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ORIGINAL ARTICLE

Allogeneic transplantation for primary myelofibrosis with BM, peripheral blood or umbilical cord blood: an analysis of the JSHCT

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To determine whether a difference in donor source affects the outcome of transplantation for patients with primary myelofibrosis (PMF), a retrospective study was conducted using the national registry data on patients who received first allogeneic hematopoietic cell transplantation (HCT) with related BM ($n=19$), related PBSCs ($n=25$), unrelated BM ($n=28$) or unrelated umbilical cord blood (UCB; $n=11$). The 5-year OS rates after related BM, related PBSC and unrelated BM transplantation were 63%, 43% and 41%, respectively, and the 2-year OS rate after UCB transplantation was 36%. On multivariate analysis, the donor source was not a significant factor for predicting the OS rate. Instead, performance status (PS) $\geqslant 2$ (vs PS 0–1) predicted a lower OS ($P=0.044$), and RBC transfusion $\geqslant 20$ times before transplantation (vs transfusion $\leqslant 9$ times) showed a trend toward a lower OS ($P=0.053$). No advantage of nonmyeloablative preconditioning regimens in terms of decreasing nonrelapse mortality or increasing OS was found. Allogeneic HCT, and even unrelated BM and UCB transplantation, provides a curative treatment for PMF patients.

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Keywords: idiopathic myelofibrosis; hematopoietic SCT; donor source; engraftment; survival

INTRODUCTION

Primary myelofibrosis (PMF) is a clonal stem cell disorder characterized by anemia, BM fibrosis, progressive splenomegaly, constitutional symptoms and a significant risk of evolution into acute leukemia.[1,2] The median age at diagnosis is ~65 years, with a median survival of ~5 years after diagnosis, depending on the presence or absence of clinically defined prognostic factors, such as those defined by the International Prognostic Scoring System (IPSS), Dynamic IPSS and Dynamic IPSS plus.[3–5] No available conventional drug therapies for PMF have been shown to prolong survival. Palliative therapeutic options include agents such as hydroxyurea, prednisone, EPO, androgens, thalidomide and lenalidomide, and nonpharmacological approaches such as blood transfusion, splenic irradiation and splenectomy.[6,7] The impact of new agents, such as Janus kinase 2 (JAK2) inhibitors, pomalidomide and histone deacetylase inhibitors, on the long-term management of PMF is under investigation.[7,8] The only known curative therapy for PMF is allogeneic hematopoietic cell transplantation (HCT).[9]

The largest retrospective study of PMF patients undergoing allogeneic BM or PBSC transplantation reported OS of 30–40% at 5 years after transplantation with nonrelapse mortality (NRM) of 24–43% at 1 year after transplantation.[10] The prospective study in patients with PMF or secondary myelofibrosis to evaluate a nonmyeloablative preconditioning regimen followed by mainly PBSC transplantation achieved an OS of 51% at 5 years after transplantation with NRM of 16% at 1 year after transplantation.[11] The issues of the choice of stem cell source, the choice of conditioning regimen and the timing of transplantation are currently under debate.[6–9,12,13]

To determine whether a difference in stem cell source affects the outcome of HCT for PMF patients, a retrospective study was conducted using the national registry data on patients who received first allogeneic HCT in Japan with BM, PBSCs or umbilical cord blood (UCB).

PATIENTS AND METHODS

Patients

Clinical data for patients with PMF who received first allogeneic HCT in Japan were extracted from the Transplant Registry Unified Management Program (TRUMP) system, which is a registry of the outcomes of Japanese transplant patients.[14] Patients who had progressed to myelofibrosis from polycythemia vera, essential thrombocythemia, leukemia or other disease were excluded. This study was approved by the Data Management Committee of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and by the ethics committee of the Nagoya University School of Medicine (no. 2012–0270).

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Definitions

Hematopoietic recovery was defined as time to ANC $\geqslant 0.5 \times 10^9$/L, time to reticulocytes $\geqslant 10‰$ and time to platelets $\geqslant 50 \times 10^9$/L for 3 consecutive days. Engraftment failure was defined as no neutrophil recovery by day 60. Acute and chronic GVHD were diagnosed and graded according to established criteria.[15,16] Based on the report by the Center for International Blood and Marrow Transplant Research (CIBMTR),[17] the conditioning regimens were classified as myeloablative if TBI >8 Gy, oral BU $\geqslant 9$ mg/kg, i.v. BU $\geqslant 7.2$ mg/kg or melphalan >140 mg/m^2 was included in the conditioning regimen, whereas other conditioning regimens were classified as nonmyeloablative.

End points

The primary end point was OS. The secondary end points were engraftment, GVHD, relapse and NRM.

Statistical analysis

The probabilities of hematopoietic recovery, acute and chronic GVHD, relapse and NRM were estimated on the basis of cumulative incidence curves.[18] The probability of OS was estimated according to the Kaplan–Meier method.[19] The groups were compared using the log-rank test. Competing risk regression analysis was used to identify factors associated with NRM. The adjusted probability of OS was estimated using Cox's proportional hazards model, with consideration of other significant clinical variables in the final multivariate models.[20] All variables significant at $P<0.10$ on univariate analysis were included in multivariate stepwise analyses. All tests were two sided, and $P<0.05$ was considered significant. The data were analyzed by STATA version 12 statistical software (StataCorp, College Station, TX, USA).

RESULTS

Patient and transplantation characteristics

A total of 83 patients met the inclusion criteria. Patient and transplantation characteristics are summarized in Table 1. The median age at transplantation was 53 years, and most patients (66%) were male. Transplants were performed between 1993 and 2009, but the majority (90%) of them were performed after 2000. This population consisted of 47 BM transplants, 25 PBSC transplants and 11 UCB transplants. Of the 44 related donor transplants, 40 (91%) were performed from serological HLA-A, B and DR 6/6 matched donor; 28 unrelated BM transplants included 16 (57%) HLA-A, B and DRB1 alleles 6/6 matched donors and 11 (39%) HLA-A, B and DRB1 alleles 5/6 matched donors; all (100%) unrelated UCB transplants were performed from serological HLA-A, B and DR 5/6 or 4/6 matched donors. Most patients (76%) received a nonmyeloablative regimen. The median follow-up for living patients was 40 (range, 0.4–150) months.

Engraftment

Seven patients (8%) died without engraftment within 60 days after transplantation, including heart failure on day 5 after UCB transplant ($n=1$), primary disease on day 7 after related PBSC transplant ($n=1$), infection on day 11 after unrelated BM transplant ($n=1$), multiple organ failure on day 12 after unrelated BM transplant ($n=1$), heart failure on day 18 after unrelated BM transplant ($n=1$), infection on day 30 after unrelated BM transplant ($n=1$) and thrombotic microangiopathy on day 56 after UCB transplant ($n=1$). Another patient (1%) received a second transplant on day 28 because of lack of engraftment signs at that time.

Neutrophil recovery on day 60 occurred in 92% (95% confidence interval (CI), 57–99%) of related BM, 92% (71–98%) of related PBSCs, 79% (58–90%) of unrelated BM and 82% (45–95%) of unrelated UCB (Figure 1a). Unrelated BM and unrelated UCB (vs related BM) transplantations were significantly associated with a lower probability of neutrophil recovery ($P=0.015$ and $P=0.016$, respectively), whereas related PBSC transplantation was

Table 1. Patient and transplantation characteristics ($n=83$)

	N *(%)*
Age at transplant, evaluable n	83
21–39 Years	9 (11)
40–49 Years	22 (27)
50–59 Years	37 (44)
60–79 Years	15 (18)
Median age (range), years	53 (21–79)
Sex, evaluable n	83
Female	28 (34)
Male	55 (66)
Transplant year, evaluable n	83
1993–1999	8 (10)
2000–2004	22 (27)
2005–2009	53 (63)
Performance status at transplant, evaluable n	70
0–1	54 (77)
$\geqslant 2$	16 (23)
Time from diagnosis to transplant, evaluable n	80
<1 Years	33 (41)
1–2 Years	16 (20)
$\geqslant 2$ Years	31 (39)
Median (range), years	1.5 (0.1–21.0)
Frequency of RBC transfusion before transplant, evaluable n	51
$\leqslant 9$	26 (51)
10–19	8 (16)
$\geqslant 20$	17 (33)
Frequency of PLT transfusion before transplant, evaluable n	51
$\leqslant 9$	38 (74)
10–19	4 (8)
$\geqslant 20$	9 (18)
Use of JAK2 inhibitor before transplant, evaluable n	77
Yes	0 (0)
No	77 (100)
Splenectomy before transplant, evaluable n	78
Yes	2 (3)
No	76 (97)
DIPSS at transplant	78
Low	8 (10)
Intermediate–1	17 (22)
Intermediate–2	50 (64)
High	3 (4)
Splenomegaly at transplant	78
Yes	59 (76)
No	19 (24)
CMV serostatus, evaluable n	58
Negative	5 (9)
Positive	53 (91)
Donor source, evaluable n	83
Related BM	19 (23)
Related PBSCs	25 (30)
Unrelated BM	28 (34)
Unrelated umbilical cord blood	11 (13)
Sex matching between patient and donor, evaluable n	71
Match	35 (49)
Female patient and male donor	15 (21)
Male patient and female donor	21 (30)
ABO matching between patient and donor, evaluable n	65
Match	34 (52)
Mismatch	31 (48)
Preconditioning regimen, evaluable n	71
Myeloablative	17 (24)
Nonmyeloablative	54 (76)
Prophylaxis for GVHD, evaluable n	81
CsA based	37 (46)
Tacrolimus based	42 (52)
Others	2 (2)
Use of JAK2 inhibitor after transplant, evaluable n	78
Yes	0 (0)
No	78 (100)

Abbreviations: DIPSS = Dynamic International Prognostic Scoring System; JAK2 = Janus kinase 2.

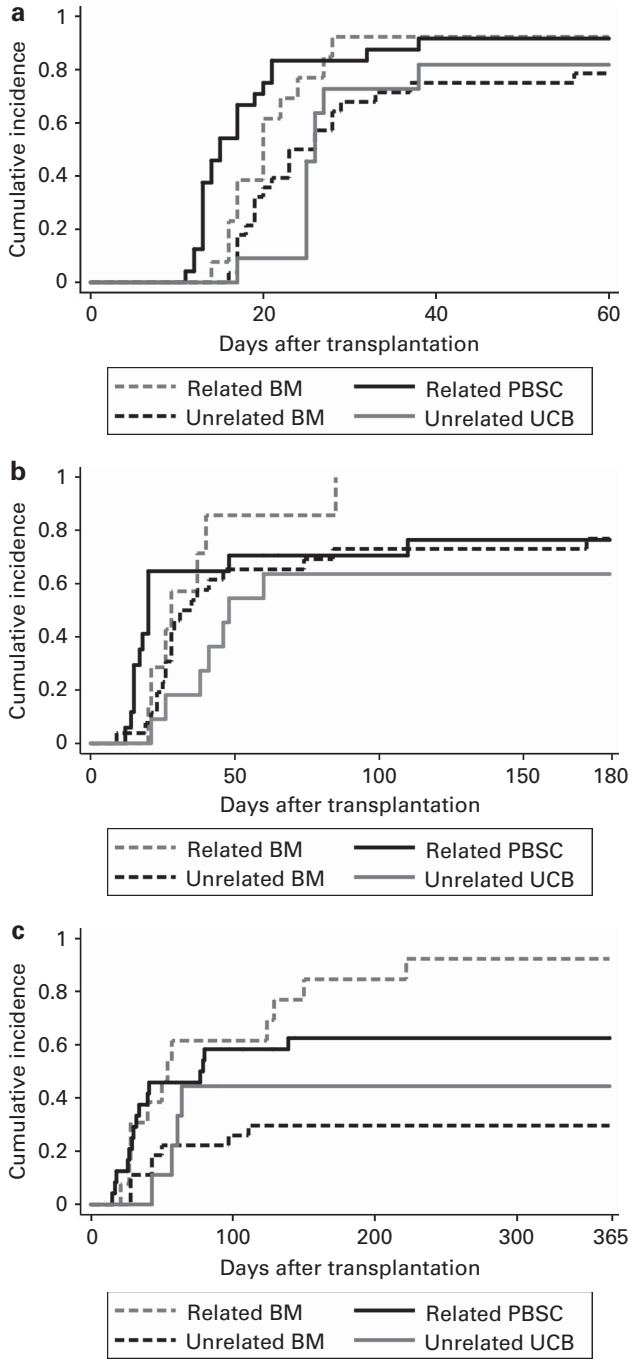

Figure 1. Hematopoietic recoveries after transplantation in PMF patients. (**a**) Cumulative incidences of neutrophil recovery after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown. (**b**) Cumulative incidences of reticulocyte recovery after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown. (**c**) Cumulative incidences of platelet recovery after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown.

not significantly different from related BM transplantation ($P = 0.46$). The median days for neutrophil recovery in patients receiving related BM, related PBSCs, unrelated BM and unrelated UCB were 20, 14, 21 and 25, respectively.

Reticulocyte recovery on day 180 occurred in 100% of related BM, 75% (46–90%) of related PBSC, 77% (56–89%) of unrelated BM and 64% (30–85%) of unrelated UCB transplantations (Figure 1b). Unrelated UCB (vs related BM) transplantation was significantly associated with a lower probability of reticulocyte recovery ($P = 0.012$), whereas related PBSC and unrelated BM transplantations were not significantly different from related BM transplantation ($P = 0.57$ and $P = 0.076$, respectively). The median days for reticulocyte recovery in patients receiving related BM, related PBSCs, unrelated BM and unrelated UCB were 28, 17, 28 and 41, respectively.

Platelet recovery on day 365 occurred in 92% (57–99%) of related BM, 63% (40–78%) of related PBSC, 30% (14–47%) of unrelated BM and 44% (14–72%) of unrelated UCB transplantations (Figure 1c). Unrelated BM and unrelated UCB transplantations (vs related BM) were significantly associated with a lower probability of platelet recovery ($P < 0.001$ and $P = 0.027$, respectively), whereas related PBSC transplantation was not significantly different from related BM transplantation ($P = 0.20$). The median days for platelet engraftment in patients receiving related BM, related PBSCs, unrelated BM and unrelated UCB were 50, 32, 43 and 57, respectively.

GVHD

The incidences of grade II–IV and III–IV acute GVHD on day 100 were 17% (95% CI, 4–37%) and 6% (0–22%) in related BM, 32% (15–50%) and 16% (5–33%) in related PBSC, 29% (14–46%) and 14% (4–30%) in unrelated BM and 10% (1–36%) and 0% in unrelated UCB transplantations, respectively. There was no significant difference in the incidence of grade II–IV acute GVHD among stem cell sources, whereas the incidence of grade III–IV acute GVHD was significantly lower after unrelated UCB transplantation than after related BM transplantation ($P < 0.001$).

The incidences of chronic GVHD at 2 years after transplantation were 35% (95% CI, 14–57%) in related BM, 52% (31–69%) in related PBSC, 25% (11–42%) in unrelated BM and 18% (3–44%) in unrelated UCB transplantations. There was no significant difference in the incidence of chronic GVHD among stem cell sources.

Relapse

Relapse rates at 2 and 5 years after transplantation were 5% (95% CI, 0–21%) and 12% (2–33%) in related BM, 8% (1–22%) and 12% (3–28%) in related PBSC and 4% (0–18%) and 4% (0–18%) in unrelated BM transplantations, respectively. No patient relapsed after UCB transplantation, in which the longest follow-up was 48 months.

NRM

NRM rates at 2 and 5 years after transplantation were 33% (95% CI, 13–54%) and 33% (13–54%) in related BM, 45% (24–63%) and 50% (28–69%) in related PBSC and 61% (38–77%) and 61% (38–77%) in unrelated BM transplantations, respectively (Figure 2). NRM at 2 years after unrelated UCB transplantation was 64% (30–85%), and NRM at 5 years after UCB transplantation was not evaluable because of lack of patients alive beyond 5 years after transplantation. NRM rates after related PBSC and unrelated BM transplantation were not significantly different from that after related BM transplantation ($P = 0.28$ and $P = 0.068$, respectively), whereas unrelated UCB transplantation (vs related BM) was significantly associated with a significantly higher NRM ($P = 0.021$).

To identify predictive factors for higher NRM, multivariate analysis for all clinical features listed in Table 1 was performed, and the final multivariate model is shown in Table 2. PS $\geqslant 2$ and unrelated BM were predictive factors for higher NRM. For patients with performance status (PS) 0–1 ($n = 54$), NRM rates at 2 and 5 years after transplantation were 37% (23–50%) and 40% (26–54%),

respectively. For patients with PS $\geqslant 2$ ($n = 16$), NRM at 2 years was 77% (45–92%), and NRM at 5 years was not evaluable because of lack of patients alive beyond 5 years after transplantation.

OS

OS rates at 2 and 5 years after transplantation were 63% (95% CI, 38–80%) and 63% (38–80%) in related BM, 48% (28–66%) and 43% (23–61%) in related PBSC and 41% (21–59%) and 41% (21–59%) in unrelated BM transplantations, respectively (Figure 3). The OS rate at 2 years after unrelated UCB transplantation was 36% (11–63%), and the OS rate at 5 years after UCB transplantation was not evaluable because of a lack of patients alive beyond 5 years after transplantation (longest follow-up, 48 months). There was no significant difference among stem cell donor sources ($P = 0.15$).

Cox's proportional hazards model was used with all clinical features listed in Table 1, and the final multivariate model is shown in Table 2. After adjustment by PS and frequency of RBC transfusion, which were significant on univariate analysis, donor source was not a significant factor for predicting OS. Instead, PS $\geqslant 2$ predicted a lower OS rate, and RBC transfusion $\geqslant 20$ times before transplantation showed a trend toward a lower OS. We confirmed that there was no significant difference in the frequencies of PS $\geqslant 2$ between patients receiving different stem cell sources (2 of 13 related BM, 6 of 24 related PBSC, 5 of 27 unrelated BM and 3 of 6 unrelated UCB transplantations; $P = 0.30$). Similarly, we confirmed that there was no significant difference in the frequencies of RBC transfusion $\geqslant 20$ times between patients receiving different stem cell sources (2 of 8 related BM, 5 of 18 related PBSC, 8 of 20 unrelated BM and 2 of 5 unrelated UCB transplantations; $P = 0.80$).

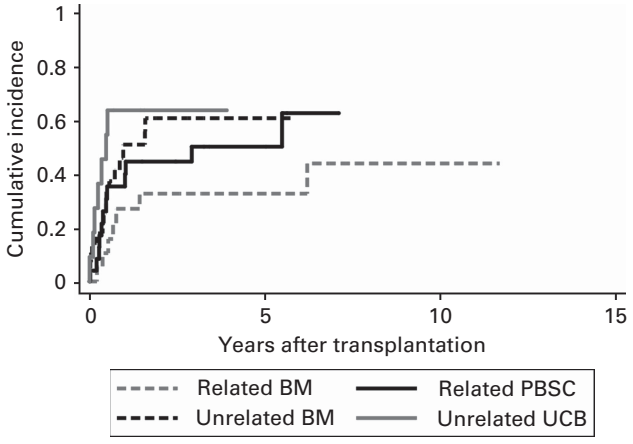

Figure 2. NRM after transplantation in PMF patients. Cumulative incidences of NRM after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown.

Causes of death

The causes of death after transplantation are summarized in Table 3. For patients after related donor transplantation ($n = 23$), the most common cause of death was primary disease ($n = 9$, 39%), followed by infection ($n = 4$, 17%) and organ failure ($n = 3$, 13%). For patients after unrelated donor transplantation ($n = 22$), the most common causes of death were infection ($n = 7$, 32%) and organ failure ($n = 7$, 32%), followed by GVHD ($n = 3$, 14%), and only 1 patient (5%) died of primary disease.

DISCUSSION

The present study confirmed 5-year OS of 63%, 43% and 41% after related BM, related PBSC and unrelated BM transplantations, respectively. These results are comparable to previous reports in which long-term survival rates in patients with PMF or secondary myelofibrosis were 30–67% after transplantation.[10,11,21–26] This is the first report of UCB transplantation for more than 10 patients with PMF, and a 2-year OS of 36% was confirmed.

Several investigators have examined factors to predict outcomes after allogeneic HCT for PMF patients. The largest retrospective study of PMF patients from the CIBMTR demonstrated that Karnofsky score of $<90\%$ and the presence of blasts in peripheral blood, but not donor source, predicted lower disease-free survival of patients who had received BM or PBSC transplantation from related or unrelated donors.[10] Other retrospective studies including both PMF and secondary myelofibrosis demonstrated negative predictors for OS of higher patient age, nonchronic phase disease, RBC transfusion >20 times, increased comorbidity score, intermediate-2 and high scores of the Dynamic IPSS and non-HLA-matched sibling donor.[11,21,24,26,27] In the present study, multivariate analysis demonstrated that PS $\geqslant 2$ predicted a lower OS and that RBC transfusion $\geqslant 20$ times before transplantation showed a trend toward a lower OS (Table 2). Unexpectedly, the stem cell source was not a significant factor for OS. One possibility is that a significant association between stem cell source and OS was not detected because of a lack of statistical power, namely, the small

Table 2. Significant factors in multivariate analyses for nonrelapse mortality and OS after transplantation

	Nonrelapse mortality HR (95% CI)	P-*value*	*Overall survival* HR (95% CI)	P-*value*
Performance status at transplant				
0–1	1.0		1.0	
$\geqslant 2$	3.36 (1.42–7.95)	0.006	2.67 (1.03–6.95)	0.044
Frequency of RBC transfusion[a]				
$\leqslant 9$	NA		1.0	
10–19	NA		0.48 (0.97–2.36)	0.37
$\geqslant 20$	NA		2.42 (0.99–5.93)	0.053
Donor source				
Related BM	1.0		1.0	
Related PBSCs	2.43 (0.73–8.07)	0.15	3.86 (0.81–18.44)	0.091
Unrelated BM	3.58 (1.07–12.01)	0.039	3.13 (0.66–14.79)	0.15
Unrelated umbilical cord blood	2.71 (0.49–14.86)	0.25	3.79 (0.60–23.91)	0.16

Abbreviations: CI = confidence interval; HR = hazard ratio; NA = not applicable.
[a]Frequency of RBC transfusion before transplantation.

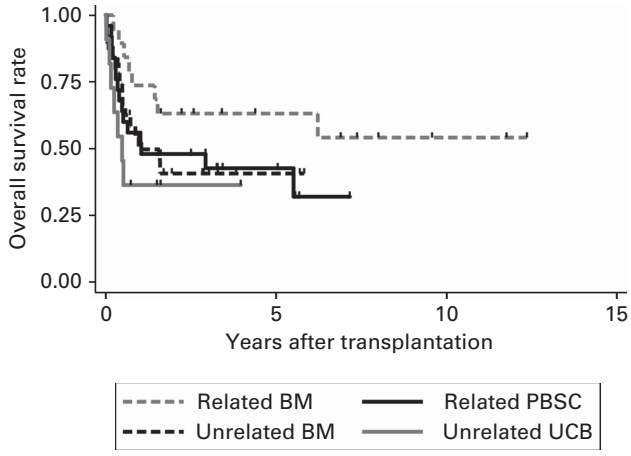

Figure 3. OS rates after transplantation in PMF patients. OS rates after related BM (gray and dash line), related PBSC (black and solid line), unrelated BM (black and dash line) and unrelated UCB (gray and solid line) transplantations are shown.

Table 3. Causes of death

	Related BM, n *(%)*	*Related PBSC,* n *(%)*	*Unrelated BM,* n *(%)*	*Unrelated UCB,* n *(%)*
Primary disease	2 (25)	7 (46)	1 (7)	0
Infection	1 (13)	3 (20)	6 (40)	1 (14)
Interstitial pneumonitis	2 (25)	0	1 (7)	0
ARDS	0	0	1 (7)	0
GVHD	1 (13)	1 (7)	2 (13)	1 (14)
Organ failure	1 (13)	2 (13)	3 (20)	4 (58)
Graft failure	1 (13)	0	0	0
Bleeding	0	1 (7)	1 (7)	0
Other	0	1 (7)	0	1 (14)
Total	8 (100)	15 (100)	15 (100)	7 (100)

Abbreviations: ARDS = acute respiratory distress syndrome; UCB = umbilical cord blood.

number of patients in each group, and the short-term follow-up. In particular, the number of patients with UCB transplantation was very small, and therefore, careful interpretation of these data is required. Further analysis with data including more patients undergoing UCB transplantation is required in order to determine the effect of UCB transplantation on outcomes of PMF patients. Another possibility is that the HCT outcome for PMF patients is more adversely affected by the deterioration in a patient's systemic condition as a consequence of multiple transfusions of blood and so on, rather than by the difference in stem cell sources.

In practice, UCB transplantation may be avoided in the treatment of PMF patients because of delayed engraftment and a higher probability of graft failure.[9] The present study demonstrated that UCB transplantation was significantly associated with a lower probability of hematopoietic recovery in comparison with related BM transplantation (Figure 1). The incidences of neutrophil recovery at 60 days and platelet recovery at 1 year were 82% and 44% for UCB transplantation, respectively. In a recent report of nonmyeloablative UCB transplantation for 14 patients with myelofibrosis, including 1 patient with PMF and 13 patients with secondary myelofibrosis, the incidences of neutrophil recovery at 60 days and platelet recovery at 100 days were 93% and 43%, respectively.[28] Thus, careful management is required for PMF patients, especially in the early period after unrelated UCB transplantation.

NRM was 30–60% (Figure 2), which is higher than in previous studies from large, well-known transplant center(s).[22–24,26,27,29–32] This may be explained by the large number of the participating centers, the heterogeneity of patients' clinical features and the fact that 18% of patients were $\geqslant$60 years in the present study.

Nonmyeloablative preconditioning regimens have advantages of less NRM and a broader applicability in elderly patients and may, therefore, be appropriate for PMF patients. After small studies demonstrated the feasibility of allogeneic HCT with nonmyeloablative preconditioning for myelofibrosis,[33–35] Kröger *et al.*[11] prospectively treated 103 patients with PMF or post essential thrombocythemia and post polycythemia vera myelofibrosis with BU and fludarabine-based nonmyeloablative preconditioning. They reported encouraging 1-year NRM of 16% and 5-year OS of 67%. The Swedish group compared results from 10 patients undergoing nonmyeloablative transplant with 17 patients undergoing myeloablative transplant for secondary myelofibrosis. NRM was lower in the nonmyeloablative group than in the myeloablative group (10% vs 30%). With a median follow-up of 55 months, 9 (90%) of 10 patients undergoing nonmyeloablative transplant and 9 (55%) of 16 patients undergoing myeloablative transplant survived.[36] In contrast, the present study could not find any advantage of nonmyeloablative preconditioning in terms of decreasing NRM or increasing OS (Table 2). Other retrospective studies, including a large study (n = 289), also did not find any favorable affect with nonmyeloablative preconditioning.[10,22,24] In retrospective studies, drugs and doses of preconditioning regimens were heterogeneous, which could partly explain the failure to detect an advantage of nonmyeloablative preconditioning. There has been no randomized study to compare the efficacy of nonmyeloablative and myeloablative preconditioning for patients with PMF. The advantage of nonmyeloablative preconditioning for patients with PMF remains in question.

The molecular assessment of the *JAK2* mutation was performed in a very limited number of patients (six cases for pretransplant mutation and four cases for post transplant mutation). Therefore, we were unable to analyze association between the presence of pretransplant *JAK2* mutation and transplant outcomes or between the minimum residual disease and relapse after transplant. However, the present study clearly demonstrated that allogeneic BM and PBSC transplantations provide long-term survival for PMF patients and suggested the feasibility of UCB transplantation for PMF patients. Given the constant improvement in supportive care for transplant patients and the beginning of the use of molecular targeted therapy for myelofibrosis, the NRM and relapse rates may be further decreased. Allogeneic HCT should be considered in the treatment plan for PMF patients. The indications for allogeneic HCT in PMF patients have to be defined in a future study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

Institutes participating in this study: Japanese Red Cross Asahikawa Hospital; Hokkaido University Hospital; Sapporo Medical University Hospital; Sapporo Hokuyu Hospital; Akita University Hospital; Iwate Medical University; Tohoku University Hospital; Fukushima Medical University Hospital; Nagaoka Red Cross Hospital; Gunmaken Saiseikai Maebashi Hospital; Tsukuba Memorial Hospital; Chiba University Hospital; Kameda Medical Center; National Defense Medical College Hospital; Saitama Medical Center, Jichi Medical University; Keio University Hospital; Tokyo Metropolitan Cancer and Infectious diseases Center, Komagome Hospital; Toranomon Hospital; National Cancer Center Hospital; Tokyo Women's Medical University Hospital; Institute of Medical Science, University of Tokyo; Nippon Medical School Hospital; Kanagawa Cancer Center; Yokohama City University Medical Center; Nagano Red Cross Hospital; Shinshu University Hospital; Toyama Prefectural Central Hospital; Kurobe City Hospital; Kanazawa University Hospital; Shizuoka General Hospital; Japanese Red Cross Shizuoka Hospital; Hamamatsu University Hospital; Hamamatsu Medical Center; Anjo Kosei Hospital; Fujita Health University Hospital; Japanese Red Cross Nagoya Daiichi Hospital; Japanese Red Cross Nagoya Daini Hospital; Meitetsu Hospital; Nagoya University Hospital; Nara Medical University Hospital; Tenri Hospital; Takanohara Central Hospital; Kyoto University Hospital; Kyoto-Katsura Hospital; Osaka Red Cross Hospital; Osaka Medical Center for Cancer and Cardiovascular Diseases; Takatsuki Red Cross Hospital; Seichokai Fuchu Hospital; Kinki University Hospital; Wakayama Medical University Hospital; Hyogo College of Medicine; Institute of Biomedical Research and Innovation; Kurashiki Central Hospital; Okayama Medical Center; Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital; Shimane Prefectural Central Hospital; Yamaguchi University Hospital; Ehime University Hospital; Ehime Prefectural Central Hospital; Kochi Medical School Hospital; Kitakyushu Municipal Medical Center; University of Occupational and Environmental Health; Kyushu Cancer Center; Kyushu Medical Center; Kyushu University Hospital; Kurume University Hospital; Ryukyu University Hospital.