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Brief Article

Hematopoietic Cell Transplantation for Acute Panmyelosis with Myelofibrosis: A Retrospective Study in Japan

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A B S T R A C T

Acute panmyelosis with myelofibrosis (APMF) is a rare subtype of acute myeloid leukemia characterized by acute onset of cytopenias and bone marrow fibrosis in the absence of splenomegaly. Because the prognosis of APMF is extremely poor even after chemotherapy, hematopoietic cell transplantation (HCT) has been used to treat APMF. However, the outcome after HCT for APMF remains unclear. To evaluate the outcomes and prognostic factors after HCT as a therapeutic modality for APMF, we retrospectively analyzed the Japanese registration data of 40 APMF patients who received allogeneic and syngeneic HCT between 2005 and 2015. The median age at HCT was 53.5 years (range, 16 to 70). The disease status at HCT was first complete remission (CR1) in 13 patients (33%). The probability of overall survival and the cumulative incidence of relapse at 3 years were 24% and 59%, respectively. Univariate analysis identified that female sex and disease status CR1 at the time of HCT were significantly associated with higher overall survival. Although APMF patients have a poor long-term prognosis even after syngeneic and allogeneic HCT, these data suggested that allogeneic HCT offered a curative option for APMF.

INTRODUCTION

Acute panmyelosis with myelofibrosis (APMF) is a rare subtype of acute myeloid leukemia according to the World Health Organization classification [1]. APMF is characterized by acute onset of cytopenias and bone marrow fibrosis in the absence of splenomegaly [2-5]. A standard treatment has not been established for APMF. Treatment modalities for APMF have considerable heterogeneity, including chemotherapies such as danazol, lenalidomide, and zoledronate [2,3,6,7]. However, such treatments have limited efficacy, and most patients will die from progressive disease, such as bone marrow failure and development of overt acute myeloid leukemia. The prognosis of APMF is extremely poor, with reported median survivals of 2 to 9 months [2-5]. Therefore, hematopoietic cell transplantation (HCT) has been used to treat APMF [8-12]. However, the efficacy

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of HCT as a therapeutic modality for APMF remains unclear. To clarify the outcomes and prognostic factors in APMF patients treated with HCT, we performed a retrospective analysis using a nationwide Japanese database.

METHODS

Clinical data were provided by the Transplant Registry Unified Management Program of the Japanese Data Center for Hematopoietic Cell transplantation [13-15]. Inclusion criteria consisted of patients with APMF who received HCT. Study endpoints were overall survival (OS), relapse, transplant-related mortality (TRM), and neutrophil and platelet engraftment.

The probability of OS was calculated using the Kaplan-Meier method, and the log-rank test was used to compare the groups in a univariate analysis. The probability of relapse, TRM, and neutrophil and platelet engraftment were calculated using cumulative incidence curves, taking into account competing risks, and Gray's test was used to compare the groups in a univariate analysis. For TRM, relapse was a competing event. In contrast, TRM was a competing event for relapse. For neutrophil and platelet engraftment, death before day 28 was a competing event. Cytogenetic subgroups were defined according to the National Comprehensive Cancer Network Guidelines for acute myeloid leukemia [16].

The myeloablative conditioning regimen was defined according to the criteria of the Center for International Blood and Marrow Transplant Research, whereas other regimens were classified as reduced-intensity conditioning [17]. Univariate analyses were performed using the following variables: age (16 to 54 versus ≥55 years), sex (male versus female), cytogenetics (other than poor versus poor), disease status at HCT (first complete remission [CR1] versus other than CR1), the interval time from diagnosis to HCT (<6 months versus ≥6 months), donor source (bone marrow transplantation [BMT]/peripheral blood stem cell transplantation from a related or syngeneic donor [RBMT/PBSCT] versus BMT from an unrelated donor versus cord blood transplantation from an unrelated donor [UCBT]), conditioning regimen (myeloablative conditioning versus reduced-intensity conditioning), graft-versus-host disease prophylaxis (calcineurin inhibitor with methotrexate versus without methotrexate), and number of allogeneic HCTs (1 versus ≥2). A multivariate analysis could not be performed because of the small sample size.

All *P* values were 2-sided, and all statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [18], a graphical user interface for the R 3.0.2 software program (R Foundation for Statistical Computing, Vienna, Austria). The institutional review board approved this retrospective study.

RESULTS

Patient characteristics, disease status, and transplant procedures are listed in Table 1. Forty patients with APMF underwent syngeneic (n = 1) and allogeneic (n = 39) HCT between 2005 and 2015. The median age at HCT was 53.5 years (range, 16 to 70). The median WBC count at diagnosis was 3400/μL (range, 200 to 94,600) among 39 assessable patients, and extramedullary involvement at diagnosis was observed in 3 patients (8%). Among 36 assessable patients, 21 patients (53%) had intermediate, and 15 patients (38%) poor cytogenetics. The disease status at HCT was CR1 in 13 patients (33%), all of whom received induction chemotherapy before HCT. The median proportions of blasts in bone marrow and peripheral blood were 25% (range, 0 to 90%) and 12.5% (range, 0 to 89%) among 15 and 20 assessable patients, respectively. A total of 11 patients (28%) received RBMT/PBSCT, 16 (40%) received BMT from an unrelated donor, and 13 (33%) received UCBT. The myeloablative conditioning regimen (58%) and calcineurin inhibitor and methotrexate-based graft-versus-host disease prophylaxis (73%) were more commonly performed in this study group. The median time from diagnosis to HCT was 5 months (range, 1 to 45), and the median period of follow-up for survivors after HCT was 40 months (range, 2 to 139).

In the entire cohort the probability of OS at 3 years was 24% (95% confidence interval [CI], 12% to 39%] (Figure 1A). In a

Table 1
Patient Characteristics, Disease Status, and Transplant Procedures

Characteristic	Value
No. of patients	40
Median age, yrs (range)	53.5 (16-70)
Age	
16-54 yr	22 (55)
≥55 yr	18 (45)
Sex	
Male	33 (83)
Female	7 (18)
Median WBC count at diagnosis, /μL (range)	3400 (200-94,600)
Extramedullary involvement at diagnosis	
Absent	37 (93)
Present	3 (8)
Cytogenetics	
Intermediate	21 (53)
Poor	15 (38)
Unknown	4 (10)
Disease status at HCT*	
CR1	13 (33)
Primary induction failure	10 (25)
Refractory relapse	11 (28)
Untreated	6 (15)
Median bone marrow blasts at HCT, % (range)	25 (0-90)
Median peripheral blood blasts at HCT, % (range)	12.5 (0-89)
Median time from diagnosis to HCT, mo (range)	5 (1-45)
Time from diagnosis to HCT	
<6 mo	22 (55)
≥6 mo	18 (45)
Donor source	
RBMT/PBSCT	10 (25)
Syngeneic PBSCT	1 (3)
Unrelated BMT	16 (40)
UCBT	13 (33)
Conditioning regimen	
MAC	23 (58)
TBI+CY	5
TBI+CA	2
TBI+CY+CA	2
BU based	8
FLU+MEL based	6
RIC	17 (43)
FLU+BU+TBI	2
FLU+BU+CY+TBI	2
FLU+BU	2
FLU+MEL+TBI	4
Other FLU based	5
Others	2
GVHD prophylaxis	
CI+MTX	29 (73)
CI+MMF	7 (18)
CI	3 (8)
None	1 (3)
No. of allogeneic HCTs	
1	32 (80)
≥2	8 (20)
Causes of second or subsequent HCT	
Relapse after previous HCT	6 (15)
Graft failure after previous HCT	2 (5)
Year of HCT	
2005-2009	17 (43)
2010-2015	23 (58)

Values are n (%) unless otherwise defined. MAC indicates myeloablative conditioning; TBI, total body irradiation; CY, cyclophosphamide; CA, cytosine arabinoside; BU, busulfan; FLU, fludarabine; MEL, melphalan; RIC, reduced-intensity conditioning; GVHD, graft-versus-host disease, CI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolate mofetil.

* Primary induction failure was defined as failure to achieve complete remission with induction chemotherapy. Refractory relapse was defined as failure to achieve complete remission with salvage chemotherapy after first or subsequent relapse. Untreated was defined as no induction chemotherapy before the conditioning regimen.

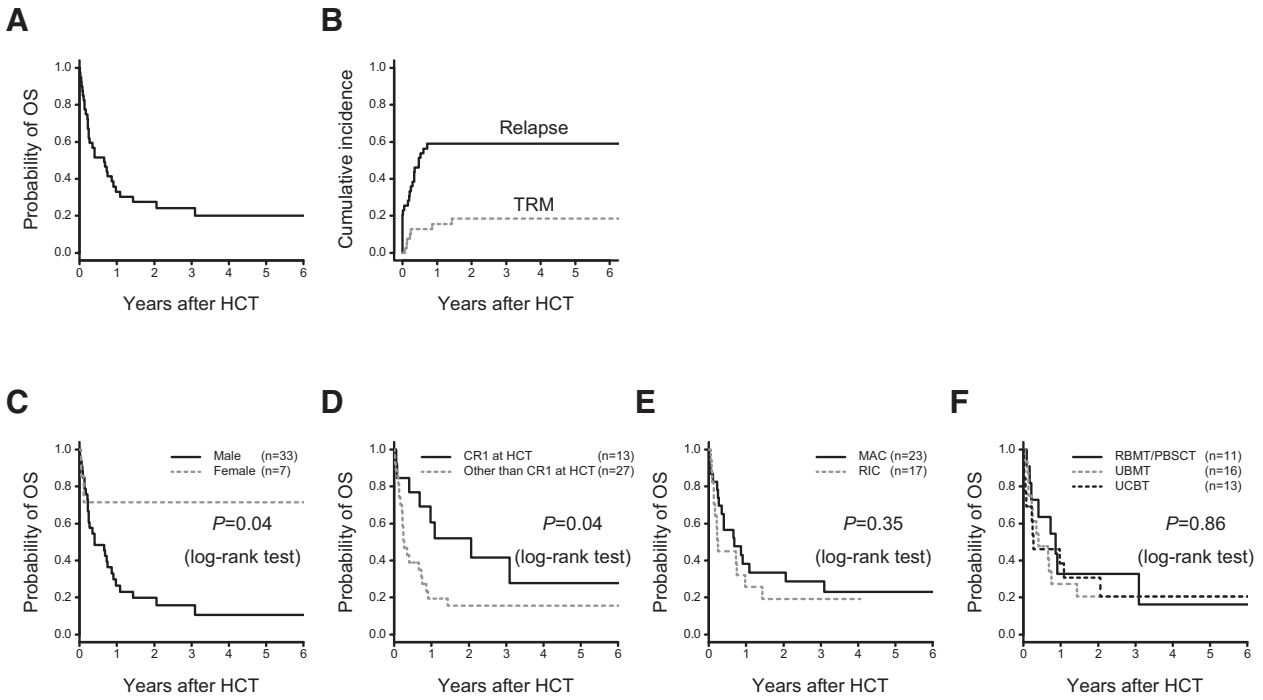

Figure 1. OS, relapse, and TRM after HCT for APMF. (A) OS among the entire cohort. (B) Relapse and TRM among the entire cohort. (C) OS according to sex. (D) OS according to disease status at HCT. (E) OS according to intensity of the conditioning regimen. (F) OS according to donor source.

univariate analysis female sex and CR1 at HCT were significantly associated with better OS (Figure 1C,D). On the other hand, donor source and intensity of conditioning regime did not affect survival (Figure 1E,F).

The cumulative incidences of relapse and TRM at 3 years were 59% (95% CI, 42% to 73%) and 19% (95% CI, 8% to 33%), respectively (Figure 1B). No significant factors were associated with relapse and TRM in the univariate analysis. At the last follow-up 30 patients had died. Causes of death were relapse in 17 patients, infection with or without graft-versus-host disease in 6 patients, organ failure in 4 patients, hemorrhage in 1 patient, graft failure in 1 patient, and unknown in 1 patient. Among 17 relapsed patients, 3 patients died of relapse with infection, 1 patient died of relapse with hemorrhage, and the remaining 13 patients died of disease progression of APMF.

Neutrophil engraftment occurred in 33 of 40 patients (75%), with a median time to achieve neutrophils $> .5 \times 10^9$/L of 17 days (range, 13 to 53). The cumulative incidence of neutrophil engraftment at 28 days was 78% (95% CI, 60% to 88%) (Figure 2A). In a univariate analysis donor source alone was significantly associated with achievement of neutrophil engraftment (Figure 2B). The cumulative incidence of neutrophil engraftment was significantly lower in patients receiving UCBT compared with patients receiving RBMT/PBSCT ($P < .001$) or BMT from an unrelated donor ($P = .04$).

Among 7 patients who did not achieve neutrophil engraftment, 5 patients developed relapse before neutrophil engraftment, and primary graft failure occurred in the remaining 2 patients (5%) only after UCBT. Of 2 patients experienced primary graft failure, 1 patient died of primary graft failure on day 27 and 1 patient received salvage second HCT on day 40.

Platelet engraftment occurred in 23 patients, with a median time to an untransfused platelet count $> 20 \times 10^9$/L of 34 days (range, 14 to 105). The cumulative incidence of platelet recovery at 100 days was 56% (95% CI, 38% to 71%) (Figure 2C). In a univariate analysis disease status at HCT alone was significantly associated with achievement of platelet engraftment (Figure 2D).

DISCUSSION

Several studies have shown that APMF is associated with poor response to chemotherapy, and median survival time is usually less than 1 year [2-5]. Because allogeneic HCTs have curative potential for relapsed, refractory, and poor prognostic myeloid malignancies [19], HCT has been attempted to treat APMF. Although a limited number of APMF cases treated with HCT have been reported [8-12], the outcome of HCT in patients with APMF has never been systematically studied. Although 1 case of long-term survival treated with autologous HCT for APMF has been reported [8], the patient treated with autologous HCT was not included in the Transplant Registry Unified Management Program data. Thus, our study was the first report to demonstrate the outcomes of syngeneic and allogeneic HCT for APMF with a relatively large number of patients. Our data demonstrated that the probability of OS at 3 years was 24%. CR1 at HCT was the most significant prognostic indicator for survival, indicating that APMF patients likely benefit from allogeneic HCT in CR1.

Previous studies showed that the degree of bone marrow fibrosis significantly affected hematopoietic engraftment and survival after allogeneic HCT for myeloid malignancies, including myelofibrosis [20-24]. In fact, neutrophil and platelet engraftment were poor in our study. Because we were unable to use grade of bone marrow fibrosis because of insufficient data, further studies are required to clarify the impact of grade of bone marrow fibrosis on the outcomes after allogeneic HCT for APMF. Moreover, our study confirmed that CBT was significantly associated with a lower cumulative incidence of neutrophil engraftment, which is consistent with a previous report in patients with primary myelofibrosis [25]. However, donor source did not affect survival in our study. Therefore, for APMF patients who lack an HLA-identical sibling donor, allogeneic HCT from an unrelated adult donor or cord blood should be considered.

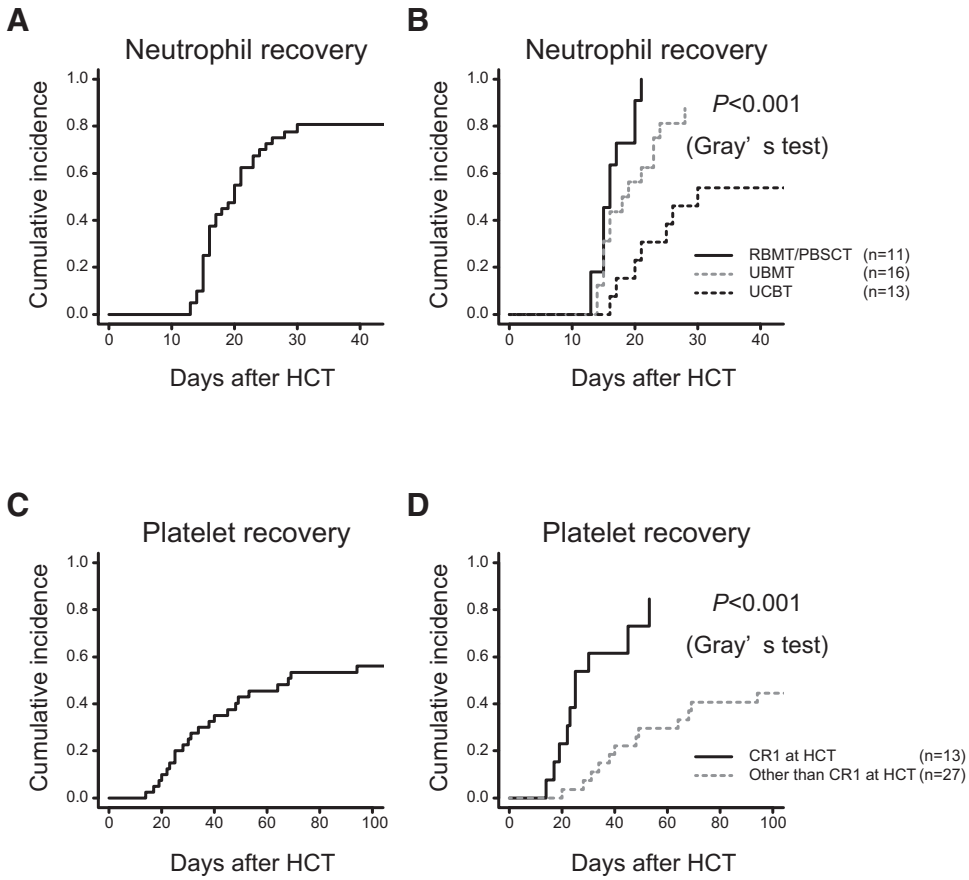

Figure 2. Neutrophil and platelet recovery after HCT for APMF. (A) Neutrophil recovery among the entire cohort. (B) Neutrophil recovery according to donor source. (C) Platelet recovery among the entire cohort. (D) Platelet recovery according to disease status at HCT.

In conclusion, this registry-based study confirmed that patients with APMF have a poor outcome because of a high relapse rate even after syngeneic and allogeneic HCT. Female sex and CR1 at HCT were significant prognostic indicators for better survival. Although allogeneic HCT offered a curative option for APMF, novel treatment strategies that could be an effective bridge to HCT after achievement of CR1 are required for APMF.

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