Allogeneic Hematopoietic Stem Cell Transplantation for Post-essential Thrombocythemia and Post-polycythemia Vera Myelofibrosis

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Abstract:
Objective Little information is available about the outcome of allogeneic hematopoietic stem cell transplantation (HSCT) for patients with secondary myelofibrosis from essential thrombocythemia (ET) and polycythemia vera (PV). A nationwide retrospective study of the outcome of HSCT for post-ET and post-PV myelofibrosis was conducted in Japan.

Patients and Methods Clinical data for patients with post-ET (n=29) and post-PV (n=9) myelofibrosis who had received first allogeneic HSCT were extracted from the Transplant Registry Unified Management Program, which is a registry of the outcomes of HSCT in Japan.

Results Five patients died without neutrophil recovery within 60 days after transplantation. The incidence of neutrophil recovery was significantly lower in umbilical cord blood (UCB) transplantation than in related donor transplantation (40% vs. 92%, p=0.010). The 1-year non-relapse mortality for post-ET and post-PV myelofibrosis was 35% and 27%, respectively (p=0.972). No patient or transplantation characteristics were associated with non-relapse mortality. The 4-year overall survival for post-ET and post-PV myelofibrosis was 46% and 65%, respectively (p=0.362). A univariate analysis identified UCB transplantation (vs. related donor, p=0.017) and ≥10 times red blood cell transfusions before transplantation (vs. <10 times, p=0.037) as predictive of a lower overall survival.

Conclusion Allogeneic HSCT provides a long-term survival for at least some patients with post-ET and post-PV myelofibrosis. Further studies with more patients are required to determine the best alternative donor.

Key words: myelofibrosis, essential thrombocythemia, polycythemia vera, hematopoietic stem cell transplantation, cord blood

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**Introduction**

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm characterized by sustained thrombocytois in the peripheral blood and increased numbers of megakaryocytes in the bone marrow (1). ET has a long symptom-free period with the absence of life-threatening thromboembolic or hemorrhagic events. However, myelofibrosis occurs in about 10% of patients with a diagnosis of ET (2). Polycythemia vera (PV) is another chronic myeloproliferative neoplasm characterized by increased red blood cell production independent of the mechanisms that normally regulate erythropoiesis (3). The major symptoms of PV are related to hypertension or vascular abnormalities caused by the increased red blood cell mass. The incidence of myelofibrosis in patients with a diagnosis of PV is reported to be about 10-20% (2).

Despite the remarkable benefits of Janus kinase (JAK) inhibitors in terms of reducing splenomegaly and disease-related symptoms (4, 5), current drug therapy for post-ET and post-PV myelofibrosis is not curative and unlikely to prolong the survival (6). The only potentially curative therapy for secondary myelofibrosis is allogeneic hematopoietic stem cell transplantation (HSCT) (7). Nonetheless, there are few reports focusing on the outcomes of HSCT for patients with post-ET and post-PV myelofibrosis (8-10).

We herein report the results of a nationwide retrospective study to analyze the clinical outcomes of HSCT for post-ET and post-PV myelofibrosis in Japan.

**Materials and Methods**

**Patients**

Clinical data for patients with post-ET and post-PV myelofibrosis who had received first allogeneic HSCT were extracted from the Transplant Registry Unified Management Program (TRUMP), which is a registry of the outcomes of HSCT in Japan (11, 12). This program is sponsored by the Japan Society for Hematopoietic Cell Transplantation and the Japanese Data Center for Hematopoietic Cell Transplantation. More specifically, the clinical data for patients with “1” in the “no” column, “myelofibrosis” in the “mpd_subtype” column, and “secondary” in the “denovo Secondary” column were extracted from the TRUMP data. We then divided those patients into post-ET or post-PV myelofibrosis according to “ET” or “PV” in the “sec_malig_dx” column. Patients with other diseases, such as “AML”, “MDS”, “macroglobulinemia”, “Lyomyelofibrosis”, or “macroglobulinemia,” in the “sec_malig_dx” column were excluded. Thus, neither primary myelofibrosis nor secondary myelofibrosis from diseases other than ET and PV was included in this study.

This study was approved by the Data Management Committee of the Japan Society for Hematopoietic Cell Transplantation and by the Ethics Committee of the Nagoya University School of Medicine.

**Definitions**

The conditioning regimen intensity was classified as myeloablative conditioning or reduced-intensity conditioning based on the report by the Center for International Blood and Marrow Transplant Research (13). Neutrophil recovery was defined as an absolute neutrophil count of at least 0.5 x 10^9/L 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 (14, 15).

**Endpoints**

The primary endpoint of this study was the overall survival (OS) after allogeneic HSCT in patients with post-ET and post-PV myelofibrosis. Other endpoints included neutrophil recovery, acute and chronic GVHD, relapse rate, non-relapse mortality (NRM), causes of death, and the impacts of patient and transplant characteristics on the transplant outcome.

**Statistical analyses**

The probabilities of neutrophil recovery, the acute and chronic GVHD rate, the relapse rate, and NRM stratified by primary disease and donor sources were estimated based on cumulative incidence curves (16). A competing risk regression analysis was used to identify factors associated with NRM. The probabilities of the OS stratified by primary disease and donor sources were estimated according to the Kaplan-Meier method (17). The groups were compared using the log-rank test. Cox’s proportional hazards model was used to identify factors associated with the OS (18). All tests were two-sided, and p<0.05 was considered significant. The data were analyzed by the STATA version 12 statistical software program (StatCorp, College Station, USA).

**Results**

**Patient and transplantation characteristics**

Twenty-nine patients with post-ET myelofibrosis and nine with post-PV myelofibrosis met the inclusion criteria. Transplantation was performed between 2005 and 2017. The median age at transplantation was 55 years old (range, 40-68 years old). Patient and transplantation characteristics stratified by primary disease are summarized in Table 1. Of the 13 related donor transplantation cases, 2 (15%) were performed with bone marrow (BM) from a serological HLA-A, -B, and -DR 6/6 matched donor, and 11 (85%) were performed with peripheral blood stem cells (PB) from a serological HLA-A, -B, and -DR 6/6 matched donor. Of the 19 unrelated donor transplantation cases, 18 (95%) were performed with BM from HLA-A, -B, -C, and -DRB1 alleles 8/8 matched (n=13), 7/8 matched (n=3), 6/8 matched (n=1), or 4/8 matched (n=1) donors, and 1 (5%) was performed...
| Table  1. Patient and Transplantation Characteristics Stratified by Primary Disease (n=38). |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Post-ET          | Post-PV         | p value         |
| Number of patients             | 29              | 9               |                 |
| Median age (range), y           | 53 (40-68)      | 57 (45-61)      |                 |
| Age at transplant, n (%)        |                 |                 |                 |
| 40-54 y                         | 16 (55)         | 3 (33)          | 0.45            |
| 55-68 y                         | 13 (45)         | 6 (67)          |                 |
| Sex, n (%)                      |                 |                 |                 |
| Male                            | 17 (59)         | 7 (78)          | 0.44            |
| Female                          | 12 (41)         | 2 (22)          |                 |
| Performance status at transplant, n (%) |                 |                 |                 |
| 0 or 1                          | 25 (86)         | 9 (100)         | 0.55            |
| ≥2                              | 4 (14)          | 0 (0)           |                 |
| Time from diagnosis to transplant, n (%) |                 |                 |                 |
| <3 y                            | 16 (55)         | 3 (33)          | 0.45            |
| ≥3 y                            | 13 (45)         | 6 (67)          |                 |
| Frequency of RBC transfusion before transplant, n (%) |                 |                 |                 |
| <10 times                       | 9 (31)          | 4 (45)          | 0.11            |
| ≥10 times                       | 17 (59)         | 2 (22)          |                 |
| Unknown                         | 3 (10)          | 3 (33)          |                 |
| Frequency of PLT transfusion before transplant, n (%) |                 |                 |                 |
| <10 times                       | 19 (66)         | 6 (67)          | 0.52            |
| ≥10 times                       | 7 (24)          | 1 (11)          |                 |
| Unknown                         | 3 (10)          | 2 (22)          |                 |
| DIPSS at transplant, n (%)      |                 |                 |                 |
| Low or intermediate-1           | 2 (7)           | 0 (0)           | 0.60            |
| Intermediate-2 or high          | 9 (31)          | 4 (44)          |                 |
| Unknown                         | 18 (62)         | 5 (56)          |                 |
| Splenomegaly at transplant, n (%) |                 |                 |                 |
| No                              | 1 (4)           | 0 (0)           | 0.76            |
| Yes                             | 10 (34)         | 4 (44)          |                 |
| Unknown                         | 18 (62)         | 5 (56)          |                 |
| Use of JAK inhibitor before transplant, n (%) |                 |                 |                 |
| No                              | 4 (14)          | 1 (11)          | 0.83            |
| Yes                             | 4 (14)          | 2 (22)          |                 |
| Unknown                         | 21 (72)         | 6 (67)          |                 |
| Donor, n (%)                    |                 |                 |                 |
| Related donor                   | 10 (34)         | 3 (33)          | 0.94            |
| Unrelated donor                 | 14 (49)         | 5 (56)          |                 |
| Umbilical cord blood            | 4 (14)          | 1 (11)          |                 |
| HLA-haplo donor                 | 1 (3)           | 0 (0)           |                 |
| Conditioning regimen, n (%)     |                 |                 |                 |
| Myeloablative conditioning      | 17 (59)         | 4 (44)          | 0.70            |
| Reduced-intensity conditioning  | 12 (41)         | 5 (56)          |                 |
| Prophylaxis for GVHD, n (%)     |                 |                 |                 |
| Tacrolimus+methotrexate         | 14 (48)         | 6 (67)          | 0.31            |
| Cyclosporine+methotrexate       | 9 (31)          | 3 (33)          |                 |
| Other*                          | 6 (21)          | 0 (0)           |                 |
| Use of antithymocyte globulin at transplant, n (%) |                 |                 |                 |
| No                              | 26 (90)         | 7 (78)          | 0.57            |
| Yes                             | 3 (10)          | 2 (22)          |                 |

*Other includes tacrolimus alone (n=1), tacrolimus+mycophenolate mofetil (n=3), cyclosporine alone (n=1), and cyclosporine+mycophenolate mofetil+post-transplant cyclophosphamide (n=1).

ET: essential thrombocythemia, PV: polycythemia vera, RBC: red blood cell, PLT: platelet, DIPSS: Dynamic International Prognostic Scoring System, JAK: Janus kinase, GVHD: graft-versus-host disease.
with PB from an HLA-A, -B, -C, and -DRB1 alleles 7/8 matched donor. All five unrelated umbilical cord blood (UCB) transplantation cases were performed with a single unit of UCB from a serological HLA-A, -B, and -DRB1 alleles 7/8 matched donor. UCB contained a median of 2.67 (range, 2.01-3.81)×10^6/kg cryopreserved total nucleated cells and a median of 0.78 (range, 0.55-0.95)×10^6/kg cryopreserved CD34-positive cells. One patient with post-ET myelofibrosis received PB transplantation from an HLA one haplotype-mismatched related donor (HLA-haplo donor) with post-transplant cyclophosphamide. There were no significant differences in the patient or transplantation characteristics between post-EV and post-PV myelofibrosis. The median follow-up duration for living patients was 4.3 (0.3-9.7) years.

The patient and transplantation characteristics stratified by the donor are summarized in Table 2. The patient’s sex, splenomegaly at transplant, and prophylaxis for GVHD were significantly different between donors, although the number of patients in each donor group was small. In UCB transplantation, 3 patients received myeloablative conditioning (cytarabine 12 g/m^2+cyclophosphamide 120 mg/kg+total body irradiation 12 Gy, fludarabine 180 mg/m^2+intravenous busulfan 12.8 mg/kg+total body irradiation 2 Gy, or fludarabine 180 mg/m^2+intravenous busulfan 12.8 mg/kg+melphalan 80 mg/m^2), and 2 received reduced-intensity conditioning (fludarabine 125 mg/m^2+melphalan 140 mg/m^2+total body irradiation 4 Gy or fludarabine 180 mg/m^2+melphalan 80 mg/m^2+total body irradiation 4 Gy). One patient received tacrolimus+methotrexate, two received cyclosporine+ methotrexate, and two received tacrolimus+mycophenolate mofetil as prophylaxis for GVHD.

**Engraftment**

Five patients (13%) died without engraftment within 60 days after transplantation, due to bleeding (n=2) on days 7 and 48, bacterial infection (n=1) on day 15, acute respiratory distress syndrome (n=1) on day 15, and multiple organ failure (n=1) on day 12. The incidences of neutrophil recovery on day 60 in patients with post-ET and post-PV myelofibrosis were 17% (95% CI, 6-34%) and 13% (1-42%), respectively (p=0.720). The incidences of chronic GVHD at 1 year after related donor transplantation were 31% (9-55%), 32% (13-53%), and 40% (5-75%), respectively, and those at 4 years were 42% (27-64%) and 11% (1-39%), respectively (p=0.145). The incidences of chronic GVHD at 1 year after unrelated donor transplantation were 31% (9-55%), 32% (13-53%), and 40% (5-75%), respectively, and those at 4 years after unrelated donor and UCB transplantation were 31% (9-55%) and 42% (18-64%), respectively (unrelated donor vs. related donor, p=0.832). A patient receiving HLA-haplo donor transplantation developed neither acute GVHD nor chronic GVHD. Use of JAK inhibitor before transplantation was not associated with the incidences of acute or chronic GVHD.

**Relapse**

Fourteen patients relapsed after transplantation. Five cases were diagnosed as hematological relapse, two as cytogenetic relapse, and four as molecular relapse; the diagnostic methods were unknown in three patients. The relapse rates at 1 year in patients with post-ET and post-PV myelofibrosis were 42% (95% CI, 24-59%) and 11% (1-39%), respectively, and those at 4 years were 47% (27-64%) and 11% (1-39%), respectively (p=0.145). The relapse rates at 1 year after related donor, unrelated donor, and UCB transplantation were 31% (9-55%), 32% (13-53%), and 40% (5-75%), respectively, and those at 4 years after related donor and unrelated donor transplantation were 31% (9-55%) and 42% (18-64%), respectively (unrelated donor vs. related donor, p=0.676). A patient receiving HLA-haplo donor transplantation relapsed on day 150. Use of JAK inhibitor before transplantation was not associated with the relapse rate.

**NRM**

The NRM rates at 1 year in patients with post-ET and post-PV myelofibrosis were 35% (95% CI, 14-57%) and 27% (4-59%), respectively, and those at 4 years were 35% (14-57%) and 27% (4-59%), respectively (Fig. 2a). The NRM rates at 1 year after related donor, unrelated donor, and UCB transplantation were 11% (1-39%), 42% (15-67%), and 50% (6-84%), respectively, and those at 4 years after related donor and unrelated donor transplantation were 11% (1-39%) and 42% (15-67%), respectively (Fig. 2b). To identify risk factors for NRM, a univariate analysis was per-
Table 2. Patient and Transplantation Characteristics Stratified by Donor (n=38).

|                                | Related | Unrelated | UCB | HLA-haplo | p value |
|--------------------------------|---------|-----------|-----|-----------|---------|
| Number of patients             | 13      | 19        | 5   | 1         |         |
| Median age (range), y          | 53 (40-59) | 53 (40-68) | 62 (57-68) | 49       |         |
| Age at transplant, n (%)       |         |           |     |           |         |
| 40-54 y                        | 7 (54)  | 11 (58)   | 0 (0) | 1 (100)   | 0.09    |
| 55-68 y                        | 6 (46)  | 8 (42)    | 5 (100) | 0 (0)     |         |
| Sex, n (%)                     |         |           |     |           |         |
| Male                           | 4 (31)  | 15 (79)   | 4 (80) | 1 (100)   | 0.03    |
| Female                         | 9 (69)  | 4 (21)    | 1 (20) | 0 (0)     |         |
| Primary disease, n (%)         |         |           |     |           |         |
| ET                             | 10 (77) | 14 (74)   | 4 (80) | 1 (100)   | 0.94    |
| PV                             | 3 (23)  | 5 (26)    | 1 (20) | 0 (0)     |         |
| Performance status at transplant, n (%) |       |           |     |           |         |
| 0 or 1                         | 11 (85) | 17 (89)   | 5 (100) | 1 (100)   | 0.79    |
| ≥2                             | 2 (15)  | 2 (11)    | 0 (0) | 0 (0)     |         |
| Time from diagnosis to transplant, n (%) |       |           |     |           |         |
| <3 y                           | 9 (69)  | 7 (37)    | 2 (40) | 1 (100)   | 0.22    |
| ≥3 y                           | 4 (31)  | 12 (63)   | 3 (60) | 0 (100)   |         |
| Frequency of RBC transfusion before transplant, n (%) |       |           |     |           |         |
| <10 times                      | 5 (38)  | 7 (37)    | 0 (0) | 1 (100)   | 0.17    |
| ≥10 times                      | 8 (62)  | 7 (37)    | 4 (80) | 0 (0)     |         |
| Unknown                        | 0 (0)   | 5 (26)    | 1 (20) | 0 (0)     |         |
| Frequency of PLT transfusion before transplant, n (%) |       |           |     |           |         |
| <10 times                      | 10 (77) | 12 (63)   | 2 (40) | 1 (100)   | 0.52    |
| ≥10 times                      | 3 (24)  | 3 (16)    | 2 (40) | 0 (0)     |         |
| Unknown                        | 0 (0)   | 4 (21)    | 1 (20) | 0 (0)     |         |
| DIPSS at transplant, n (%)     |         |           |     |           |         |
| Low or intermediate-1          | 1 (8)   | 1 (5)     | 0 (0) | 0 (0)     | 0.64    |
| Intermediate-2 or high         | 4 (31)  | 5 (26)    | 3 (60) | 1 (100)   |         |
| Unknown                        | 8 (61)  | 13 (69)   | 2 (40) | 0 (0)     |         |
| Splenomegaly at transplant, n (%) |       |           |     |           |         |
| No                             | 0 (0)   | 0 (0)     | 0 (0) | 1 (100)   | <0.01   |
| Yes                            | 5 (38)  | 6 (32)    | 3 (60) | 0 (0)     |         |
| Unknown                        | 8 (62)  | 13 (68)   | 2 (40) | 0 (0)     |         |
| Use of JAK inhibitor before transplant, n (%) |       |           |     |           |         |
| No                             | 1 (8)   | 3 (16)    | 1 (20) | 0 (0)     | 0.17    |
| Yes                            | 4 (31)  | 0 (0)     | 2 (40) | 0 (0)     |         |
| Unknown                        | 8 (61)  | 16 (84)   | 2 (40) | 1 (100)   |         |
| Conditioning regimen, n (%)    |         |           |     |           |         |
| Myeloablative conditioning     | 10 (77) | 7 (37)    | 3 (60) | 1 (100)   | 0.12    |
| Reduced-intensity conditioning  | 3 (23)  | 12 (63)   | 2 (40) | 0 (0)     |         |
| Prophylaxis for GVHD, n (%)    |         |           |     |           |         |
| Tacrolimus+methotrexate         | 2 (15)  | 17 (90)   | 1 (20) | 0 (0)     | <0.01   |
| Cyclosporine+methotrexate      | 9 (70)  | 1 (5)     | 2 (40) | 0 (0)     |         |
| Other*                         | 2 (15)  | 1 (5)     | 2 (40) | 1 (100)   |         |
| Use of antithymocyte globulin at transplant, n (%) |       |           |     |           |         |
| No                             | 11 (85) | 16 (84)   | 5 (100) | 1 (100)   | 0.78    |
| Yes                            | 2 (15)  | 3 (16)    | 0 (0) | 0 (0)     |         |

*pOther includes tacrolimus alone (n=1), tacrolimus+mycophenolate mofetil (n=3), cyclosporine alone (n=1), and cyclosporine+mycophenolate mofetil+post-transplant cyclophosphamide (n=1).

UCB: umbilical cord blood, HLA-haplo: HLA one haplotype-mismatched related, ET: essential thrombocytopenia, PV: polycythemia vera, RBC: red blood cell, PLT: platelet, DIPSS: Dynamic International Prognostic Scoring System, JAK: Janus kinase, GVHD: graft-versus-host disease

formed for all categorical variables listed in Table 1. No patient or transplantation characteristics were significantly associated with NRM (Table 3). Use of JAK inhibitor before transplantation was not associated with the NRM rate.
OS

The OS rates at 1 year in patients with post-ET and post-PV myelofibrosis were 51% (95% CI, 31-67%) and 65% (25-87%), respectively, and those at 4 years were 46% (27-64%) and 65% (25-87%), respectively (log-rank, p=0.362) (Fig. 3a). The OS rates at 1 year after related donor, unrelated donor, and UCB transplantation were 69% (37-87%), 50% (26-70%), and 20% (1-58%), respectively, and those at 4 years after related donor and unrelated donor transplantation were 69% (37-87%) and 50% (26-70%), respectively (log-rank, p=0.0259) (Fig. 3b). To identify risk factors for the OS, a univariate analysis was performed for all categorical variables listed in Table 1. UCB transplantation and a higher frequency of RBC transfusion before transplantation were significantly associated with a lower OS (Table 3). Other patient and transplantation characteristics were not significantly associated with the OS. Use of JAK inhibitor before transplantation was not associated with the OS rate.

Causes of death

In addition to five patients who died without engraftment, as previously described, 13 patients died of hepatic venoocclusive disease (n=1); GVHD (n=1); thrombotic microangiopathy (n=1); bacterial (n=2), fungal (n=1), and viral (n=1) infections; interstitial pneumonia (n=1); acute respiratory distress syndrome (n=1); multiple organ failure (n=1); and relapse (n=3).

Discussion

The present study demonstrated no significant differences in the incidence of neutrophil recovery, incidences of acute and chronic GVHD, relapse rate, NRM, and the OS between post-ET and post-PV myelofibrosis. Little information has been available comparing transplant outcomes between post-ET and post-PV myelofibrosis. Lussana et al. reported no marked differences in the 3-year NRM and OS rates between post-ET and post-PV myelofibrosis (10). In contrast, Ballen et al. reported a significantly higher 5-year NRM for post-ET myelofibrosis than for post-PV myelofibrosis (9). Thus, whether or not the transplant outcomes for post-ET and post-PV myelofibrosis are equivalent remains controversial.

The OS was significantly lower in UCB transplantation than in related donor transplantation. NRM was not significantly different between UCB and related donor transplantation. However, the incidence of neutrophil recovery was significantly lower in UCB transplantation than in related donor transplantation. These results suggest that efforts to increase the incidence of neutrophil recovery may help improve the OS in UCB transplantation for secondary myelofibrosis. Nonetheless, the present cohort included only five patients undergoing UCB transplantation. Robin et al. evaluated 35 UCB transplantation cases for myelofibrosis, includ-
myeloid leukemia, and reported a 2-year OS of 44% (19). The recent nationwide retrospective study of HSCT for Japanese patients with primary myelofibrosis reported that the 1- and 4-year OS rates in UCB transplantation (n=29) were 48% and 27%, respectively, and that NRM was significantly higher in UCB transplantation than in HLA-matched related donor BM transplantation (21). Further analyses with more patients are required to evaluate the differences in the transplant outcomes for secondary myelofibrosis between UCB transplantation and related or unrelated donor transplantation.

Frequent (≥10 times) RBC transfusion before transplantation was identified as a risk factor for the OS. This is compatible with previous analyses of HSCT for primary myelofibrosis (21-23). The Japanese national registry includes the Dynamic International Prognostic Scoring System (DIPSS) score, but not the DIPSS Plus score, which takes into account the information on RBC transfusion dependency and thrombocytopenia (24). Therefore, if the DIPSS Plus score had been available, it might have been identified as a predictor of the transplant outcome.

The median ages at transplantation for post-ET and post-PV myelofibrosis were 53 and 57 years old, respectively. These ages are younger than the median ages of the general patient cohorts of ET (approximately 55 years old), PV (approximately 64 years old), and primary myelofibrosis (approximately 65 years old) (2, 25). A younger patient age is reported to be associated with a higher OS in HSCT for

Table 3. Univariate Analysis of Non-relapse Mortality and Overall Survival.

|                      | HR (95% CI) | p value |
|----------------------|-------------|---------|
| **Non-relapse mortality** |             |         |
| Primary disease      |             |         |
| ET (n=29)            | 1           |         |
| PV (n=9)             | 1.03 (0.22-4.89) | 0.972   |
| Donor                |             |         |
| Related donor (n=13) | 3.62 (0.39-33.93) | 0.259   |
| Unrelated donor (n=19) | 6.51 (0.51-83.24) | 0.150   |
| Umbilical cord blood (n=5) |         |         |
| **Overall survival** |             |         |
| Primary disease      |             |         |
| ET (n=29)            | 1           |         |
| PV (n=9)             | 0.57 (0.16-1.96) | 0.370   |
| Donor                |             |         |
| Related donor (n=13) | 1           |         |
| Unrelated donor (n=19) | 1.62 (0.50-5.26) | 0.423   |
| Umbilical cord blood (n=5) |         |         |
| Frequency of RBC transfusion before transplantation | | |
| <10 times (n=13)     | 5.63 (1.36-23.29) | 0.017   |
| ≥10 times (n=19)     | 3.93 (1.08-14.22) | 0.037   |

The results of univariate analysis for primary disease, donor, and significant factors are shown selectively.
HR: hazard ratio, CI: confidence interval, ET: essential thrombocythemia, PV: polycythemia vera, UCB: umbilical cord blood

Figure 3. The OS rate after transplantation. (a) The OS rates after transplantation in patients with post-ET (black line) and post-PV (grey line) myelofibrosis are shown. (b) The OS rates after related donor (black and solid line), unrelated donor (grey and solid line), and UCB (black and dash line) transplantation are shown. OS: overall survival, ET: essential thrombocythemia, PV: polycythemia vera, UCB: umbilical cord blood
myelofibrosis (21, 26, 27). Thus, it should be noted that the efficacy of HSCT for secondary myelofibrosis might have been accentuated in this study.

A comparison of transplant outcomes of Japanese patients with primary (21) and secondary (present study) myelofibrosis is summarized in Table 4. HLA-matched related donor PB transplantation for secondary myelofibrosis showed a lower NRM and higher OS than that for primary myelofibrosis; however, this was not replicated in unrelated donor BM and UCB transplantation. Some studies have reported no significant differences in the NRM or OS between primary and secondary myelofibrosis (28-31). However, a recent study reported a significantly higher OS in patients with secondary myelofibrosis than with primary myelofibrosis (26). A more recent study reported the opposite results, finding that the OS was significantly lower in patients with secondary myelofibrosis than in those with primary myelofibrosis (27). Taken together, these findings underscore the importance of analyzing the transplant outcome of secondary myelofibrosis in distinction from primary myelofibrosis.

In conclusion, it was confirmed that allogeneic HSCT provides a long-term survival for at least some patients with post-ET and post-PV myelofibrosis. Future studies with a large number of patients are needed to determine the best alternative donor, including UCB and HLA-haplo donor, the best preconditioning regimen for successful engraftment, and the best timing for allogeneic HSCT.

Table 4. Comparison of Transplant Outcomes of Japanese Patients with Primary and Secondary Myelofibrosis.

| HLA-matched related donor PB transplantation | PMF (21) | SMF (present study) |
|--------------------------------------------|---------|---------------------|
| Number of patients                         | 48      | 13*                 |
| Neutrophil recovery on day 60              | 94 (82-98)% | 92 (57-99)%         |
| Median time to neutrophil recovery         | 16 d    | 17 d                |
| Grade II-IV acute GVHD on day 100          | 27 (16-40)% | 15 (2-39)%          |
| Chronic GVHD at 1 y                        | 38 (25-52)% | 23 (6-47)%          |
| Relapse at 1 y                             | 17 (8-29)% | 31 (9-55)%          |
| Relapse at 4 y                             | 17 (8-29)% | 31 (9-55)%          |
| NRM at 1 y                                | 36 (22-50)% | 11 (1-39)%          |
| NRM at 4 y                                | 41 (26-56)% | 11 (1-39)%          |
| OS at 1 y                                 | 58 (43-71)% | 69 (37-87)%         |
| OS at 4 y                                 | 52 (37-65)% | 69 (37-87)%         |
| Unrelated donor BM transplantation         |         |                     |
| Number of patients                         | 91      | 19***               |
| Neutrophil recovery on day 60              | 86 (77-92)% | 89 (64-97)%         |
| Median time to neutrophil recovery         | 21 d    | 24 d                |
| Grade II-IV acute GVHD on day 100          | 27 (18-36)% | 5 (0-21)%           |
| Chronic GVHD at 1 y                        | 31 (22-41)% | 6 (0-24)%           |
| Relapse at 1 y                             | 11 (6-19)% | 32 (13-53)%         |
| Relapse at 4 y                             | 13 (7-21)% | 42 (18-64)%         |
| NRM at 1 y                                | 30 (21-41)% | 42 (15-67)%         |
| NRM at 4 y                                | 48 (36-59)% | 42 (15-67)%         |
| OS at 1 y                                 | 61 (50-70)% | 50 (26-70)%         |
| OS at 4 y                                 | 46 (35-57)% | 50 (26-70)%         |
| UCB transplantation                        |         |                     |
| Number of patients                         | 29      | 5                   |
| Neutrophil recovery on day 60              | 79 (58-90)% | 40 (5-75)%          |
| Median time to neutrophil recovery         | 25 d    | 29 d                |
| Grade II-IV acute GVHD on day 100          | 31 (16-48)% | 20 (1-58)%          |
| Chronic GVHD at 1 y                        | 15 (5-31)% | 20 (1-58)%          |
| Relapse at 1 y                             | 14 (4-30)% | 40 (5-75)%          |
| NRM at 1 y                                | 41 (22-60)% | 50 (6-84)%          |
| OS at 1 y                                 | 48 (29-64)% | 20 (1-58)%          |

*Two patients with BM transplantation from HLA-matched related donor are included.  
**95% confidence interval is in parentheses.  
***One patient with PB transplantation from unrelated donor is included.  
PMF: primary myelofibrosis, SMF: secondary myelofibrosis, PB: peripheral blood stem cell, GVHD: graft-versus-host disease, NRM: non-relapse mortality, OS: overall survival, BM: bone marrow, UCB: umbilical cord blood.
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