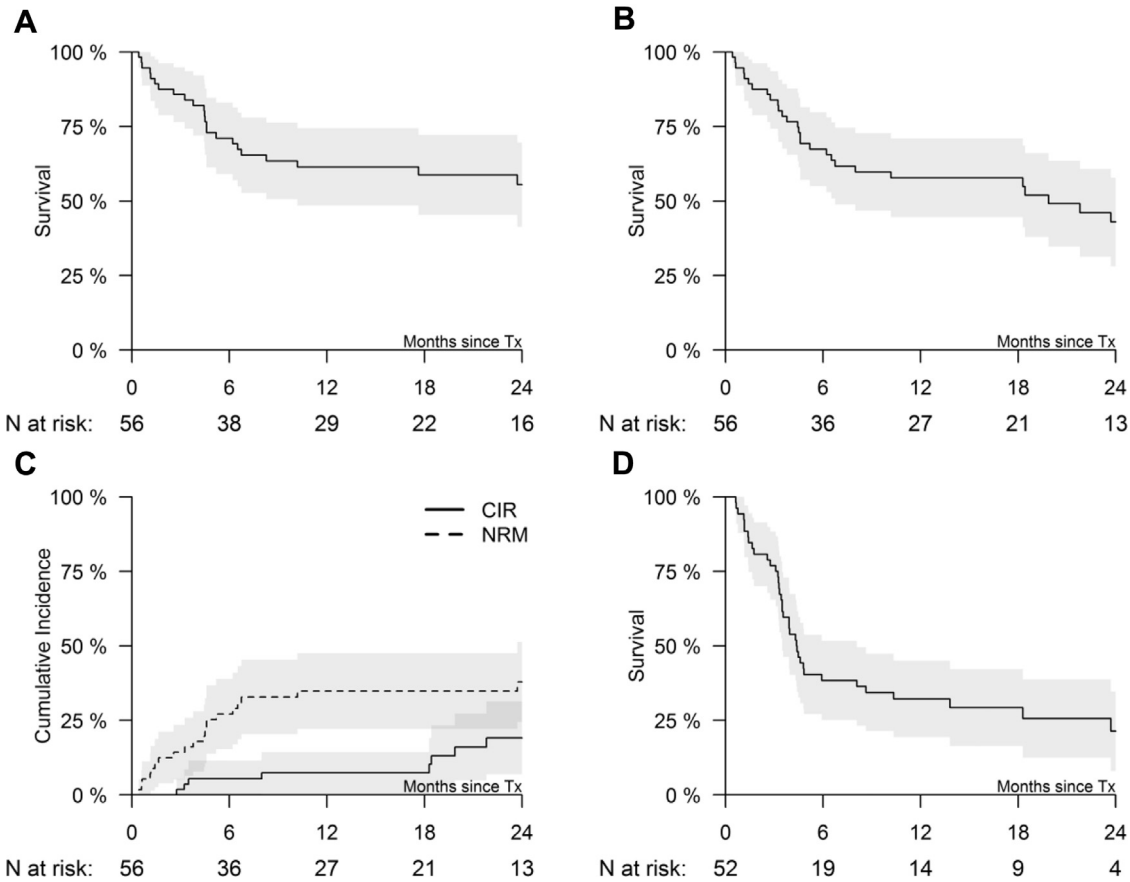

Figure 2. (A) OS and (B) PFS post-transplant of the entire cohort as estimated by the Kaplan-Meier method. (C) CIR and NRM for the entire cohort. (D) GVHD-free relapse-free survival.

that with registry data we are relying on adequate definition of secondary graft failure by the treating physicians.

In our retrospective multicenter series only 2 patients received DLIs, the median CD34 cell dose was higher but with a wider range, and data on second grafts or stem cell boosts were not readily available. Bone marrow was the stem cell source in 61% of the patients in this cohort but appeared not to affect engraftment rates or the conditioning regimen intensity. Strategies in place for sibling and MUD transplants probably need to be used to enhance and maintain engraftment including consideration of DLIs and an early second SCT in the event of poor graft function or late graft failure. Moreover, in the setting of bulky splenomegaly and primary graft failure, consideration could be given to post-SCT splenectomy. Given the rates of graft failure, it may be warranted to have potential second donors identified in case these are needed on an emergent basis. Issues with sustained engraftment would have also contributed to the relatively high NRM in this cohort, akin to what has been described for MMUD in MF. The authors did not have access to chimerism data and did not attempt to differentiate between the physician nominated relapse or graft failure, and it is possible due to the difficulty with applying these definitions that mortality attributed to relapse may be NRM and vice versa.

In general, aGVHD rates within this cohort appeared to be relatively low at 28% for grades II to IV (16% to 40%) and 9% for grades III to IV (2% to 17%). However, the cumulative incidence of limited/extensive cGVHD at 2 years was 48% (34% to 61%), similar to that experienced with MUDs in previous studies [9–12]. Regarding relapse, although a longer follow-up period is required, the CIR was 19% at 2 years and is not dissimilar to the long-term results from the prospective EBMT RIC-alloSCT study, which demonstrated a relapse risk of up to 22% at 3 years and approximately 28% at 5 years [3].

NRM in this series was relatively high and may be dependent on the type of donor used. Prospective data from the FLudarabine Busulphan Anti-thymocyte Globulin (FBATG) reduced intensity conditioned peripheral blood stem cell haploidentical transplants [3] reported by the EBMT were 16% but varied by donor from 10% MSD to 38% for MMUD. Likewise, NRM was also high in the prospective study of MF patients conditioned with fludarabine-melphalan-antithymocyte globulin [14] where NRM was 22% in the sibling donor and up to 59% in the unrelated donor group. However, engraftment was lower at 79% for unrelated donors compared with sibling donors, and this may well directly influence the high NRM rates. The NRM with both Volunteer unrelated donor (VUD) and haploidentical donors where engraftment rates exceeded 95% was low at 16% [3,4].

MMUD outcomes were worse with an increased hazard ratio for both OS and NRM compared with both MSDs and MUDs. Of note, it was previously hypothesized that recipients with MF may be more sensitive to HLA disparity due to the nature of their underlying disease and general debilitation, and indeed perhaps one could hypothesize the inherent immune deregulation [15]. Initial reports concerning the use of umbilical cord blood for patients with fibrotic bone marrows reported neutrophil engraftment between 80% and 93% by day 60, early full donor chimerism by day 14, and low aGVHD of 36%. However, the OS at 4 years was disappointing at 29%,

Table 3
Univariate Analysis of Factors Affecting OS and PFS Outcomes at 1 Year after Allo-SCT Are Reported for Subgroups

	No. of Cases	1 -Year OS (%)	1 -Year PFS (%)	1 -Year GVHD-Free Relapse-Free Survival (%)
Total	56	61 (48-74)	58 (45-71)	32 (19-45)
Age				
<60 yr	33	63 (46-80)	56 (39-74)	37 (19-55)
≥60 yr	23	60 (39-80)	60 (39-80)	26 (8-44)
		$P = .9$	$P = .5$	$P = .4$
Gender				
Male	32	56 (39-73)	50 (32-67)	25 (10-41)
Female	24	69 (51-88)	69 (51-88)	45 (24-66)
		$P = .3$	$P = .1$	$P = .2$
Donor–recipient gender match				
F–M	8	50 (15-85)	38 (4-71)	14 (0-40)
F–F	7	71 (38-100)	71 (38-100)	50 (10-90)
M–F	17	69 (46-92)	69 (46-92)	43 (18-68)
M–M	24	58 (38-78)	54 (34-74)	29 (10-47)
		$P = .8$	$P = .4$	$P = .4$
JAK2				
Wild-type	13	85 (65-100)	77 (54-100)	31 (6-56)
Mutated	20	50 (28-72)	50 (28-72)	30 (10-50)
		$P = .07$	$P = .2$	$P = .5$
Interval of diagnosis to transplant				
<36 mo	23	78 (60-95)	73 (54-92)	40 (20-61)
≥36 mo	33	52 (34-69)	48 (31-66)	29 (13-45)
		$P = .09$	$P = .1$	$P = .4$
Diagnosis				
Primary MF	42	63 (49-78)	61 (46-76)	31 (17-45)
Secondary MF	14	55 (28-82)	48 (21-75)	42 (14-70)
		$P = .8$		$P = .4$
TBI				
No	50	62 (48-75)	60 (46-73)	35 (22-49)
Yes	6	62 (21-100)	—	—
		$P = .9$		
Stem cell source				
Bone marrow	37	61 (46-77)	61 (46-77)	30 (15-45)
PBSCs	19	61 (39-84)	51 (27-74)	40 (17-64)
		$P = 1$	$P = .4$	$P = .7$
PTCy				
No	12	73 (47-99)	65 (37-93)	42 (14-70)
Yes	44	58 (43-73)	56 (41-71)	31 (17-45)
		$P = .2$	$P = .4$	$P = .6$
MAC				
No	17	55 (29-80)	48 (22-74)	34 (9-60)
Yes	39	64 (49-79)	62 (46-77)	34 (18-48)
		$P = .5$	$P = .3$	$P = .9$

Values in parentheses are 95 confidence intervals.

because of a high rate of relapse and a high transplant-related mortality at 35% [6,16,17]. Higher relapse rates and worse survival make this a less attractive stem cell source, compounded by the fact that strategies to enhance or maintain engraftment are limited by the current inability to boost the graft source.

There has been a global increase in MMRD transplants [18] with both T cell–depleted [19] and unmanipulated graft protocols conditioned with either antithymocyte globulin [20] or PTCy [21,22]. However, MMRD transplants in MF have been limited to small numbers included in large series of patients transplanted for MF [4] or haploidentical transplant protocol development for hematologic disease [23]. Raiola et al. [23] described the use of thiotepa, busulfan, and fludarabine or TBI and fludarabine with PTCy, cyclosporine, and mycophenolate mofetil as GVHD prophylaxis and bone marrow as the graft source for a variety of conditions. Updated results included 16 MF patients among a total of 148 patients. Impressively, only 1 patient with MF and an enlarged spleen failed to engraft [23,24]. In both these studies the median time to neutrophil engraftment was 18 days. aGVHD grades II to IV was 24% with 10% experiencing grades III to IV aGVHD, and the cumulative incidence of moderate to severe cGVHD was 12%. This study suggested that patients older than 60 experienced higher aGVHD and cGVHD rates and that disease phase predicted relapse [24].

A major drawback of our current study is the absence of both molecular and cytogenetic data in describing overall patient risk, and that may aid prediction of outcomes after allo-SCT. Molecular monitoring should be investigated prospectively in this setting. Furthermore, there are little data to guide the use of DLI, either preemptive or salvage, in the setting of MMRD for MF. Others [25–27] have previously described the effective use of $CD34^+$ selected stem cell infusion for poor graft function and DLI for mixed-donor chimerism in MSD and MMUD transplants. Prospective studies of these approaches in the MMRD setting are needed to see if rates of late graft loss, as highlighted by our study, can be reduced. It will also be important to study the effect of HLA donor-directed antibodies in mediating graft rejection in this setting.

In conclusion, we demonstrate in a large cohort of MF patients the feasibility of using an MMRD approach with over 80% neutrophil engraftment, acceptable GVHD, and OS at a median of 2.5 years follow-up. Strategies to enable sustained engraftment and reduce relapse and NRM that remain relatively

high need to be used in prospective studies to improve outcomes. Further comparisons of MUD and MMUD transplants are required with longer follow-up in a prospective fashion.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

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

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bbmt.2018.10.017.

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