Biol Blood Marrow Transplant 20 (2014) 2029–2033

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia Patients with Central Nervous System Involvement

Jun Aoki [1,2,3,*], Ken Ishiyama [1,2], Shuichi Taniguchi [4], Takahiro Fukuda [5], Kazuteru Ohashi [1], Hiroyasu Ogawa [6], Heiwa Kanamori [3], Tetsuya Eto [7], Koji Iwato [8], Hisashi Sakamaki [1], Yasuo Morishima [9], Tokiko Nagamura [10], Yoshiko Atsuta [11,12], Akiyoshi Takami [13]

[1] *Department of Hematology, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan*
[2] *Department of Hematology, Tokyo Metropolitan Otsuka Hospital, Tokyo, Japan*
[3] *Department of Hematology, Kanagawa Cancer Center, Yokohama, Japan*
[4] *Department of Hematology, Toranomon Hospital, Tokyo, Japan*
[5] *Divisoin of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan*
[6] *Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan*
[7] *Department of Hematology, Hamanomachi Hospital, Fukuoka, Japan*
[8] *Department of Hematology, Hiroshima Red Cross Hospital & Atomic-Bomb Survivors Hospital, Hiroshima, Japan*
[9] *Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Aichi, Japan*
[10] *Department of Cell Processing and Transfusion, Institute of Medical Science, University of Tokyo, Tokyo, Japan*
[11] *Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan*
[12] *Nagoya University Graduate School of Medicine, Nagoya, Japan*
[13] *Department of Internal Medicine, Division of Hematology, Aichi Medical University, Aichi, Japan*

Article history:
Received 3 July 2014
Accepted 1 September 2014

Keywords:
Acute myeloid leukemia
Central nervous system involvement

A B S T R A C T

Central nervous system (CNS) involvement in adult acute myeloid leukemia (AML) is rare and associated with poor outcomes. Therefore, CNS involvement in AML is an indicator for allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, the impact of CNS involvement in AML on the outcome of allo-HSCT remains unclear. We performed a large-scale nationwide retrospective analysis to elucidate the outcomes of allo-HSCT on AML with CNS involvement (CNS+AML). Clinical data were collected from a registry database of the Japan Society for Hematopoietic Cell Transplantation. CNS involvement was defined as the infiltration of leukemia cells into the CNS or myeloid sarcoma in the CNS identified at any time from diagnosis to transplantation. One hundred fifty-seven patients with CNS+AML underwent allo-HSCT between 2006 and 2011. The estimated overall survival, cumulative incidence of relapse and nonrelapse mortality at 2 years for CNS+AML (51.2%, 30.2%, and 14.5%, respectively) were comparable with those for AML without CNS involvement (48.6%, 27.4%, and 22.0%, respectively). Univariate and multivariate analyses indicated that the development of chronic graft-versus-host disease, disease status, and cytogenetic risk category were independent prognostic factors for overall survival for CNS+AML. These results suggest that allo-HSCT may improve outcomes in patients with CNS+AML.

INTRODUCTION

Central nervous system (CNS) involvement in acute myeloid leukemia (AML) is a rare complication, occurring in 2% to 5% of patients at the time of AML diagnosis [1,2]. Predisposing factors for AML with CNS involvement (CNS+AML) include higher level of lactate dehydrogenase and WBC counts at diagnosis, chromosome 16 inversion and chromosome 11 abnormality, French-American-British (FAB) subgroup M4 and M5, and younger age [3-5].

Outcomes for patients with CNS+AML are poor [5,6], and optimal treatment is yet to be established, mainly because of the rarity of this condition. Although conventional therapy, such as intrathecal chemotherapy with methotrexate and/or cytarabine, irradiation, and systemic chemotherapy with high-dose cytarabine, are effective, the remission duration is short and relapse rate is high [5-7]. Dekker et al. [8] reported

Financial disclosure: See Acknowledgments on page 2032.

* Correspondence and reprint requests: Jun Aoki, MD, PhD, Department of Hematology, Kanagawa Cancer Center, 2-3-2, Nakao, Asahi-ku, Yokohama, Kanagawa 241-8515, Japan.
E-mail address: jaoki-thk@umin.ac.jp (J. Aoki).

http://dx.doi.org/10.1016/j.bbmt.2014.09.001
1083-8791/

the median survival time after diagnosis of CNS disease was about 10 months without allogeneic hematopoietic stem cell transplantation (allo-HSCT). Therefore, allo-HSCT is considered optimal for patients with CNS+AML. However, the impact of CNS involvement on the outcomes after allo-HSCT remains unclear. Therefore, we conducted a nationwide retrospective study to examine the outcome of patients with CNS+AML who underwent allo-HSCT.

METHODS

Study Population

Clinical data were collected from the registry database of the Japan Society for Hematopoietic Cell Transplantation. Patients with AML (excluding acute promyelocytic leukemia) older than age 15 years who underwent allo-HSCT for the first time between January 2006 and December 2011 were extracted from the database. We retrospectively analyzed the clinical features and the outcome of patients with CNS+AML. Outcomes after allo-HSCT for patients with CNS+AML were compared with those of patients with AML without CNS involvement (CNS−AML), and prognosis factors for overall survival (OS) in patients with CNS+AML were examined. This study was approved by the Institutional Review Board of the Tokyo Metropolitan Otsuka Hospital.

Statistical Analysis

OS was defined as the number of days from allo-HSCT until death from any cause. The incidence of relapse was defined as the number of days from allo-HSCT to relapse of the underlying disease. Nonrelapse mortality (NRM) was defined as the number of days from allo-HSCT to death without relapse. Any patient who was alive at the last follow-up date was censored. OS and NRM were analyzed in all patients, and relapse was analyzed in patients who achieved complete remission (CR).

CNS involvement was defined as infiltration of leukemia cells into the CNS or myeloid sarcoma in the CNS, as identified at any time from diagnosis to transplantation. Patients with other concurrent extramedullary disease were included.

The myeloablative conditioning (MAC) regimen was classified as either total body irradiation (TBI) >8 Gy or regimens containing oral busulfan ≥9 mg/kg (or intravenous injection in equivalent doses) or melphalan >140 mg/m^2. Other regimens were classified as reduced-intensity conditioning [9]. Cytogenetic subgroups were classified according to the Southwest Oncology Group definition [10]. HLA mismatch was defined as incompatibility between the recipient and donor when at least a 1-antigen mismatch was detected at the serological level of HLA-A, -B, or -DR.

Fisher's exact test and the Mann-Whitney test were used for comparison of categorical and continuous variables, respectively. OS was estimated by the Kaplan-Meier method and was compared using a log-rank test. Relapse and NRM were considered competing risk events for each other and were compared using Gray's test. The Cox proportional hazard model was used for multivariate analysis of prognostic factors. Covariates found to be significant in univariate analysis ($P < .1$) were included in the model. The following variables were compared in univariate analysis: age at allo-HSCT, gender, donor source, serological HLA mismatch, donor−recipient gender mismatch, gender, ABO mismatch, FAB classification (M4/M5 or others) and conditioning regimen (non−TBI-based MAC, TBI-based MAC, or reduced-intensity conditioning), Eastern Cooperative Oncology Group performance status, cytogenetic risk category, and incidence of acute or chronic graft-versus-host disease (GVHD). The impact of chronic GVHD on other outcomes was always studied as a time-dependent variable. *P* values were 2-sided, and differences were considered to be statistically significant when $P < .05$. All statistical analyses were performed using EZR (R version 2.13.0 [11].

RESULTS

Patient Characteristics

Of the 5068 AML patients who underwent first allo-HSCT, 157 patients were CNS+AML and 4911 patients were CNS−AML. Table 1 shows their clinical characteristics. The median age was lower and the proportion of male patients was higher in the CNS+AML group than in the CNS−AML group. A higher proportion of patients had non-CR disease status and worse Eastern Cooperative Oncology Group performance status at allo-HSCT in the CNS+AML group than in the CNS−AML group. The proportion of patients receiving TBI-based MAC regimens was higher in the CNS+AML group than in the CNS−AML group. The incidence of favorable cytogenetic risk category and M4/M5 FAB classification was higher in the CNS+AML group than in the CNS−AML group.

Table 1
Patient Characteristic

	CNS+AML	CNS−AML	*P*
Median age, yr (range)	45 (17-68)	50 (16-82)	<.001
<50	99 (63.1%)	2434 (49.6%)	
≥50	58 (36.9%)	2477 (50.6%)	<.001
Gender			
Male	109 (69.4%)	2877 (58.6%)	
Female	48 (30.6%)	2034 (41.4%)	.006
Disease status			
CR	66 (42.0%)	2602 (53.0%)	
Non-CR	91 (58.0%)	2308 (47.0%)	.007
Donor source			
Related	40 (25.5%)	1557 (31.7%)	
Unrelated BM/PB	75 (47.8%)	1959 (39.9%)	
Unrelated CB	42 (26.8%)	1385 (28.2%)	.123
Serological HLA match			
Match	95 (60.5%)	2851 (58.1%)	
Mismatch	62 (39.5%)	2045 (41.6%)	.622
Conditioning			
TBI-based MAC	88 (56.1%)	1992 (40.6%)	
Non−TBI-based MAC	29 (18.5%)	1273 (25.9%)	
RIC	40 (25.5%)	1624 (33.1%)	<.001
Performance status			
0, 1	125 (79.6%)	4360 (88.8%)	
2-4	31 (19.7%)	523 (10.6%)	.001
Cytogenetic risk category			
Favorable	34 (21.7%)	544 (11.1%)	
Intermediate	62 (39.5%)	2287 (46.6%)	
Unfavorable	55 (35.0%)	1485 (30.2%)	
Unknown	4 (2.5%)	465 (9.5%)	<.001
FAB classification			
M4/5	67 (42.7%)	1100 (22.4%)	
Other	84 (53.5%)	3395 (69.1%)	<.001

BM indicates bone marrow; PB, peripheral blood; CB, cord blood; MA, myeloablative conditioning; RIC, reduced-intensity conditioning.

Transplantation Outcomes of the CNS+AML Group and CNS−AML Group

The probability of OS was comparable in the CNS+AML group and the CNS−AML group (2-year OS rates in the CNS+AML group and the CNS−AML group were 51.2% and 48.6%, respectively [$P = .847$]; Figure 1A). Subgroup analysis according to age, disease status, and cytogenetic risk category was performed. The probability of OS in the CNS+AML group and the CNS−AML group was similar in both patients younger than 50 years and patients aged 50 years or older (Figure 1B), in both patients with CR and non-CR at the time of allo-HSCT (Figure 1C), and in patients with all cytogenetic risk categories (Supplemental Figure 1). The cumulative incidence of relapse and NRM were not significantly different (2-year cumulative incidences of relapse in the CNS+AML group and the CNS−AML group were 30.2% and 27.4%, respectively [$P = .418$] [Figure 2A], and the 2-year NRM rates in the CNS+AML group and the CNS−AML group were 14.5% and 22.0%, respectively [$P = .142$] [Figure 2B]). Multivariate analysis showed that CNS involvement did not affect OS significantly after adjusting for covariates (Table 2).

Outcome of Allo-HSCT for OS in the CNS+AML Group

Further analysis of the CNS+AML group was performed. Six patients received CNS irradiation as part of the conditioning regimen; their OS did not significantly differ from that of patients who did not receive CNS irradiation ($P = .343$). Multivariate analysis showed the development of