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Allogeneic Hematopoietic Cell Transplantation for Leukemic Transformation Preceded by Philadelphia Chromosome–Negative Myeloproliferative Neoplasms: A Nationwide Survey by the Adult Acute Myeloid Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation

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A B S T R A C T

To clarify the outcome of allogeneic hematopoietic cell transplantation (HCT) for leukemic transformation (LT) preceded by Philadelphia chromosome–negative (Ph-neg) myeloproliferative neoplasms (MPNs), we conducted a retrospective study using the national registry database of the Japan Society for Hematopoietic Cell Transplantation. From 2000 to 2013, 39 patients underwent their first allogeneic HCT with related bone marrow or peripheral blood stem cells (n = 8), unrelated bone marrow (n = 15), and unrelated umbilical cord blood (n = 16). The median patient age was 57 years. The underlying Ph-neg MPNs included 21 cases of essential thrombocythemia, 11 cases of primary myelofibrosis, and 7 cases of polycythemia vera. The median interval between the diagnosis of LT and transplantation was 134 days. Thirty-two cases (82%) were not in remission at the time of transplantation. The 2-year overall survival rate was 29.2% (95% confidence interval [CI], 15.5% to 44.3%). The median follow-up of the surviving patients was 1989.5 days (range, 285 to 3270). The cumulative incidences of relapse and nonrelapse mortality at 2 years were 34.4% (95% CI, 19.6% to 49.8%) and 34.2% (95% CI, 19.6% to 49.4%), respectively. The study results suggested that allogeneic HCT provides long-term survival in approximately one-third of patients with LT preceded by Ph-neg MPNs.

INTRODUCTION

Leukemic transformation (LT) is an unavoidable event for approximately 10% to 20% of patients with Philadelphia chromosome–negative (Ph-neg) myeloproliferative neoplasms (MPNs), for whom the prognosis is generally dismal [1]. Although allogeneic hematopoietic cell transplantation (HCT) may be the only curative treatment, the majority of such patients are elderly and have not been considered favorable candidates for allogeneic HCT in the past. However, the recent development of the reduced-intensity conditioning (RIC) regimen and supportive therapy have allowed even high-risk elderly patients to undergo allogeneic HCT. Recently,

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several groups have published results regarding allogeneic HCT for LT preceded by Ph-neg MPNs [2-7]. These studies demonstrated that allogeneic HCT could provide long-term disease control for patients with LT preceded by Ph-neg MPNs. The aim of this study was to clarify the outcome of allogeneic HCT for LT preceded by Ph-neg MPNs using the Japanese registry data.

STUDY DESIGN

Patients

Data on patients who underwent first allogeneic HCT for LT preceded by Ph-neg MPNs from 2000 to 2013 were collected from the Transplant Registry Unified Management Program system, which is the national registry database of the Japan Society for Hematopoietic Cell Transplantation. Further investigation was conducted in 2015 and 2016 using a questionnaire mailed to each participating hospital to confirm the complete karyotype information. The study was approved by the data management committee of the Japan Society for Hematopoietic Cell Transplantation and the institutional review board of Toranomon Hospital. Patients with acute panmyelosis with myelofibrosis or a past history of allogeneic HCT were excluded from the analysis.

Definitions

Neutrophil engraftment was defined as the first of 3 consecutive days during which the absolute neutrophil count was $\geq .5 \times 10^9$/L. *Platelet engraftment* was defined temporally, as for neutrophils, when the platelet count was $\geq 20 \times 10^9$/L. Acute and chronic graft-versus-host disease (GVHD) were diagnosed and graded according to established criteria [8,9]. The conditioning regimens were classified as myeloablative conditioning if total body irradiation ≥ 8 Gy fractionated, oral busulfan > 8 mg/kg, intravenous busulfan > 6.4 mg/kg, or melphalan > 140 mg/m^2 were included in the conditioning regimen. The other conditioning regimens were classified as RIC [10,11]. A *complex karyotype* was defined as the presence of 3 or more chromosomal abnormalities.

Endpoints

The primary endpoint was overall survival (OS). The secondary endpoints were neutrophil and platelet engraftment, GVHD, relapse, and nonrelapse mortality (NRM).

Statistical Analysis

The probabilities of neutrophil and platelet engraftment, acute and chronic GVHD, relapse, and NRM were estimated on the basis of cumulative incidence curves. Competing events were death or relapse without engraftment for the cumulative incidence of neutrophil and platelet engraftment, death or relapse without GVHD for the cumulative incidence of acute and chronic GVHD, death without relapse for the cumulative incidence of relapse, and relapse for NRM. The probability of OS was estimated according to the Kaplan-Meier method. We used the log-rank test to compare the groups. The data were analyzed using EZR version 1.25 statistical software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [12].

RESULTS

Patient and Transplantation Characteristics

A total of 39 patients met the inclusion criteria. Patient characteristics are summarized in Table 1. The median patient age at the time of transplantation was 57 years (range, 22 to 71). The underlying Ph-neg MPNs included 21 cases of essential thrombocythemia (ET), 11 cases of primary myelofibrosis (PMF), and 7 cases of polycythemia vera (PV). The additional investigation using the questionnaire method provided us with the complete karyotype information at the time of LT diagnosis for 30 of 39 patients (77%). The karyotype was normal in 5 cases, complex in 15 cases, classified as other in 13 cases, and unknown in 6 cases. The median number of days between the LT diagnosis and transplantation was 134 days (range, 24 to 369). The disease status at the time of transplantation included the first complete remission for 7 cases, first relapse for 3 cases, primary induction failure for 17 cases, and untreated for 12 cases. A total of 32 cases (82%) were not in remission. The donor source was related bone marrow (R-BM) or peripheral blood stem cells (R-PB) for 8 cases (R-BM, n = 3; R-PB, n = 5), unrelated bone marrow (UBM) in 15 cases, and unrelated umbilical cord blood (UCB) in 16 cases. Among the 8 R-BM/R-PB transplantations, 6 (75%) were performed from serologically HLA-A, -B, and -DR 6/6 or 5/6–matched donors; the 15 UBM transplantations included 12 (80%) serologically HLA-A, -B, -DR 6/6–matched donors and 3 (20%) serologically HLA-A, -B, -DR 5/6 matched donors; and the 16 UCB transplantations included 15 (94%) serologically HLA-A, -B, -DR 5/6 or 4/6–matched donors. The median transplanted cell doses were as follows: 1.46×10^8/kg nucleated cells for R-BM (range, 1.34 to 1.56×10^8, n = 3), 4.8×10^6/kg CD34$^+$ cells for R-PB (range, 4.68 to 4.85×10^6, n = 2), 1.45×10^8/kg nucleated cells for UBM (range, .72 to 1.9×10^8, n = 15), and 2.43×10^7/kg nucleated cells and $.72 \times 10^5$/kg CD34$^+$ cells for UCB (range, 1.98 to 3.54×10^7, .36

Table 1
Patient Characteristics

Characteristic	Value
Age at transplantation, evaluable n	39
Age, median (range), yr	57 (22-71)
Gender, evaluable n	n = 39
Male	21 (54)
Female	18 (46)
Underlying MPN, evaluable n	n = 39
ET	21 (54)
PMF	11 (28)
PV	7 (18)
WBC at AML diagnosis, evaluable n	n = 39
Median (range), /uL	8300 (250-338,000)
Karyotype at LT diagnosis, evaluable n	n = 33
Normal	5 (15)
Complex	15 (45)
Others	13 (40)
Days between LT diagnosis and HCT, evaluable n	n = 39
Median	134
Range	24-369
Disease status before HCT, evaluable n	n = 39
First CR	7 (18)
First relapse	3 (8)
Primary induction failure	17 (44)
Untreated	12 (31)
PS before HCT, evaluable n	n = 37
0	14 (38)
1	11 (30)
2	7 (19)
3	3 (8)
4	2 (5)
Donor cell source, evaluable n	n = 39
R-BM/R-PB	8 (21)
UBM	15 (38)
UCB	16 (41)
Conditioning regimen, evaluable n	n = 39
MAC	15 (38)
RIC	24 (62)

AML indicates acute myeloid leukemia; MAC, myeloablative conditioning.