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Comparison of Outcomes of Allogeneic Transplantation for Primary Myelofibrosis among Hematopoietic Stem Cell Source Groups

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A B S T R A C T

The choice of alternative donor is a major issue in allogeneic hematopoietic stem cell transplantation (HSCT) for patients with primary myelofibrosis (PMF) without an HLA-matched related donor. We conducted this retrospective study using the Japanese national registry data for 224 PMF patients to compare the outcomes of first allogeneic HSCT from HLA-matched related donor bone marrow (Rtd-BM), HLA-matched related donor peripheral blood stem cells (Rtd-PB), HLA-matched unrelated donor bone marrow (UR-BM), unrelated umbilical cord blood (UR-UCB), and other hematopoietic stem cell grafts. Nonrelapse mortality (NRM) rates at 1 year after Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantations were 16%, 36%, 30%, 41%, and 48%, respectively. Multivariate analysis identified UR-UCB transplantation, other transplantation, frequent RBC transfusion before transplantation, and frequent platelet (PLT) transfusion before transplantation as predictive of higher NRM. Relapse rates at 1 year after Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation were 14%, 17%, 11%, 14%, and 15%, respectively. No specific factor was associated with the incidence of relapse. Overall survival (OS) at 1 and 4 years after Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation were 81% and 71%, 58% and 52%, 61% and 46%, 48% and 27%, and 48% and 41%, respectively. Multivariate analysis identified older patient age, frequent RBC transfusion before transplantation, and frequent PLT transfusion before transplantation as predictive of lower OS. In conclusion, UR-UCB transplantation, as well as UR-BM transplantation, can be selected for PMF patients without an HLA-identical related donor. However, careful management is required for patients after UR-UCB transplantation because of the high NRM. Further studies including more patients after HLA-haploidentical related donor and HLA-mismatched unrelated donor transplantation would provide more valuable information for patients with PMF when making decisions regarding the choice of alternative donor.

INTRODUCTION

It was initially anticipated that the use of hematopoietic stem cell transplantation (HSCT) to treat primary myelofibrosis (PMF) might decrease due to the widespread availability of Janus kinase (JAK) inhibitors [1]. However, so far JAK inhibitor therapy has not resulted in the induction of complete or partial

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remission, and whether it produces prolonged survival in patients with PMF remains controversial [2]. In fact, registration data from the Center for International Blood and Marrow Transplant Research (CIBMTR) show a progressive increase in the number of HSCTs for patients with PMF, particularly from unrelated donors, every year over the last decade [1]. The situation is similar in Japan. According to an annual report from the Japanese Data Center for Hematopoietic Cell Transplantation, the use of HSCT for myeloproliferative neoplasms other than chronic myelogenous leukemia has increased in recent years (http://www.jdchct.or.jp/data/).

The issue of alternative donor selection for PMF patients without an HLA-matched related donor is currently under debate [3]. A retrospective study from the CIBMTR for PMF patients showed that HSCT from HLA-matched unrelated donors was associated with higher nonrelapse mortality (NRM) and lower overall survival (OS) compared with HSCT from HLA-matched related donors [4]. In contrast, other studies demonstrated no significant difference in NRM and OS between HLA-matched unrelated and related donors [5,6]. There is no evidence to support the superiority of the use of peripheral blood stem cells (PB) over bone marrow (BM) in HSCT for PMF patients; however, most patients receive PB grafts instead of BM grafts from related and unrelated donors [4–8]. Umbilical cord blood (UCB) transplantation is rarely performed in patients with PMF, presumably to avoid graft failure; however, the European Group for Blood and Marrow Transplantation (EBMT) reported that 16 of 20 (80%) PMF patients who received UCB grafts achieved neutrophil recovery [9]. HSCT from HLA-haploidentical related donors with post-transplantation cyclophosphamide has shown encouraging results [10]. Thus, various alternative donors are now available for PMF patients. The problem is that comparative studies of outcomes of PMF patients after HSCT among various hematopoietic stem cell sources are very limited.

In the present study, clinical data of 224 PMF patients after HSCT with related donor BM, related donor PB, unrelated donor BM, unrelated UCB, and other transplantation were analyzed retrospectively.

METHODS

Patients

A total of 224 patients with PMF who had undergone first allogeneic HSCT were included in this study. Eighty-three of these patients have been reported previously [11]. Transplantation data were obtained from the Transplant Registry Unified Management Program system, a registry of the outcomes of Japanese HSCT recipients sponsored by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japanese Data Center for Hematopoietic Cell Transplantation [12,13]. The primary physician of each patient chose the stem cell source. This study was planned by the Adult CML/MPN Working Group of the JSHCT and was approved by the Data Management Committee of the JSHCT and by the Ethics Committee of the Nagoya University School of Medicine.

Definitions

HLA-matched related donor BM (Rtd-BM) and PB (Rtd-PB) were defined as BM or PB from a serologic 6/6 HLA-A, -B, and -DR matched related donor. HLA-matched unrelated donor BM (UR-BM) was defined as BM from an 8/8 or 7/8 HLA-A, -B, -C, and -DRB1 allele matched unrelated donor. Unrelated UCB (UR-UCB) was defined as UCB from a serologic at least 4/6 HLA-A, -B, and -DR matched unrelated donor. Myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) was classified based on the report by the CIBMTR [14]. Neutrophil, reticulocyte, and platelet (PLT) recoveries were defined as an absolute neutrophil count of at least $.5 \times 10^9$/L, a reticulocyte count of at least 10 per mill, and a PLT count of at least 20×10^9/L, respectively, for 3 consecutive days. Engraftment failure was defined as no neutrophil recovery by day +60. Acute graft-versus-host disease (GVHD) and chronic GVHD were diagnosed and graded based on traditional criteria [15,16]. An unfavorable karyotype was defined as a complex karyotype or 1 or 2 abnormalities in +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement [17].

Endpoints

The primary endpoint of this study was to assess the impact of hematopoietic stem cell source on NRM. Other endpoints were to assess the impacts of hematopoietic stem cell source on hematopoietic recovery, GVHD, relapse, and OS rates.

Statistical Analysis

The probabilities of hematopoietic recovery, GVHD, NRM, and relapse rate stratified by hematopoietic stem cell source were estimated on the basis of cumulative incidence curves [18]. Competing-risk regression analysis was used to identify factors associated with NRM. The probability of OS stratified by hematopoietic stem cell source was estimated using the Kaplan-Meier method [19]. The groups were compared using the Wilcoxon test. The adjusted probability of OS was estimated using a Cox proportional hazards model, with consideration of other significant clinical variables in the final multivariate models [20]. All variables significant at $P < .05$ on univariate analysis were included in multivariate stepwise analyses. All tests were 2-sided, and $P < .05$ was considered significant. The data were analyzed using Stata version 12 (StataCorp, College Station, TX).

RESULTS

Patient and Transplantation Characteristics

Patient and transplantation characteristics are summarized in Table 1. One hundred fifty-two male patients and 72 female patients, with a median age of 55 years (range, 21 to 79 years), met the inclusion criteria. All UR-UCB transplantations were performed with a single cord blood unit. Other stem cell sources (n = 34) included serologic 5/6 or 4/6 HLA-A, -B, and -DR matched Rtd-BM (n = 1) or -PB (n = 5); HLA-haploidentical Rtd-BM (n = 1) or -PB (n = 6); 6/8 or 5/8 HLA-A, -B, -C, and -DRB1 allele matched UR-BM (n = 16); and 8/8 or 7/8 HLA-A, -B, -C, and -DRB1 allele matched UR-PB (n = 5). The median duration of follow-up for living patients was 48 months (range, 0.3 to 202 months).

Engraftment

Sixteen patients (7%) died without experiencing engraftment within 60 days after transplantation, due to infection on days +11, +18, +22, +27, and +43 after UR-BM (n = 5) and on day +43 after UR-UCB (n = 1); organ failure on day +21 after Rtd-PB (n = 1), on days +12 and +37 after UR-BM (n = 2), and on day +2 after UR-UCB (n = 1); bleeding on day +13 after Rtd-PB (n = 1) and on day +8 after UR-BM (n = 1); thrombotic microangiopathy on day +56 after UR-UCB (n = 1); hepatic veno-occlusive disease on day +12 after Rtd-PB (n = 1); hyperacute GVHD on day +14 after other transplantation (n = 1); and acute respiratory distress syndrome on day +8 after other transplantation (n = 1).

The incidence of neutrophil recovery on day +60 in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation were 100%, 94% (95% confidence interval [CI], 82% to 98%), 86% (95% CI, 77% to 92%), 79% (95% CI, 58% to 90%), and 91% (95% CI, 74% to 97%), respectively (Figure 1A). Compared with HLA-matched Rtd-BM transplantation, the incidence of neutrophil recovery after HLA-matched Rtd-PB transplantation was significantly higher ($P = .039$), whereas that after UR-UCB transplantation was significantly lower ($P = .005$). The median time to neutrophil recovery after HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation was 21, 16, 21, 25, and 23 days, respectively.

The incidence of reticulocyte recovery on day +100 in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation was 100%, 73% (95% CI, 56% to 84%), 80% (95% CI, 70% to 87%), 71% (95% CI, 49% to 85%), and 71% (95% CI, 52% to 84%), respectively (Figure 1B). The incidence of reticulocyte recovery was significantly lower after HLA-matched UR-BM, UR-UCB, and other transplantation than after HLA-matched Rtd-BM transplantation ($P = .004$, $<.001$, and .006,

Table 1
Patient and Transplantation Characteristics (n = 224)

Characteristic	Value
Sex, evaluable N	224
Male, n (%)	152 (68)
Female, n (%)	72 (32)
Age at transplantation, evaluable N	224
21-45 yr, n (%)	44 (20)
46-55 yr, n (%)	75 (33)
56-65 yr, n (%)	83 (37)
66-79 yr, n (%)	22 (10)
Age, yr, median (range)	55 (21-79)
Year of transplantation, evaluable N	224
1993-2009, n (%)	90 (40)
2010-2016, n (%)	134 (60)
Time from diagnosis to transplantation, evaluable N	221
<1 yr, n (%)	104 (47)
1-2 yr, n (%)	42 (19)
≥2 yr, n (%)	75 (34)
Frequency of RBC transfusion before transplantation, evaluable N	181
≤9, n (%)	89 (49)
10-19, n (%)	29 (16)
≥20, n (%)	63 (35)
Frequency of PLT transfusion before transplantation, evaluable N	181
≤9, n (%)	131 (72)
10-19, n (%)	13 (7)
≥20, n (%)	37 (21)
JAK2 mutation before transplantation, evaluable N	51
No, n (%)	24 (47)
Yes, n (%)	27 (53)
Use of JAK inhibitor before transplantation, evaluable N	137
No, n (%)	118 (86)
Yes, n (%)	19 (14)
Splenomegaly at transplantation, evaluable N	135
No, n (%)	35 (26)
Yes, n (%)	100 (74)
DIPSS at transplantation, evaluable N	131
Low or intermediate-1, n (%)	37 (28)
Intermediate-2, n (%)	82 (63)
High, n (%)	12 (9)
Chromosome karyotype, evaluable N	152
Favorable, n (%)	138 (91)
Unfavorable, n (%)	14 (9)
Performance status at transplantation, evaluable N	213
0 or 1, n (%)	179 (84)
≥2, n (%)	34 (16)
Cytomegalovirus serostatus, evaluable N	196
Negative, n (%)	32 (16)
Positive, n (%)	164 (84)
Stem cell source, evaluable N	224
HLA-matched Rtd-BM, n (%)	22 (10)
HLA-matched Rtd-PB, n (%)	48 (21)
HLA-matched UR-BM, n (%)	91 (41)
UR-UCB, n (%)	29 (13)
Other, n (%)	34 (15)
Sex-matching between patient and donor, evaluable N	210
Male patient and male donor, n (%)	79 (38)
Male patient and female donor, n (%)	63 (30)
Female patient and male donor, n (%)	36 (17)
Female patient and female donor, n (%)	32 (15)
ABO-matching between patient and donor, evaluable N	210
Match, n (%)	101 (48)
Major mismatch, n (%)	39 (19)
Minor mismatch, n (%)	45 (21)
Major/minor mismatch, n (%)	25 (12)
Conditioning regimen, evaluable N	223
MAC, n (%)	108 (48)
RIC, n (%)	115 (52)
Prophylaxis for GVHD, evaluable N	221
Calcineurin inhibitor with methotrexate, n (%)	174 (78)
Calcineurin inhibitor with mycophenolate mofetil, n (%)	19 (9)
Other, n (%)	28 (13)
Use of antithymocyte globulin at transplantation, evaluable N	223
No, n (%)	198 (89)
Yes, n (%)	25 (11)

respectively). The median time to reticulocyte recovery after HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation was 27, 20, 33, 35, and 28 days, respectively.

The incidence of PLT recovery on day +180 in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation was 94% (95% CI, 65% to 99%), 69% (95% CI, 54% to 80%), 65% (95% CI, 54% to 74%), 61% (95% CI, 40% to 77%), and 45% (95% CI, 27% to 61%), respectively (Figure 1C). The incidence of PLT recovery was significantly lower after HLA-matched UR-BM, UR-UCB, and other transplantation than after HLA-matched Rtd-BM transplantation ($P = .001$, .001, and <.001, respectively). The median time to PLT recovery after HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation was 40, 23, 40, 55, and 36 days, respectively.

GVHD

The incidences of grade II-IV and III-IV acute GVHD on day +100 in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation were 23% (95% CI, 8% to 41%) and 5% (95% CI, 0 to 19%), 27% (95% CI, 16% to 40%) and 19% (95% CI, 9% to 31%), 27% (95% CI, 18% to 36%) and 10% (95% CI, 5% to 17%), 31% (95% CI, 16% to 48%) and 10% (95% CI, 3% to 24%), and 26% (95% CI, 13% to 42%) and 15% (95% CI, 5% to 28%), respectively. There were no significant differences in the incidences of grade II-IV and III-IV acute GVHD among the various stem cell sources. The incidence of chronic GVHD at 1 year post-transplantation in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation was 30% (95% CI, 12% to 50%), 38% (95% CI, 25% to 52%), 31% (95% CI, 22% to 41%), 15% (95% CI, 5% to 31%), and 13% (95% CI, 4% to 27%), respectively; there was no significant difference in the incidence of chronic GVHD among the various stem cell sources.

NRM

NRM at 1 and 4 years in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation were 16% (95% CI, 4% to 35%) and 22% (95% CI, 7% to 42%), 36% (95% CI, 22% to 50%) and 41% (95% CI, 26% to 56%), 30% (95% CI, 21% to 41%) and 48% (95% CI, 36% to 59%), 41% (95% CI, 22% to 60%) and 62% (95% CI, 35% to 81%), and 48% (95% CI, 29% to 65%) and 58% (95% CI, 32% to 78%), respectively (Figure 2). NRM was significantly higher after UR-UCB and other transplantation than after HLA-matched Rtd-BM ($P = .046$ and .033, respectively). Multivariate

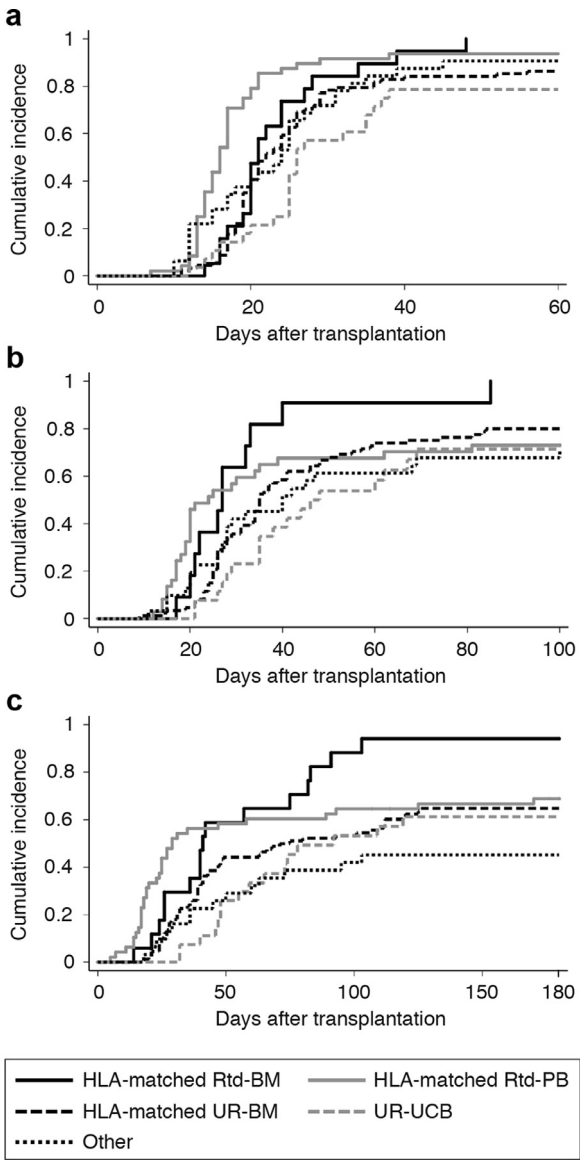

Figure 1. Hematopoietic recovery of PMF patients after transplantation.
(a) Cumulative incidences of neutrophil recovery after HLA-matched Rtd-BM (black solid line), HLA-matched Rtd-PB (gray solid line), HLA-matched UR-BM (black dashed line), UR-UCB (gray dashed line), and other (black dotted line) transplantation are shown. **(b)** Cumulative incidences of reticulocyte recovery after HLA-matched Rtd-BM (black solid line), HLA-matched Rtd-PB (gray solid line), HLA-matched UR-BM (black dashed line), UR-UCB (gray dashed line), and other (black dotted line) transplantation are shown. **(c)** Cumulative incidences of PLT recovery after HLA-matched Rtd-BM (black solid line), HLA-matched Rtd-PB (gray solid line), HLA-matched UR-BM (black dashed line), UR-UCB (gray dashed line), and other (black dotted line) transplantation are shown.

analysis was performed for all clinical features listed in Table 1. Receipt of ≥20 RBC transfusions before transplantation, 10 to 19 PLT transfusions before transplantation, UR-UCB transplantation, and other transplantation were predictive of higher NRM (Table 2). There were no significant differences in the frequencies of RBC and PLT transfusions among stem cell source groups (data not shown). HLA-matched Rtd-PB and UR-BM transplantation showed a trend toward a higher NRM. Although performance status ≥2 at transplantation was a significant predictor of higher NRM on univariate analysis, it was not significant on multivariate analysis.

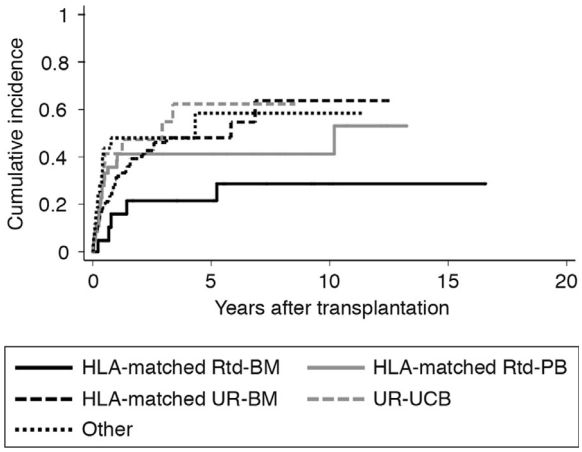

Figure 2. NRM of PMF patients after transplantation. Cumulative incidences of NRM after HLA-matched Rtd-BM (black solid line), HLA-matched Rtd-PB (gray solid line), HLA-matched UR-BM (black dashed line), UR-UCB (gray dashed line), and other (black dotted line) transplantation are shown.

Table 2
Significant Factors on Multivariate Analysis for Nonrelapse Mortality after Transplantation

Factor	HR (95% CI)	*P* Value
Frequency of RBC transfusion before transplantation		
≤9	1	
10-19	0.86 (0.39-1.92)	.712
≥20	2.05 (1.06-3.98)	.034
Frequency of PLT transfusion before transplantation		
≤9	1	
10-19	3.56 (1.57-8.05)	.002
≥20	1.14 (0.59-2.19)	.704
Donor source		
HLA-matched Rtd-BM	1	
HLA-matched Rtd-PB	3.57 (0.87-14.6)	.077
HLA-matched UR-BM	3.24 (0.82-12.7)	.092
UR-UCB	4.70 (1.13-19.6)	.034
Other	4.38 (1.05-18.3)	.043

Relapse

Forty-one patients relapsed after transplantation; 37 were diagnosed with hematologic relapse, 3 were cytogenetic relapse, and 1 was molecular relapse. Relapse rates at 1 and 4 years in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation were 14% (95% CI, 4% to 32%) and 14% (95% CI, 4% to 32%), 17% (95% CI, 8% to 29%) and 17% (95% CI, 8% to 29%), 11% (95% CI, 6% to 19%) and 13% (95% CI, 7% to 21%), 14% (95% CI, 4% to 30%) and 24% (95% CI, 10% to 42%), and 15% (95% CI, 6% to 30%) and 21% (95% CI, 8% to 39%), respectively. There was no significant difference in the incidence of relapse among stem cell sources. Multivariate analysis demonstrated no factors associated with the incidence of relapse.

OS

OS rates at 1 and 4 years in HLA-matched Rtd-BM, Rtd-PB, UR-BM, UR-UCB, and other transplantation were 81% (95% CI, 57% to 92%) and 71% (95% CI, 47%-86%), 58% (95% CI, 43% to 71%) and 52% (95% CI, 37% to 65%), 61% (95% CI, 50% to 70%)

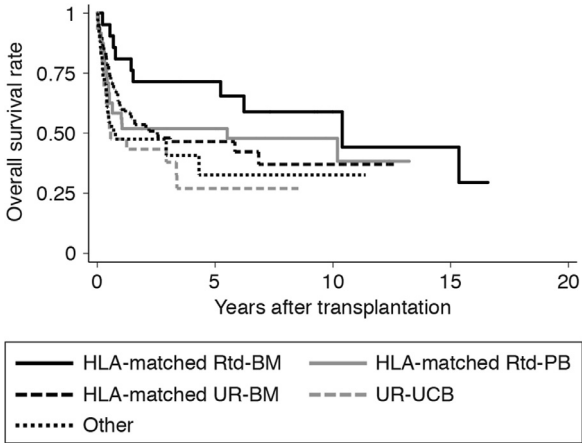

Figure 3. OS rates of PMF patients after transplantation. OS rates after HLA-matched Rtd-BM (black solid line), HLA-matched Rtd-PB (gray solid line), HLA-matched UR-BM (black dashed line), UR-UCB (gray dashed line), and other (black dotted line) transplantation are shown.

and 46% (95% CI, 35% to 57%), 48% (95% CI, 29% to 64%) and 27% (95% CI, 11% to 46%), and 48% (95% CI, 30% to 64%) and 41% (95% CI, 22% to 59%), respectively ($P = .032$) (Figure 3). Cox's proportional hazards model was used with all clinical features listed in Table 1. Although UR-UCB and other transplantation were significantly related to lower OS on univariate analysis, the associations were not significant after adjustment by age, frequency of RBC transfusion, frequency of PLT transfusion, Dynamic International Prognostic Scoring System (DIPSS), chromosome karyotype, and performance status, all of which were significant on univariate analysis. Instead, age 56 to 65 years, ≥20 RBC transfusions before transplantation, and 10 to 19 PLT transfusions before transplantation were predictive of lower OS (Table 3). Age 46 to 55 years showed a trend toward a lower OS. There were no significant differences in patient age and frequencies of RBC and PLT transfusions among stem cell source groups (data not shown). OS rates were not significantly different between the patients with and without *JAK2* mutation ($P = .597$).

Table 3
Significant Factors on Multivariate Analysis for Overall Survival Rate after Transplantation

Factor	HR (95% CI)	*P* Value
Age at transplantation, y		
21-45	1	
46-55	2.13 (1.00-4.54)	.051
56-65	3.37 (1.63-6.95)	.001
66-79	1.22 (0.47-3.21)	.684
Frequency of RBC transfusion before transplantation		
≤9	1	
10-19	0.70 (0.34-1.43)	.331
≥20	2.15 (1.26-3.66)	.005
Frequency of PLT transfusion before transplantation		
≤9	1	
10-19	3.67 (1.74-7.72)	.001
≥20	1.28 (0.73-2.27)	.388

Causes of Death

The main causes of death after transplantation are summarized in Table 4. In recipients of HLA-matched Rtd-BM and Rtd-PB transplantation, the most common cause of death was primary disease (40% and 28%, respectively), whereas in HLA-matched UR-BM and UR-UCB recipients, the most common cause of death was infection (42% and 42%, respectively).

DISCUSSION

Allogeneic HSCT is the sole available curative therapy for PMF [21]. PMF occurs primarily in older persons, with a median age at diagnosis of 65 years [22]. Older age is a negative predictor for NRM in HSCT for myelofibrosis [23,24]. Decreasing NRM is one of the most important challenges to improve the outcome of HSCT for patients with PMF.

The use of RIC is an attractive approach to decreasing NRM. A prospective study of PB transplantation with fludarabine and busulfan-based RIC for myelofibrosis patients reported NRM of 16% at 1 year after transplantation [7]. Another prospective study with fludarabine and melphalan-based RIC reported NRM at 2 years of 22% in Rtd transplantation and 59% in UD transplantation [8]. However, there has been no prospective study comparing outcomes between RIC and MAC. Retrospective studies including both RIC and MAC have not demonstrated any significant difference in NRM between these 2 groups [5,25–27]. The present study also did not find an association between the use of RIC and lower NRM. Thus, to date, there are no data to support the superiority of RIC over MAC in

Table 4
Main Causes of Death by Stem Cell Source

Cause	Rtd-BM, n (%)	Rtd-PB, n (%)	UR-BM, n (%)	UR-UCB, n (%)	Other, n (%)
Primary disease	4 (40)	7 (28)	7 (15)	5 (26)	3 (16)
Infection	1 (10)	4 (16)	20 (42)	8 (42)	4 (21)
Organ failure	1 (10)	3 (12)	7 (15)	2 (11)	1 (5)
GVHD	1 (10)	3 (12)	5 (10)	0	2 (11)
Interstitial pneumonitis	1 (10)	3 (12)	2 (4)	1 (5)	2 (11)
Bleeding	0	2 (8)	3 (6)	0	2 (11)
TMA	1 (10)	1 (4)	0	1 (5)	1 (5)
ARDS	0	0	0	1 (5)	3 (16)
VOD	0	1 (4)	0	1 (5)	1 (5)
Graft failure	1 (10)	0	1 (2)	0	0
Second malignancy	0	0	2 (4)	0	0
Other	0	1 (4)	1 (2)	0	0
Unknown	1 (10)	0	0	0	0
Total	10 (100)	25 (100)	48 (100)	19 (100)	19 (100)

ARDS indicates acute respiratory distress syndrome; TMA, thrombotic microangiopathy; VOD, hepatic veno-occlusive disease.

terms of decreasing NRM in HSCT for patients with PMF, in which engraftment failure is a major concern. The use of RIC over MAC should be carefully evaluated in young PMF patients who can receive MAC.

Rather, several studies have demonstrated the importance of donor selection in decreasing NRM. In the retrospective studies from the CIBMTR, France, and the United States for patients with PMF or secondary myelofibrosis mainly with PB transplantation, unrelated donor grafts were associated with higher NRM and lower OS than related donor grafts [4,28,29]. In contrast, the present study demonstrated in patients with PMF, BM transplantation from an HLA-matched unrelated donor showed a trend toward higher NRM compared with transplantation from an HLA-matched related donor, but they were not significantly different. The possibility remains that BM transplantation from an HLA-matched unrelated donor instead of a related donor may have a small negative impact on HSCT outcomes, unlike in the case of PB transplantation.

UR-UCB transplantation was significantly associated with a higher NRM. To the best of our knowledge, this is the only study to have compared the outcomes of UR-UCB transplantation and other HSCT. The incidence of neutrophil recovery was significantly lower in UR-UCB transplantation than in HLA-matched Rtd-BM transplantation, and the most common cause of death after UR-UCB transplantation was infection. Thus, the development of a conditioning regimen that ensures engraftment of UR-UCB may contribute to decreased NRM in UR-UCB transplantation. There was no significant difference in OS rate between UR-UCB and HLA-matched Rtd-BM transplantation, suggesting that at present, UR-UCB transplantation can be selected for PMF patients, with careful attention to high NRM.

Nevertheless, this study included the largest number of PMF patients treated with UR-UCB transplantation reported to date. The incidence of neutrophil recovery on day +60 was 79%, and OS rates at 1 and 4 years were 48% and 27%, respectively. These data provide valuable information to PMF patients who have no other alternative donors during the decision making process for receiving UR-UCB transplantation. Limited information has been available about the outcome of UR-UCB transplantation for PMF patients so far. The retrospective study from the EBMT for 20 PMF patients reported that the incidence of neutrophil recovery was 80% and event-free survival at 2 years was 35% [9]. The report from a single transplant center for patients with PMF (n = 1) and secondary myelofibrosis (n = 13) demonstrated that the incidence of neutrophil recovery on day +60 was 92.9% and OS at 4 years was 28.6% [30]. The retrospective study of 16 patients with leukemic transformation from PMF, essential thrombocytopenia, or polycythemia vera demonstrated that the incidence of neutrophil recovery on day +60 was 50%, and NRM at 2 years was 50% [31].

HLA-matched Rtd-PB transplantation showed a trend toward a higher NRM compared with HLA-matched Rtd-BM transplantation. This may result from a bias due to the small number of patients in each group, because the main causes of death were similar in the 2 groups. However, it is well known that the advantage of a low incidence of engraftment failure is offset by a high incidence of chronic GVHD in unrelated donor PB transplantation [32]. For patients with chronic myelogenous leukemia in the first chronic phase, PB transplantation from unrelated donors is reportedly associated with higher NRM and, consequently, a lower OS rate compared with UR-BM transplantation [33]. Because almost all recent studies have consisted exclusively of PB transplantation [4–6,23,24,28,34,35], it was impossible to accurately compare the outcomes between PB and BM transplantation. Further analysis is needed to determine the impact of the use of PB instead of BM on transplantation outcomes of PMF patients.

Splenomegaly may be associated with a lower incidence of engraftment [26,36], but this remains controversial [25,37,38]. Engraftment failure after HSCT for myelofibrosis patients is supposed to be caused by early pooling of hematopoietic stem cells in the spleen [39]. JAK inhibitor therapy results in reduction of splenomegaly and may contribute to engraftment [40]. In addition, JAK inhibitors down-regulate cytokine levels and may reduce the risk of GVHD. However, in the present study, neither splenomegaly nor JAK inhibitor therapy before transplantation was associated with NRM. These results are compatible with the retrospective and prospective studies demonstrating that pretransplantation ruxolitinib did not decrease the incidences of engraftment failure and GVHD or decrease the rate of NRM [23,41].

Graft failure is one of the major barriers to successful HSCT for PMF patients. In the present study, early death without engraftment was seen in as many as 16 patients (7%). However, the cumulative incidence of neutrophil recovery was comparable to that in previous reports on HSCT for PMF patients, at 4% to 20% [4–9,41,42]. The stem cell source affects neutrophil engraftment. HSCT from unrelated donors [8], with UR-UCB [9], and from HLA-mismatched donors [42] is known to be an independent risk factor for a lower incidence of neutrophil engraftment in HSCT for PMF patients. In fact, the present study demonstrates that the incidence of neutrophil recovery was significantly lower after UR-UCB transplantation than after HLA-matched Rtd-BM transplantation. Unfortunately, the degree of bone marrow fibrosis at transplantation, another risk factor for a lower engraftment rate [43], was not included in the registry data. It also must be noted that secondary graft failure could not be assessed from the registry data.

In the present study, relapse rates at 1 and 4 years were 11% to 17% and 13% to 24%, respectively. These rates are comparable with previous reports: 17% at 2 years [6], 14.8% at 2 years [23], and 25% at 5 years [24]. Older patient age and frequent RBC and PLT transfusions before transplantation were significantly associated with lower OS. Previous reports have shown that higher patient age, lower hemoglobin, and thrombocytopenia predicted lower OS [7,23,24,26,37,44,45]. Deterioration of organ function due to multiple blood transfusions may result in inferior results of HSCT. In general, patients with intermediate-2 or high-risk disease according to the DIPSS are candidates for allogeneic HSCT [46]. However, patients should be considered candidates for allogeneic HSCT regardless of risk group if they are going to be transfusion-dependent. The appropriate timing for allogeneic HSCT for PMF patients needs to be discussed further in a future study.

In the present study, the DIPSS score was not a predictor for NRM or OS. Unfortunately, the Japanese national registry does not include information on RBC transfusion dependency and thrombocytopenia (PLT $<100 \times 10^9$/L). Thus, the DIPSS Plus score [47] was not evaluable in this study. Given that transfusion dependency may reflect a high degree of bone marrow fibrosis and that frequent RBC and PLT transfusions before transplantation were significantly associated with higher NRM and lower OS, future analysis with the DIPSS Plus classification would be of considerable interest.

Although UR-UCB and other transplantation were significantly associated with lower OS on univariate analysis, they were not significant after adjustment by other factors. Considering the small numbers of patients in each stem cell source group, the present analysis might not have the power to detect an association between stem cell source groups and OS rates. On the other hand, the difference in NRM rates among stem

cell source groups should also be confirmed by a study with a large number of PMF patients.

In conclusion, the data are still insufficient to determine which alternative donor is the most appropriate for PMF patients who have no HLA-matched related donor. Given the difficulty of performing a prospective, randomized, controlled study for PMF patients with an alternative hematopoietic stem cell source, accumulation of historical data is considered an effective approach to resolving this issue.

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