locyte colony-stimulating factor, acute myeloid leukemia

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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*

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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

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* 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).

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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

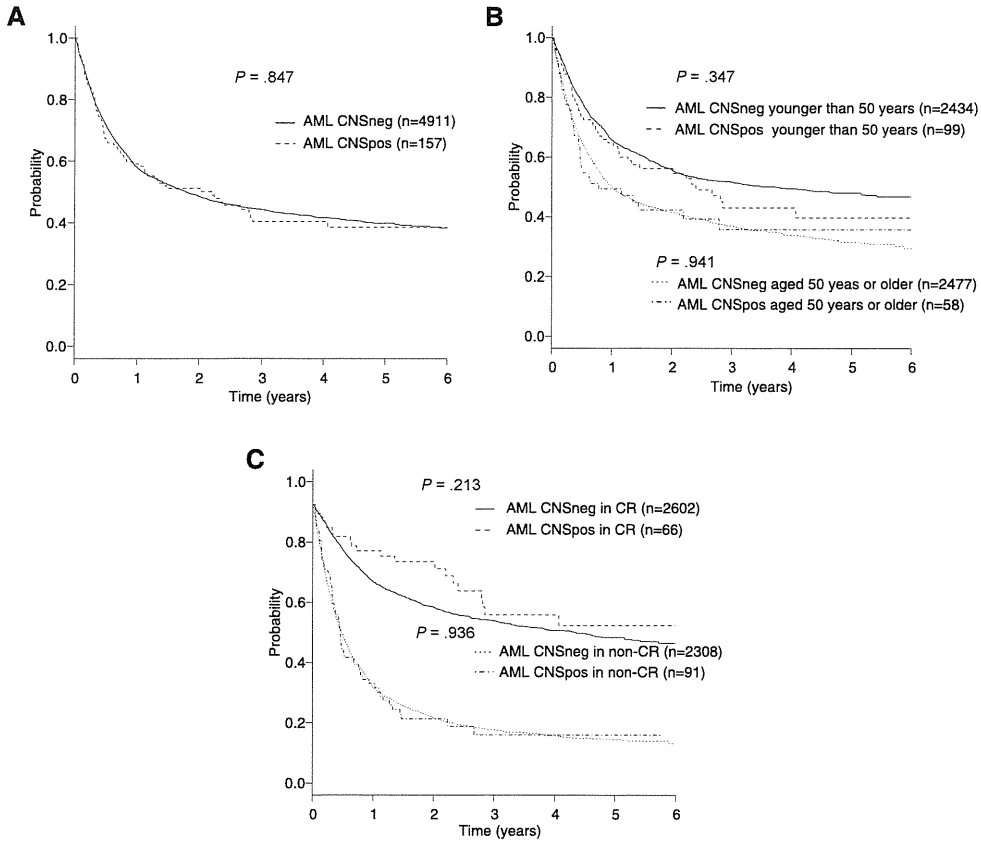

Figure 1. Survival of patients stratified by CNS involvement. (A) OS of all patients in the study. (B) OS of patients grouped according to age at transplantation. (C) OS of patients grouped according to disease status at transplantation.

chronic GVHD (hazard ratio [HR] = .471; 95% confidence interval [CI], .232 to .956; $P = .037$), non-CR at the time of allo-HSCT (HR = 4.11; 95% CI, 2.10 to 8.04; $P < .001$), and intermediate (HR = 4.185; 95% CI, 1.55 to 11.3; $P = .005$) and poor (HR = 3.59; 95% CI, 1.32 to 9.79; $P = .012$) cytogenetic risk categories were independent prognostic factor for OS (Table 3).

Forty-three patients developed relapse after allo-HSCT; systemic relapse other than CNS and CNS relapse occurred in 21 patients and 10 patients, respectively. The relapse site was not known in 12 patients.

DISCUSSION

The current analysis showed the estimated OS, relapse, and NRM rates were comparable in the CNS+AML and CNS−AML groups. Although there were significant differences in patient characteristics between the CNS+AML group and the CNS−AML group, subgroup analyses according to age, disease status, and cytogenetic risk category showed similar results to those observed in the entire study population. CNS+AML patients were significantly younger than CNS−AML patients; however, Figure 1B shows CNS involvement did not affect transplantation outcome in both patients

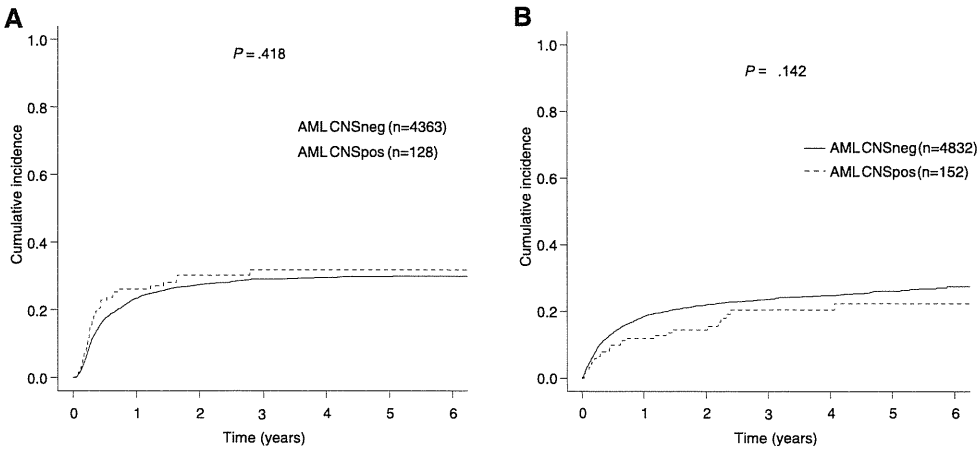

Figure 2. Cumulative incidence of events after transplantation stratified by CNS involvement. (A) Cumulative incidence of relapse of patients who achieved CR. (B) Cumulative incidence of NRM of all patients.

Table 2
Univariate and Multivariate Analysis of OS in All Patients

Variables	Risk Factors	Univariate	Multivariate		
		P	HR	95% CI	*P*
CNS involvement	No	.847	1		
	Yes		1.06	.806-1.40	.664
Age, yr	<50	<.001	1		
	≥50		1.53	1.36-1.73	<.001
Gender	Male	<.001	1		
	Female		.911	.822-1.01	.074
Disease status	CR	<.001	1		
	Non-CR		2.41	2.17-2.68	<.001
Donor source	Related	<.001	1		
	Unrelated BM/PB		.945	.825-1.08	.414
	Unrelated CB		.82	.693-.971	.021
HLA match	Match	<.001	1		
	Mismatch		1.06	.913-1.23	.438
Conditioning regimen	Non–TBI-based MAC	<.001	1		
	TBI-based MAC		1.09	.947-1.25	.231
	RIC		.979	.856-1.12	.757
Performance status	0, 1	<.001	1		
	2-4		1.63	1.38-1.92	<.001
Cytogenetic risk category	Favorable	<.001	1		
	Intermediate		.964	.811-1.15	.674
	Unfavorable		1.35	1.13-1.61	<.001
	Unknown		1.13	.907-1.41	.276
Acute GVHD	No	<.001	1		
	Yes		1.17	1.06-1.30	.003
Chronic GVHD	No	<.001	1		
	Yes		.645	.574-.724	<.001

younger than 50 years and patients aged 50 years or older. Furthermore, multivariate analysis showed that CNS involvement did not significantly affect OS. These results suggest that allo-HSCT may decrease the relapse rate and overcome the poor prognosis otherwise associated with CNS+AML. This notion is consistent with the observations of Shihadeh et al. [3], in which 4 of 5 patients who survived for more than 18 months received allo-HSCT. The clinical characteristics of patients with CNS+AML in this study were consistent with those seen in previous studies [3-5].

Mayadev et al. [12] and Bommer et al. [13] reported that persistent CNS involvement at the time of allo-HSCT was associated with dismal outocomes. However, the current study included patients in CR at the time of allo-HSCT. These differences of patient populations appear to be cause of the discrepancy.

Table 3
Univariate and Multivariate Analysis of OS in CNS+AML Patients

Variables	Risk Factors	Univariate	Multivariate		
		P	HR	95% CI	*P*
Chronic GVHD	No	.024	1		
	Yes		.471	.232-.956	.037
Disease status	CR	<.001	1		
	Non-CR		4.11	2.10-8.04	<.001
Performance status	0, 1	<.001	1		
	2-4		1.86	.927-3.72	.082
Cytogenetic risk category	Favorable	.04	1		
	Intermediate		4.19	1.55-11.3	.005
	Unfavorable		3.59	1.32-9.79	.012
	Unknown		3.34	.640-17.4	.153

The current analysis showed a significantly higher population of CNS+AML patients was in non-CR at the time of allo-HSCT compared with CNS−AML patients. Further, patients with CNS+AML in non-CR had poor outcomes, similar to previous studies [12,13]. These results suggest that additional therapy should be considered for these patients; whereas the benefit of intrathecal chemotherapy after allo-HSCT as maintenance therapy is controversial [14-17], additional cranial irradiation for remaining CNS disease might improve outcomes for AML patients after allo-HSCT [12]. Because only 6 patients received CNS irradiation as part of the conditioning regimen in our cohort, we could not sufficiently evaluate the role of CNS irradiation. Therefore, optimal additional treatment for patients with CNS+AML remains unclear, and further study is necessary.

Because lumbar puncture and intrathecal prophylaxis are not routinely performed in AML patients [18], CNS involvement was not evaluated in all patients. However, the incidence of CNS involvement is compatible with that seen in a previous report [2]. Therefore, it is considered that our cohort included a substantial proportion of those with CNS+AML from the entire registry population.

The current analysis showed a higher proportion of patients had worse Eastern Cooperative Oncology Group performance status at allo-HSCT in the CNS+AML group compared with the CNS−AML group. It may be suspected that some CNS+AML patients could not receive allo-HSCT due to poor performance status or severe comorbidity.

This analysis had some limitations. First, the data about pretransplant therapy were lacking. The pretransplant therapy for the CNS+AML group likely differed from that of the CNS−AML group and contributes to the overall outcomes for these patients, possibly with respect to relapse and NRM. Second, the CNS+AML group only represents 3% of the entire data set. Thus, there may not be enough power to detect a small difference in outcomes between the CNS+AML and CNS−AML groups.

In conclusion, our study showed that outcomes after allo-HSCT were comparable in CNS+AML and CNS−AML patients. Furthermore, the outcomes for patients in CR were similar when comparing CNS+AML and CNS−AML patients. To the best of our knowledge, the current nationwide retrospective analysis included the largest number of patients with CNS+AML who have undergone allo-HSCT within the published literature. Therefore, the current study may be useful in deciding whether patients with CNS+AML should undergo allo-HSCT.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bbmt.2014.09.001.

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ORIGINAL ARTICLE

Effect of graft sources on allogeneic hematopoietic stem cell transplantation outcome in adults with chronic myeloid leukemia in the era of tyrosine kinase inhibitors: a Japanese Society of Hematopoietic Cell Transplantation retrospective analysis

Kazuteru Ohashi · Tokiko Nagamura-Inoue · Fumitaka Nagamura · Arinobu Tojo · Kouichi Miyamura · Takehiko Mori · Mineo Kurokawa · Shuichi Taniguchi · Jun Ishikawa · Yasuo Morishima · Yoshiko Atsuta · Hisashi Sakamaki

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Abstract We retrospectively compared transplant outcomes for related bone marrow transplantation (rBMT), related peripheral blood stem cell transplantation (rPBSCT), unrelated bone marrow transplantation (uBMT), and unrelated cord blood transplantation (CBT) in 1,062 patients with chronic myeloid leukemia (CML) aged 20 years or over between January 1, 2000 and December 31, 2009 in Japan. The disease status was as follows: chronic phase 1 (CP1, $n = 531$), CP 2 or later including accelerated phase (CP2-AP, $n = 342$) and blastic crisis (BC, $n = 189$). Graft sources (GS) were rBMT ($n = 205$), uBMT ($n = 507$), rPBSCT ($n = 226$) or CBT ($n = 124$). In multivariate analysis in CP1, lower overall survival (OS) (relative risk [RR]: 6.01, 95 % confidence interval [CI]: 1.20–29.97, $P = 0.029$) and leukemia-free survival (LFS) (RR: 4.26, 95 % CI: 1.24–14.62, $P = 0.021$) were observed in uBMT compared with those in rBMT. For patients in the advanced phase of CML beyond CP1, GS had no significant impact on OS or LFS. Our results support the use of rBMT for adults with CML in CP1, but in contrast to previous reports, the superiority of rPBSCT in advanced stage of CML was not confirmed in our cohorts.

Keywords Chronic myeloid leukemia · Allogeneic hematopoietic stem cell transplantation · Graft sources

On behalf of Choric Myeloid Leukemia Working Group of the Japan Society for Hematopoietic Cell Transplantation.

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K. Ohashi (✉) · H. Sakamaki
Hematology Division, Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital, Tokyo, Japan
e-mail: k.ohashi@cick.jp

T. Nagamura-Inoue
Department of Cell Processing and Transfusion, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

T. Nagamura-Inoue
Japan Cord Blood Bank Network, Tokyo, Japan

F. Nagamura
Division of Clinical Trial Safety Management, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

A. Tojo
Department of Hematology/Oncology, Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

K. Miyamura
Department of Hematology, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan

T. Mori
Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

M. Kurokawa
Department of Cell Therapy and Transplantation Medicine, The University of Tokyo, Tokyo, Japan

S. Taniguchi
Department of Hematology, Toranomon Hospital, Tokyo, Japan

J. Ishikawa
Department of Hematology and Chemotherapy, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Y. Morishima
Division of Epidemiology/Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

Introduction

According to the Japan Society for Hematopoietic Cell Transplantation (JSHCT), the number of transplants reported annually for the treatment of CML was 306 in 2000, but drastically dropped to 46 transplants in the year 2009. Unsurprisingly, the drop in transplant activity was observed in Japan after imatinib (IM) became available as an experimental drug in 2000 and subsequently as a frontline treatment for CML in 2001. Thus, the excellent outcomes demonstrated by tyrosine kinase inhibitors (TKIs) argue against the use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) as an upfront therapy for CML in CP1; allo-HSCT is currently recommended for patients with a T315I mutation, or who failed TKIs and progress to advanced phase disease [1–6]. Moreover, the newly launched third generation TKI, ponatinib, having a unique binding mechanism allowing inhibition of BCR-ABL kinases, including those with the T315I mutation may further narrow the range of transplant indication [7, 8]. Therefore, those CML patients who undergo allo-HSCT represent a selection of high-risk patients due to more advanced disease with high rates of accelerated or blast phase. To improve transplant outcomes, comprehensive approaches in transplant strategies including timing, choice of conditioning and GS, maintenance therapy might be needed for those CML patients being selected nowadays for allo-HSCT. The main purpose of this study was to analyze the impact of GS on transplant outcome for patients with CML in the era of TKIs, particularly the role of GS in each disease status. We also clarified the prognostic factors for transplant outcomes in each disease status. We herein report our analysis of 1,062 patients, whose complete registry-based clinical data which were provided by the JSHCT.

Patients and methods

Patients

Data on a total of 1,143 patients of at least 20 years of age who had undergone allogeneic bone marrow, peripheral blood, or cord blood transplantation for CML between January 1, 2000 and December 31, 2009 were initially collected through the Transplant Registry Unified Management Program (TRUMP). Eighty-one patients were excluded from the analysis, because one or two critical data such as alive, relapse, and engraftment status with or without date of onset were missing. Other missing data were dealt as missing data in the study and the analysis numbers in each variable were described, respectively. This included data from the Japan Cord Blood Bank Network (JCBBN), the Japan Marrow Donor Program (JMDP), and JSHCT. These are the 3 largest allo-HSCT registries in Japan, and their roles have been described previously [9]. The study was approved by the data management committees of JSHCT, as well as by the ethical committee of Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital (Tokyo, Japan), where this study was organized.

Statistical analysis

The outcome endpoints were neutrophil recovery, platelet recovery, acute and chronic GVHD, relapse, transplantation-related mortality (TRM), overall survival (OS), and leukemia-free survival (LFS). The definitions of the statistical models used were in accordance with the statistical guidelines of the European Group for Blood and Marrow Transplantation (EBMT) (http://www.ebmt.org/1WhatisEBMT/whatisebmt2.html). Neutrophil recovery was defined by an absolute neutrophil count (ANC) of at least 0.5×10^9/L for 3 consecutive days, with the first day considered as the recovery day. Platelet recovery was defined by a non-transfused platelet count of at least 20×10^9/L for 3 consecutive days. Deaths occurring before day 90 or day 180 were considered as competing risks for neutrophil or platelet recovery, respectively. The graft failure rate for neutrophils was calculated for patients living without relapse for more than 30 days. Acute and chronic GVHD were diagnosed and graded at each center according to the standard criteria [10–12]. Relapse was defined on the basis of the reappearance of the blast or Philadelphia chromosome (Ph) or *BCR-ABL1* transgene by cytogenetic and/or molecular analysis, including polymerase chain reaction and fluorescence in situ hybridization. TRM was considered a sole cause of non-leukemic deaths occurring after transplantation; OS was defined as the time between transplantation and death due to any cause; LFS was defined as the time interval from allo-HSCT to a first event, either relapse or death, in patients achieving complete remission. HLA antigen disparities were categorised as either GVHD or rejection direction. Low-resolution antigens of HLA-A and HLA-B were identified for all patients by serologic typing or low-resolution molecular typing methods. While, HLA-DRB1 alleles were

Y. Morishima
Japan Marrow Donor Program, Tokyo, Japan

Y. Atsuta
Department of HSCT Data Management/Biostatistics, Nagoya University Graduate School of Medicine, Nagoya, Japan

Y. Atsuta · H. Sakamaki
Japanese Society of Hematopoietic Cell Transplantation, Nagoya, Japan

determined by high-resolution molecular typing using the sequence-based HLA typing method. In rBMT, HLA-DRB1 alleles were counted as identical, if the low-resolution antigens of HLA-A, B, and DR were identical. Data on HLA-DRBI allele were not fully available; there were 2 lacking data in CP1, 4 lacking data on CP2-AP and 2 lacking data in BC. Detail of HLA disparity toward either rejection or GVHD are noted in Table 1 and Supplementary Table 1.

Adjusted probabilities of OS and LFS were analyzed using Cox proportional-hazards regression model. The variables used were patients' age at HSCT, patients' sex, body weight at HSCT, time from diagnosis to HSCT, ABO mismatch, conditioning regimen, imatinib administration, kind of GVHD prophylaxis, and year of HSCT. Variables with more than two categories were dichotomized for the final multivariate analyses. Variables were dichotomized as the followings: patient's age at HSCT younger or older than median; patient's body weight at HSCT lighter or heavier than median; time from diagnosis to HSCT <1 year or >1 year. ABO major mismatch or others; myeloablative conditioning regimen or others; cyclosporine-based GVHD prophylaxis regimen or tacrolimus-based; year of HSCT before or after 2004. The endpoints of neutrophil and platelet recovery, acute GVHD and chronic GVHD, relapse and TRM were analyzed using cumulative incidence curves that estimated incidence according to the Fine and Gray models, in which we first used univariate models that contained each of the variables one at a time. Then all variables with a $P < 0.05$ by the likelihood-ratio test were included in a multivariate model.

Cause-specific hazard ratios were estimated with 95 % confidence intervals (CIs). Statistical analysis was performed with the R Foundation statistical computing package, version 2.12.2 (http://www.r-project.org/).

Table 1 Characteristics of patients with CML in CP1, CP2-AP, and BP

	CP1 ($n = 531$)	CP2-AP ($n = 342$)	BP ($n = 189$)
Graft source rBMT/uBMT/rPBSCT/CBT	138/258/125/10	43/176/59/64	24/73/42/50
Gender	338/193 ($P < 0.001$)	215/127 ($P < 0.001$)	123/66 ($P < 0.001$)
Male/female			
Median age at transplantation (range)	40 (20–67)	43 (21–69)	43 (20–74)
GVHD prophylaxis CyA + MTX/CyA based/FK + MTX/FK based/ others	331/27/144/12/14[a]	148/17/145/19/9[a]	88/22/58/17/2[a]
Pre-transplant IM	133/249[b]	187/108[b]	94/95 ($P = 0.94$)
Yes/no	($P < 0.001$)	($P < 0.001$)	
Duration from diagnosis to transplantation, months median (range)	12.5 (0.8–169.0)	18.2 (1.6–255.3)	15.5 (2.4–322.7)
Duration from diagnosis to transplantation ≤1 year/> 1 year	248/258[c] ($P = 0.65$)	135/195[c]	80/100[c] ($P = 0.14$)
		($P < 0.001$)	
Patient's body weight, kg Median (range)	61 (40–104)	60 (34–104)	58.5 (34–96)
Conditioning regimen Myeloablative/reduced intensity	475/53[d] ($P < 0.001$)	289/53 ($P < 0.001$)	161/28 ($P < 0.001$)
Years at transplantation 2000–2004/2005–2009	447/84 ($P < 0.001$)	211/131 ($P < 0.001$)	116/73 ($P < 0.01$)
ABO mismatch No/yes	189/161[e] ($P = 0.13$)	132/156[e] ($P = 0.16$)	64/91[e] ($P = 0.03$)
HLA disparities (rejection direction)[g] 0–1/> 2	510/19[f] ($P < 0.001$)	281/57[f] ($P < 0.001$)	145/42[f]
			($P < 0.001$)
HLA disparities (GVHD direction)[g] 0–1/> 2	507/22[f] ($P < 0.001$)	285/53[f] ($P < 0.001$)	140/47[f]
			($P < 0.001$)

CP chronic phase, *AP* accelerated phase, *BP* blastic phase, *rBMT* related bone marrow transplantation, *rPBSCT* related peripheral blood stem cell transplantation, *uBMT* unrelated bone marrow transplantation, *CBT* unrelated cord blood transplantation, *GVHD* graft-versus-host disease, *CyA* cyclosporine, *MTX* methotrexate, *FK* tacrolimus, *IM* imatinib mesylate, *HLA* human leukocyte antigen

[a] Data on GVHD prophylaxis were not fully available; there were 3 missing data in CP data, 4 missing data on CP2-AP and 2 missing data in BC

[b] Data on pre-transplant imatinib administration were not fully available; 149 data and 47 data were not retrieved in CP1 and in CP2-AP, respectively

[c] Loss of data on duration from diagnosis to transplantation (≤ 1 year/> 1 year) was noted; 25 data in CP, 12 data in CP2-AP, and 9 data in BP were not retrieved

[d] Three data regarding conditioning regimen in CP were not retrieved

[e] Loss of data on ABO mismatch was noted; 181 data in CP, 54 data in CP2-AP, and 34 data in BP were not retrieved

[f] Data on HLA-DRBI allele were not fully available; there were 2 lacking data in CP, 4 lacking data on CP2-AP and 2 lacking data in BC

[g] More detail of HLA disparity toward either rejection or GVHD is noted in supplementary Table 1

Results

Patient characteristics

Of 1,062 patients (676 men, 386 women; median age, 41 years; range, 20–74), 414 patients (39 %) had a clear history of pre-transplant IM use. Disease status was as follows: CP1 ($n = 531$), CP2-AP ($n = 342$) and BC ($n = 189$). GS were related rBMT ($n = 205$), uBMT ($n = 507$), rPBSCT ($n = 226$) and CBT ($n = 124$). The unrelated PBSCT has not been allowed in Japan until 2012 and, therefore, our data included only unrelated BMT, not PBSCT. In addition, during the study period, there were no related CBTs at all. The other variables, including GVHD prophylaxis, pre-transplant IM, body weight at allo-HSCT, duration from diagnosis to transplant, conditioning intensity, years at transplantation (2000–2004 vs. 2005–2009), ABO mismatch, HLA mismatch in either GVHD or rejection direction, are shown in Table 1.

Overall survival and leukemia-free survival

The median follow-up period was 914 days after transplantation (range 2–3,902) and 1,914 days after diagnosis (range 29–9,120). Three-year OS was 70.6 % (95 % CI, 66.8-74.7 %) for patients in CP1 at the time of transplantation, 58.9 % (95 % CI, 53.7–64.7 %) for those with CP2-AP, and 26.9 % (95 % CI, 20.9–34.6 %) for those in BC. The probability of 3-year LFS for patients in CP1, CP2-AP and BC was 64.6 % (95 % CI, 60.4–68.6 %), 46.1 % (95 % CI, 40.9–51.9 %) and 19.2 % (95 % CI, 14.1–26.1 %), respectively (data not shown).

OS and LFS according to GS in CP1, CP2-AP, and BC are shown in Fig. 1a–c, and d–f, respectively. In view of OS and LFS according to GS, 3-year OS after rBMT, rPBSCT, uBMT, and CBT in CP1 was 84.4, 70.0, 64.4, and 48.0 %, respectively (Fig. 1a). Three-year LFS after rBMT, rPBSCT, uBMT, and CBT in CP1 was 76.3, 64.3, 59.3, and 30 %, respectively (Fig. 2d). Multivariate analysis for OS identified the following factors as adverse prognostic factors for

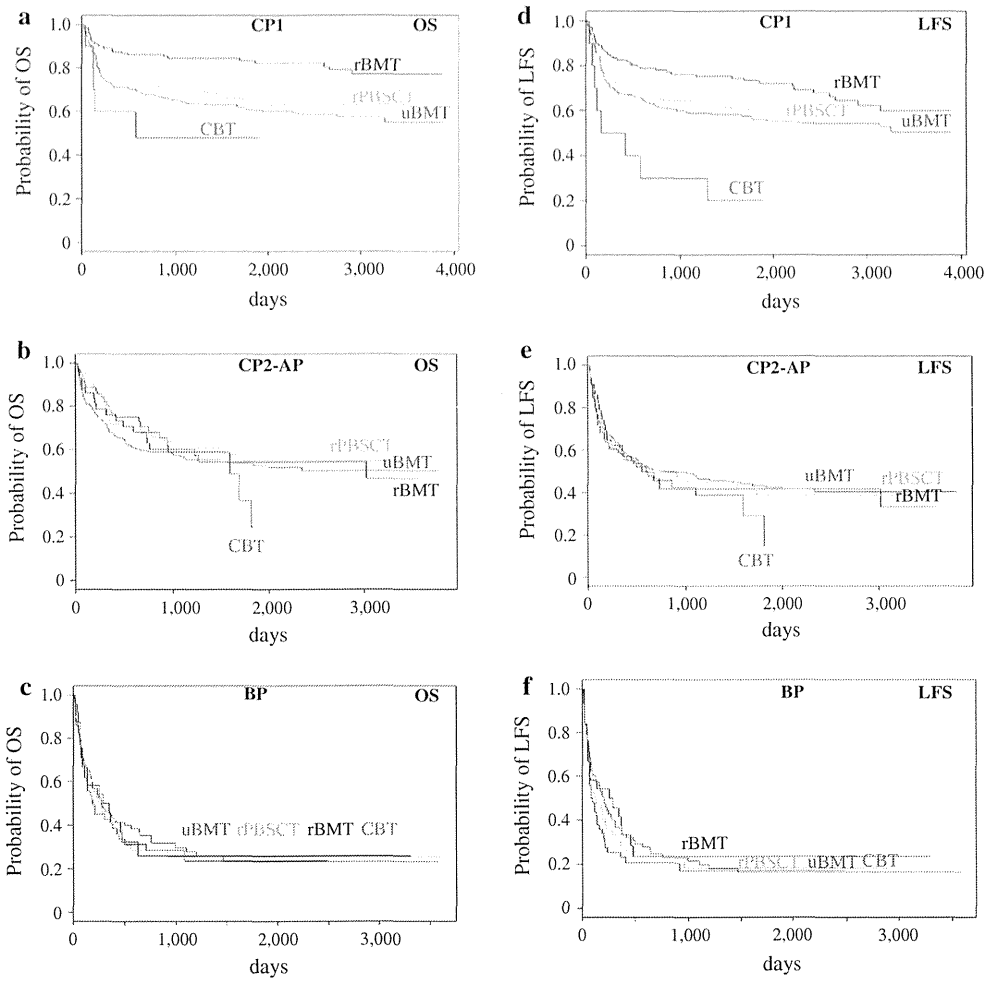

Fig. 1 Kaplan–Meier estimate of overall survival (OS) for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and leukemia-free survival (LFS) for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)

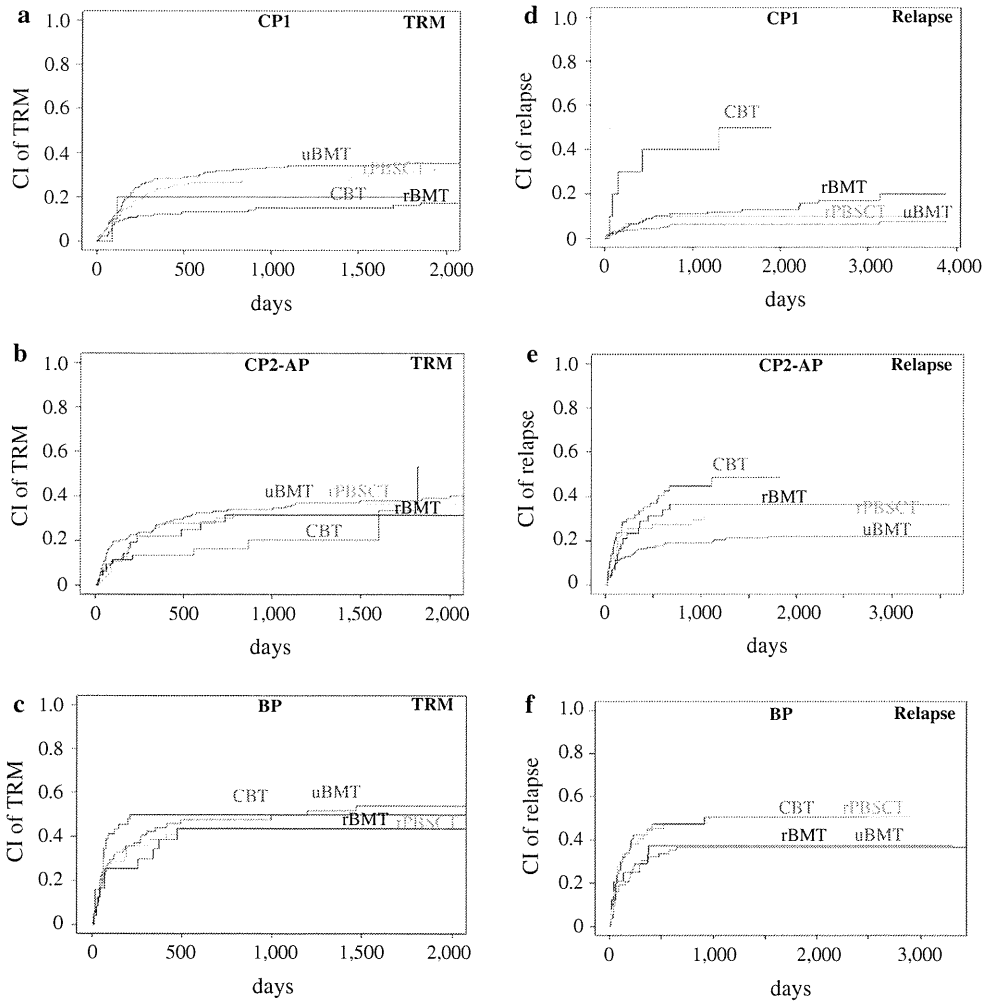

Fig. 2 The cumulative incidence of transplantation-related mortality (TRM) for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and relapse for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)

patients in CP1: older age (>median age, 40 years: HR 1.67, 95 % CI, 1.15–2.41, $P = 0.007$), ABO mismatch (HR 1.44, 95 % CI, 1.003–2.06, $P = 0.048$) (Table 2), and uBMT (RR 6.01, 95 % CI, 1.20–29.97, $P = 0.029$) (Table 3). In CP2-AP, older age (> median age, 43 years: HR 1.74, 95 % CI, 1.25–2.43, $P < 0.001$) was the only factor an adverse prognostic factor (Table 2). In BC, pre-transplant IM (HR 0.61, 95 % CI, 0.49–0.89, $P = 0.011$) was the only factor for better OS (Table 2). Concerning LFS, multivariate analysis showed that uBMT (RR 4.26, 95 % CI, 1.24–14.62, $P = 0.021$) and older age (>median age, 40 years: HR 1.43, 95 % CI, 1.02–1.99, $P = 0.038$) were adverse risk factors in CP1 (Table 2, 3). For patients in CP2-AP and BC, no significant factor for OS or LFS was found. Thus, for patients in CP1, GS could have a significant impact on survival outcomes. While, for patients in the advanced phase of CML of beyond CP1, GS could have no significant impact on OS or LFS (Table 3).

TRM and relapse

The 1-year cumulative TRM rate by disease stage was 23.1 % (95 % CI, 19.5–26.7 %) in CP1, 24.2 % (95 % CI, 19.5–28.9 %) in CP2-AP, and 43.2 % (95 % CI, 35.9–50.5 %) in BC. TRM by GS is shown in Fig. 2a–c. The TRM rate appeared low in rBMT compared with uBMT or rPBSCT in CP1 (Fig. 2a). Multivariate analysis showed that uBMT (RR 2.49, 95 % CI 1.02–6.10, $P = 0.046$) and older age (>median age, 40 years: HR 1.69, 95 % CI, 1.19–2.39, $P = 0.003$) were factors associated with a significantly increased risk of TRM in CP1 (Table 2, 3).

The 3-year cumulative relapse rate by disease stage was 9.0 % (95 % CI, 3.9–7.9 %) in CP1, 28.2 % (95 % CI, 23.3–33.1 %) in CP2-AP, and 43.6 % (95 % CI, 36.3–50.9 %) in BC. Relapse rate by GS is demonstrated in Fig. 2d–f. For patients in CP1, the relapse rate after CBT appeared to be higher than that after other GS (Fig. 2d). In multivariate analysis by the effect of GS in CP1, CBT (RR

Table 2 Multivariate analysis of risk factors for the main outcomes after allo-HSCT for CML in CP1, CP2-AP, and BP

Main outcomes	Factors	CP1				CP2-AP				BP			
		Factors	HR	(95 % CI)	*P* value	Factors	HR	(95 % CI)	*P* value	Factors	HR	(95 % CI)	*P* value
OS	Age	≤40	1			≤43	1						
		>40	1.67	1.15–2.41	0.007	>43	1.74	1.25–2.43	< 0.001				
	ABO mismatch	No	1										
		Yes	1.44	1.003–2.06	0.048								
	Pre-transplant IM									No	1		
										Yes	0.61	0.41–0.89	0.011
LFS	Age	≤40	1										
		>40	1.43	1.02–1.99	0.038								
TRM	Age	≤40	1										
		>40	1.69	1.19–2.39	0.003								
Relapse	HLA mismatch (rejection)									0, 1	1		
										≥2	1.7	1.04–2.76	0.033
	HLA mismatch (GVHD)					0, 1	1						
						≥2	3.57	1.55–8.21	0.003				
Acute GVHD (all grades[a])	Pre-transplant IM	No	1										
		Yes	0.75	0.57–0.99	0.04								
	BW					≤60 kg	1						
						>60 kg	1.35	1.01–1.82	0.045				
Acute GVHD	BW					≤60 kg	1						
(≥grade 2)						> 60 kg	1.53	1.05–2.24	0.028				
Chronic GVHD (extensive[b])	BW					≤60 kg	1						
						>60 kg	1.75	1.06–2.73	0.028	0			

OS overall survival, *LFS* leukemia-free survival, *TRM* transplantation-related mortality, *ANC* absolute neutrophil count, *GVHD* graft-versus-host disease, *IM* imatinib, *HLA* human leukocyte antigen, *BW* body weight, *HR* hazard ratio, *CI* confidence interval, *CP* chronic phase, *AP* accelerated phase, *BP* blastic phase, *imatinib* imatinib mesylate

[a] Overall grade of acute GVHD assigned according to the Center for International Blood and Marrow Transplant Research (CIBMTR) severity index

[b] Chronic GVHD was graded as limited or extensive based on the Seattle criteria

Table 3 Impact of graft sources on main outcomes after allo-HSCT for CML in CP1, CP2-AP, and BP

Main outcomes	Graft sources	CP1			CP2-AP			BP		
		RR	(95 % CI)	*p* value	RR	(95 % CI)	*p* value	RR	(95 % CI)	*p* value
OS	rBMT	1.00			1.00			1.00		
	uBMT	6.01	(1.20–29.97)	0.029	1.12	(0.33–3.79)	0.851	>99	(0.00–99.99)	0.999
	rPBSCT	1.76	(0.77–4.04)	0.180	0.84	(0.21–3.43)	0.809	1.13	(0.56–2.30)	0.727
	CBT	1.00	(0.00–99.99)	1.000	NA	NA	NA	NA	NA	NA
LFS	rBMT	1.00			1.00			1.00		
	uBMT	4.26	(1.24–14.62)	0.021	1.61	(0.55–4.74)	0.383	0.00	(0–99.99)	0.999
	rPBSCT	1.72	(0.95–3.11)	0.073	0.42	(0.14–1.31)	0.135	0.67	(0.31–1.44)	0.299
	CBT	1.00	(0.00–99.99)	1.000	NA	NA	NA	NA	NA	NA
TRM	rBMT	1.00			1.00			1.00		
	uBMT	2.49	(1.02–6.10)	0.046	1.36	(0.60–3.09)	0.47	2.71	(0.74–9.96)	0.13
	rPBSCT	1.03	(0.52–2.07)	0.93	0.94	(0.52–1.70)	0.83	1.43	(0.64–3.22)	0.39
	CBT	0.33	(0.04–2.63)	0.29	0.98	(0.60–1.60)	0.94	1.26	(0.82–1.92)	0.29
Relapse	rBMT	1.00			1.00			1.00		
	uBMT	0.33	(0.12–0.95)	0.041	0.66	(0.29–1.55)	0.34	2.23	(0.28–17.61)	0.45
	rPBSCT	1.13	(0.62–2.07)	0.68	1.17	(0.64–2.14)	0.6	1.06	(0.44–2.54)	0.9
	CBT	25.16	(1.76–369.10)	0.018	1.15	(0.74–1.80)	0.53	0.77	(0.39–1.60)	0.49
ANC recovery	rBMT	1.00			1.00			1.00		
	uBMT	0.82	(0.55–1.23)	0.35	0.83	(0.53–1.31)	0.43	0.58	(0.27–1.26)	0.17
	rPBSCT	1.31	(1.02–1.69)	0.036	1.2	(0.90–1.59)	0.21	0.91	(0.33–2.52)	0.86
	CBT	2	(0.67-5.98)	0.22	0.53	(0.42–0.67)	<0.001	0.55	(0.37–0.82)	0.003
Platelet recovery	rBMT	1.00			1.00			1.00		
	uBMT	0.75	(0.46–1.21)	0.24	0.89	(0.51–1.56)	0.68	0.21	(0.07–0.61)	0.0039
	rPBSCT	0.93	(0.69–1.26)	0.65	0.91	(0.61–1.35)	0.63	0.67	(0.28–1.57)	0.35
	CBT	1.07	(0.35–3.28)	0.9	0.78	(0.62–0.99)	0.049	0.44	(0.26–0.74)	0.0018
Acute GVHD (all grades[a])	rBMT	1.00			1.00			1.00		
	uBMT	3.35	(1.50–6.22)	<0.001	1.67	(0.92–3.02)	0.09	1.22	(0.46–3.25)	0.69
	rPBSCT	1.49	(0.94–2.37)	0.091	0.86	(0.51–1.44)	0.56	0.94	(0.32–2.73)	0.91
	CBT	1.67	(0.68–4.11)	0.26	0.76	(0.58–1.01)	0.054	1.05	(0.56–1.96)	0.87
Acute GVHD (≥grade 2)	rBMT	1.00			1.00			1.00		
	uBMT	4.28	(1.92–9.53)	<0.001	2.14	(0.93–4.94)	0.075	1.34	(0.39–4.61)	0.65
	rPBSCT	1.5	(0.82–2.72)	0.19	1.53	(0.82–2.86)	0.18	2.23	(0.36–1.39)	0.39
	CBT	1.00	(0.00–99.99)	1.000	0.84	(0.58–1.22)	0.36	1.45	(0.55–3.81)	0.45
Chronic GVHD	rBMT	1.00			1.00			1.00		
	uBMT	0.95	(0.53–1.70)	0.86	1.1	(0.45–2.68)	0.84	0.27	(0.06–1.33)	0.11
	rPBSCT	1.37	(0.97–1.92)	0.075	1.24	(0.70–2.19)	0.47	0.84	(0.22–3.20)	0.8
	CBT	8.52	(0.64–11.43)	0.11	0.8	(0.52–1.25)	0.33	0.73	(0.32–1.66)	0.46
Chronic GVHD (extensive[b])	rBMT	1.00			1.00			1.00		
	uBMT	1	(0.49–2.04)	1	0.84	(0.33–2.15)	0.72	0.69	(0.14–3.46)	0.65
	rPBSCT	1.31	(0.87–1.96)	0.19	1.19	(0.60–2.34	0.62	1.08	(0.27–4.24)	0.92
	CBT	6.61	(0.22–200.8)	0.28	0.63	(0.36–1.09)	0.097	0.77	(0.31–1.88)	0.56

OS overall survival, *LFS* leukemia-free survival, *TRM* transplantation-related mortality, *ANC* absolute neutrophil count, *GVHD* graft-versus-host disease, *RR* relative risk, *CI* confidence interval, *CP* chronic phase, *AP* accelerated phase, *BP* blastic phase, *rBMT* related bone marrow transplantation, *rPBSCT* related peripheral blood stem cell transplantation, *uBMT* unrelated bone marrow transplantation, *CBT* unrelated cord blood transplantation, *NA* not available

[a] Overall grade of acute GVHD assigned according to the Center for International Blood and Marrow Transplant Research (CIBMTR) severity index

[b] Chronic GVHD was graded as limited or extensive based on the Seattle criteria

25.16, 95 % CI 1.76–369.10, $P = 0.018$) showed higher relapse, while uBMT (RR 0.33, 95 % CI 0.12–0.95, $P = 0.041$) was lower relapse compared with those in rBMT (Table 3).

Engraftment

The cumulative neutrophil recovery rate on day 90 was 97.5 % (95 % CI, 96.1–98.9 %) in CP1, 93.2 % (95 % CI, 90.5–95.9 %) in CP2-AP, and 82.3 % (95 % CI, 76.8–87.8 %) in BC. On day 180, the cumulative platelet recovery rate, as indicated by more than 2×10^{10}/L of platelets in blood, was 91.9 % (95 % CI, 89.5–94.3 %) in CP1, 85.1 % (95 % CI, 81.2–89.0 %) in CP2-AP, and 67.2 % (95 % CI, 60.3–74.1 %) in BC. Note that the neutrophil recovery and platelet recovery rates were lower after CBT, especially in patients in the advanced phase; i.e., neutrophil recovery in CBT: 90 % in CP1, 79.4 % in CP2-AP, and 64.0 % in BC; platelet recovery after CBT: 90.0 % in CP1, 72.5 % in CP2-AP, and 52.0 % in BC (Fig. 3a–f). Multivariate analysis showed that rPBSCT (RR 1.31, 95 % CI 1.02–1.69, $P = 0.0396$ was a significant factor for early neutrophil recovery in CP1. While, CBT (RR 0.53, 95 % CI 0.42–0.67, $P < 0.001$) was a significant factor for delayed neutrophil recovery in CP2-AP (Table 3). The factor statistically associated with delayed platelet recovery was CBT in CP2-AP (RR 0.78, 95 % CI 0.62–0.99, $P = 0.0049$) and in BC (RR 0.44, 95 % CI 0.26–0.74, $P = 0.0018$). Unrelated BMT (RR 0.21, 95 % CI 0.07–0.61, $P = 0.0039$) was also a significant factor for delayed platelet recovery in BC (Table 3).

Acute and chronic GVHD

The cumulative incidence of acute GVHD at all grades before day 100 was 62.8 % (95 % CI, 58.6–67.0 %) in CP1, 63.5 % (95 % CI, 58.2–58.8 %) in CP2-AP, and 68.6 % (95 % CI, 61.3–74.9 %) in BC. Patients who underwent uBMT showed a higher incidence of acute GVHD (all grades) in CP1 and CP2-AP (Fig. 4a, b). This association was confirmed by multivariate analysis; uBMT (RR 3.35, 95 % CI 1.50–6.22, $P < 0.001$) was a significant factor in CP1 (Table 3). Pre-transplant IM (HR 0.75, 95 % CI 0.57–0.99, $P = 0.04$) was a significant risk factor for acute GVHD (all grades) in CP1 (Table 2). Focusing exclusively on grade II or higher acute GVHD, uBMT (RR 4.28, 95 % CI 1.92–9.53, $P < 0.001$) (Table 3) was a significant risk factor in CP1 (Table 2). For patients in CP2-AP, body weight (>60 kg) was a factor significantly associated with increased risk of aGVHD (all grade; RR 1.35, 95 % CI, 1.01–1.82, $P = 0.045$, grade II or higher grade; RR 1.53, 95 % CI, 1.05–2.24, $P = 0.028$) (Table 2).

The cumulative incidence of chronic GVHD among evaluable patients who survived at least 100 days after allo-HSCT was 49.4 % (95 % CI, 44.7–54.1 %) in CP1, 42.2 % (95 % CI, 36.4–48.0 %) in CP2-AP, and 37.8 % (95 %CI, 30.0–45.6 %) in BC. For patients in CP1, rPBSCT showed a higher incidence of chronic GVHD (71.4 %), which was compared to other GS (Fig. 4d); however, this significant association was not confirmed in multivariate analysis (rPBSCT: RR 1.37 95 % CI 0.97–1.92, $P = 0.075$). For patients in CP2-AP and BC, chronic GVHD after CBT occurred at rates of 23.1 and 23.8 %, respectively, which were apparently lower than that of other GS (Fig. 4e, f), but these statistical associations were not also confirmed by multivariate analysis in CP2-AP or BC (Table 3). Concerning extensive chronic GVHD, multivariate analysis showed the significant association between body weight (>60 kg; RR 1.75, 95 % CI, 1.06–2.73, $P = 0.028$) and chronic GVHD in CP2-AP (Table 2).

Discussion

Our study reviewed 1,062 Japanese adult patients who underwent allo-HSCT during the past decade (2000–2009); thus, our cohort reflects the current use and results of allo-HSCT for CML in Japan. Moreover, the TRUMP database offers the advantage of a large number of patients with extensive data, which permits multivariate analysis. The 3-year OS was 70.6 % for patients in CP1, and the probability of 3-year LFS for patients in CP1 was 64.6 %. These survival data for patients in CP1 were comparable to those reported by others [12]. Based on the report from the EBMT, which included 13,416 CML patients and was apparently the largest CML transplant database including the 3 times cohorts (i.e., 1980–1990, 1991–1999, 2000–2003), the probability of OS at 2 years for patients transplanted in CP1 from an HLA-identical sibling was 74 %, with a cumulative incidence of TRM at 2 years of 22 % and of relapse of 18 % among the most recent cohort transplanted between 2000 and 2003 ($n = 3{,}018$) [13]. The Center for International Blood and Marrow Transplant Research (CIBMTR) recently reported the transplant outcomes of 449 patients with advanced phase CML; the disease-free survival rates remained as low as 35–40 % for CP2, 26–7 % for AP, and 8–11 % for BC [14]. Our series including 432 cases of CP2-AP and 189 cases of BC showed similar survival rates, as the probabilities of 3-year LFS in CP2-AP and BC were 46.1 and 19.2 %, respectively.

Our primary object in this study was to assess the clinical impact of GS according to each disease status. Our study results revealed that the patients in CP1 who were

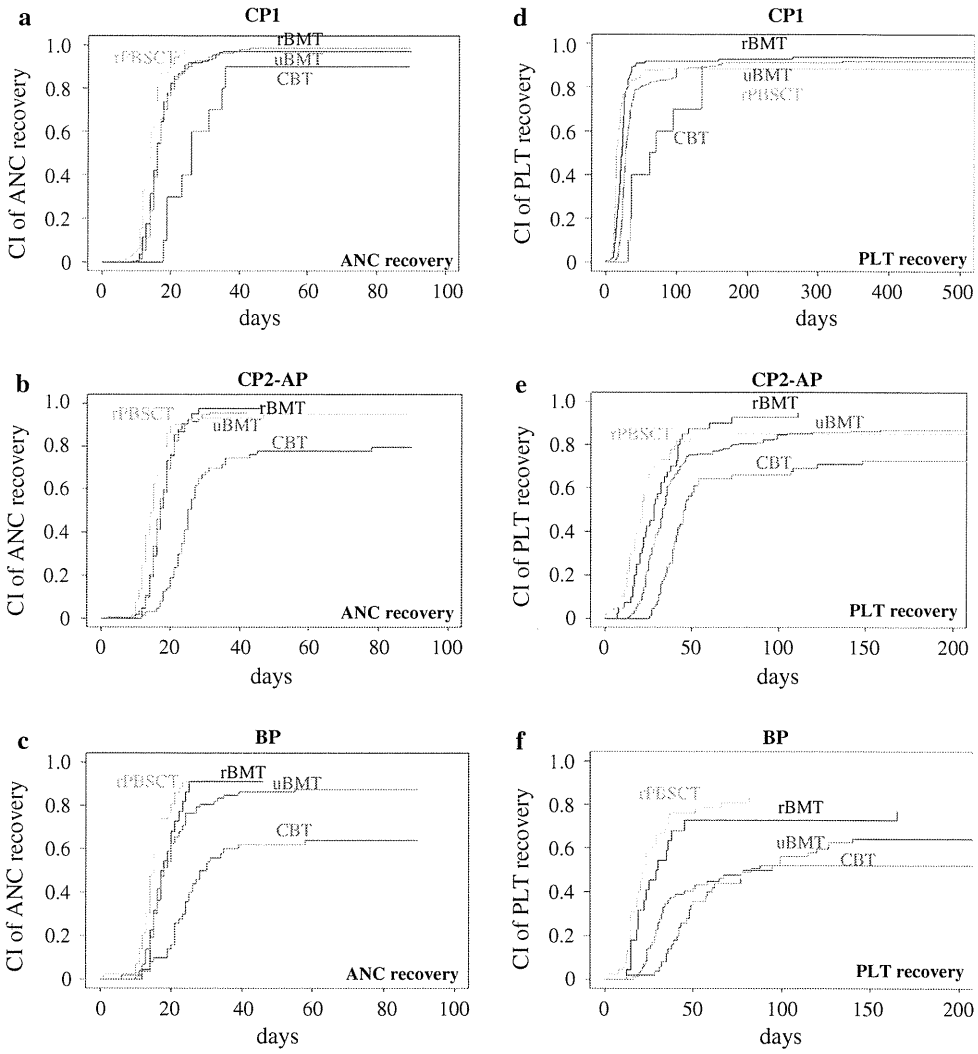

Fig. 3 The cumulative incidence of absolute neutrophil count (ANC) recovery for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and platelet (PLT) recovery for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)

treated by rBMT showed a better 3-year OS (84.4 %) with a lower 1-year cumulative incidence of TRM, but the 3-year LFS and relapse rates were similar between patients receiving rBMT and patients receiving rPBSCT. These data were essentially in line with previous reports in which the CIBMTR reported the data of CML patients undergoing rPBSCT or rBMT in CP1; the 1-year LFS and relapse rates were similar for patients receiving rBMT or rPBSCT [14]. We also assessed the clinical impact of GS in CP2-AP; our results showed that there were no significant differences in OS or LFS between GS, despite lower probabilities of relapse after uBMT and lower probabilities of TRM after CBT. These results differ from the IBMTR reports in that for patients in CP2 or AP, rPBSCT was associated with a lower incidence of treatment failure and a higher probability of LFS at 1 year [15]. Regarding GVHD, a recent prospective randomized trial showed a trend toward a higher incidence of chronic GVHD after rPBSCT (59 % after rPBSCT vs. 40 % after rBMT, $P = 0.11$) for patients in CP1 [16]. Our results may confirm this report; although multivariate analysis in our study showed that rPBSCT (RR 1.37 95 % CI 0.97–1.92, $P = 0.075$) was not a significant risk factor for developing chronic GVHD (Table 3), rPBSCT showed a higher incidence of chronic GVHD (71.4 %), which was compared to other GS in CP1 (Fig. 4d).

Several investigators have addressed the clinical impact of pre-transplant IM on post-transplant outcomes for CML [14, 17–20]. The CIBMTR data demonstrated that pre-transplant IM was associated with better survival, but revealed no statistically significant differences in TRM, relapse, and LFS for patients in CP1 [17]. Among patients transplanted in the more advanced phases beyond CP1, pre-transplant IM was not associated with TRM, relapse, LFS, OS, or acute GVHD [17]. In contrast to these studies, our analysis showed that pre-transplant IM was significantly associated with better OS for patients in BC. In addition, multivariate analysis found pre-transplant IM was a

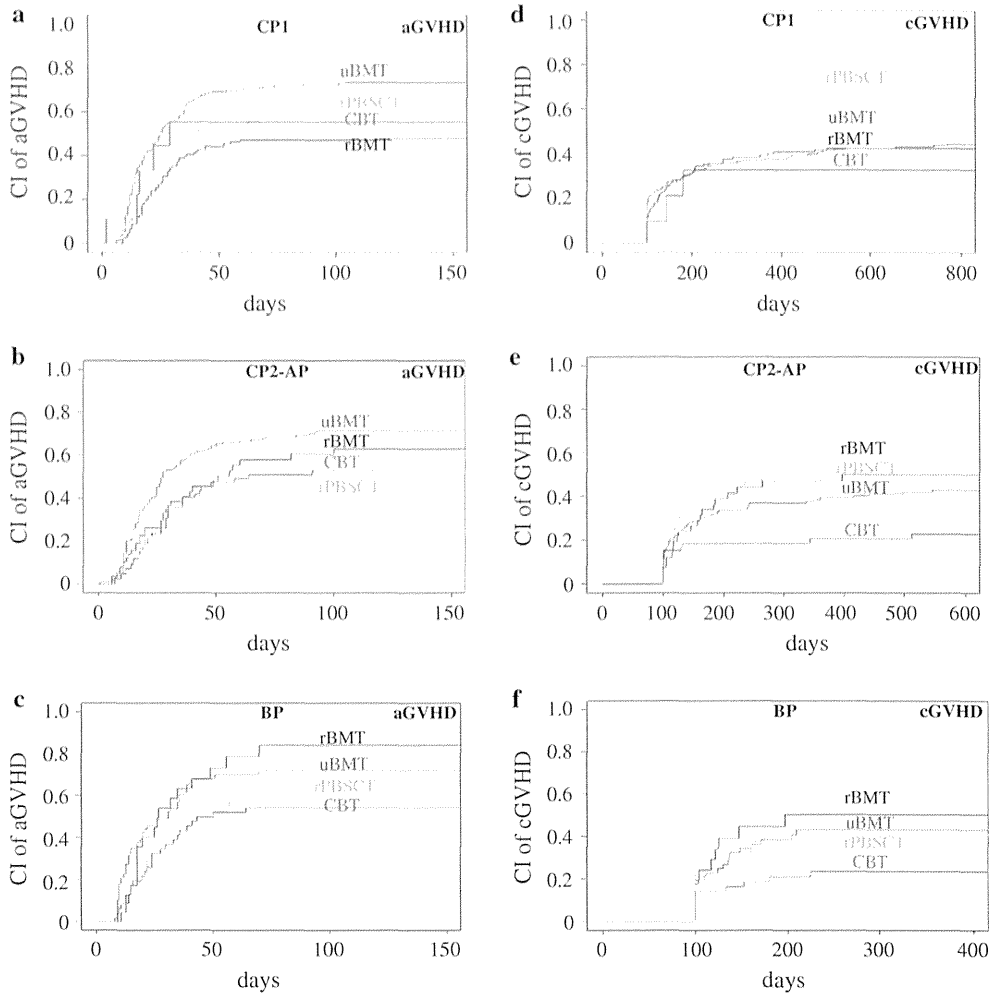

Fig. 4 The cumulative incidence of acute GVHD at all grades for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and chronic GVHD at all grades for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)

significant factor associated with acute GVHD (>grade II) in CP1 (data not shown). Despite the study in the era of TKI, half of patients were in CP1, and 61 % of patients underwent allo-HSCT without use of pre-transplant TKI in this study. We should interpret these findings with utmost caution. We assume that most patients had already initiated the conventional treatment but could not reach a new, but expensive IM treatment before allo-HSCT, as a reason for these findings. Moreover, the findings that the number of patients in CP1 underwent allo-HSCT was 447 in the early period of IM from 2000 to 2004 and only 84 from 2005 to 2009 might support our assumption. Deininger et al. reported an effect of pre-transplant IM in their study that included 70 cases of CML and 21 cases of Ph (+) acute lymphoid leukemia. These investigators compared the outcomes with historical controls identified in the EBMT database [21], and observed a trend towards higher relapse mortality and significantly less chronic GVHD in patients with pre-transplant IM (OR = 0.44, $P = 0.027$). Thus, the clinical impact of pre-transplant IM is still a contentious issue; additional studies evaluating the long-term use of IM with a larger number of patients might permit a more refined analysis of the effect of pre-transplant IM.

Although data on clinical outcomes after CBT are conflicting, CBT has apparent advantages over uBMT, including no risk to the donor and ease of availability. Previous reports, mostly from pediatric studies, have shown that, despite higher HLA mismatch, CBT carries a lower risk of acute GVHD and chronic GVHD in comparison with uBMT [22–24]. A recent Japanese retrospective analysis assessing 86 patients, including pediatric patients, disclosed the transplant outcomes of CBT: 2-year OS was 53 %; for patients in CP, AP and BC, the OS rates were 71, 59 and 32 %, respectively [25]. Although our small population with only 10 cases of CBT in CP1 may prohibit drawing meaningful conclusions, a trend of higher relapse and lower TRM, OS and LFS in CP1 was similar to results obtained by previous study groups. Nevertheless, in CP2-AP and BC, transplant outcomes after CBT were comparable to those of other GS,

suggesting CBT as an acceptable alternative option in advanced phases of CML.

As with all retrospective studies, this study had several limitations. Reported data from transplant centers were often incomplete: data on pre-transplant IM, duration from diagnosis to transplantation, and conditioning regimen could not be fully retrieved. The reasons for which patients in CP1 with IM proceeded with transplantation (planned, or IM resistance) or the reasons for delay in proceeding with transplantation in BC were unknown. Information on post-transplant use of TKIs as maintenance therapy or data on the presence of *BCR/ABL1* mutations was also unavailable in our cohort. Moreover, the selection of GS would often be governed by several unmeasured factors, but our data nonetheless provide a clinical basis for current selection of GS for the treatment of CML in the era of TKIs.

In conclusion, this retrospective study evaluated the results of allo-HSCT for CML patients according to disease status and GS. For patients in CP1, rBMT may be the preferred option for better survival, whereas rPBSCT carries a higher risk for chronic GVHD, which could be a major drawback for patients in CP1. In advanced phases, GS had no significant impact on survival, suggesting that CBT is a reasonable alternative therapy when there is no related or unrelated donor available, or when a transplant is needed urgently. In the era of the new-generation TKIs, indications for allo-HSCT and selection of GS for advanced CML need further evaluation.

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Conflict of interest The authors declare no conflict of interest.

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Second Solid Cancers after Allogeneic Hematopoietic Cell Transplantation Using Reduced-Intensity Conditioning

Olle Ringdén [1], Ruta Brazauskas [2], Zhiwei Wang [3], Ibrahim Ahmed [4], Yoshiko Atsuta [5], David Buchbinder [6], Linda J. Burns [7], Jean-Yves Cahn [8], Christine Duncan [9], Gregory A. Hale [10], Joerg Halter [11], Robert J. Hayashi [12], Jack W. Hsu [13], David A. Jacobsohn [14], Rammurti T. Kamble [15], Naynesh R. Kamani [16], Kimberly A. Kasow [17], Nandita Khera [18], Hillard M. Lazarus [19], Alison W. Loren [20], David I. Marks [21], Kasiani C. Myers [22], Muthalagu Ramanathan [23], Wael Saber [3], Bipin N. Savani [24], Harry C. Schouten [25], Gérard Socie [26], Mohamed L. Sorror [27], Amir Steinberg [28], Uday Popat [29], John R. Wingard [13], Jonas Mattsson [1], Navneet S. Majhail [30,*]

[1] *Center for Allogeneic Stem Cell Transplantation, Karolinka University Hospital, Stockholm, Sweden*
[2] *Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Center for International Bone and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Department of Pediatric Hematology & Oncology, University of New Mexico, Albuquerque, New Mexico*
[5] *Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[6] *Division of Pediatric Hematology, Children's Hospital of Orange County, Orange, California*
[7] *Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, Minnesota*
[8] *Clinique Universitaire d'Hématologie, University Hospital, Grenoble, France*
[9] *Pediatric Stem Cell Transplantation Program, Dana Farber Cancer Institute, Boston, Massachusetts*
[10] *Department of Hematology Oncology, All Children's Hospital, St. Petersburg, Florida*
[11] *Department of Hematology, University Hospital Basel, Basel, Switzerland*
[12] *Division of Pediatric Hematology/Oncology, Washington University, St. Louis Children's Hospital, St. Louis, Missouri*
[13] *Division of Hematology & Oncology, Shands HealthCare, University of Florida, Gainesville, Florida*
[14] *Division of Blood and Marrow Transplantation, Children's National Medical Center, Washington, DC*
[15] *Center for Gene Therapy, Baylor College of Medicine Center for Cell and Gene Therapy, Houston, Texas*
[16] *AABB Center for Cellular Therapies, Bethesda, Maryland*
[17] *Pediatric Bone Marrow Transplantation Program, University of North Carolina Hospitals, Chapel Hill, North Carolina*
[18] *Department of Hematology/Oncology, Mayo Clinic Arizona, Phoenix, Arizona*
[19] *Division of Hematology and Oncology, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, Ohio*
[20] *Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*
[21] *Adult BMT Unit, Bristol Children's Hospital, Bristol, United Kingdom*
[22] *Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio*
[23] *Division of Hematology/Oncology, UMass Memorial Medical Center, Worcester, Massachusetts*
[24] *Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, Tennessee*
[25] *Department of Medicine and Hematology, Academische Ziekenhuis Maastricht, Maastricht, Netherlands*
[26] *Service d'Hematologie-Greffe de Moelle, Hopital Saint Louis, Paris, France*
[27] *Clinical Research Division, Fred Hutchinson Cancer Research Center, and Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington*
[28] *Department of Hematology and Medical Oncology, Mount Sinai Medical Center, Los Angeles, California*
[29] *Department of Stem Cell Transplantation, MD Anderson Cancer Center, Houston, Texas*
[30] *Blood & Marrow Transplant Program, Cleveland Clinic, Cleveland, Ohio*

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We examined risk of second solid cancers after allogeneic hematopoietic cell transplantation (AHCT) using reduced-intensity/nonmyeloablative conditioning (RIC/NMC). RIC/NMC recipients with leukemia/myelodysplastic syndrome (MDS) (n = 2833) and lymphoma (n = 1436) between 1995 and 2006 were included. In addition, RIC/NMC recipients 40 to 60 years of age (n = 2138) were compared with patients of the same age receiving myeloablative conditioning (MAC, n = 6428). The cumulative incidence of solid cancers was 3.35% at

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* Correspondence and reprint requests: Navneet S. Majhail, MD, MS, Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Ave., Desk R35, Cleveland, OH 44195.

E-mail address: majhain@ccf.org (N.S. Majhail).

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10 years. There was no increase in overall cancer risk compared with the general population (leukemia/MDS: standardized incidence ratio [SIR] .99, $P = 1.00$; lymphoma: SIR .92, $P = .75$). However, risks were significantly increased in leukemia/MDS patients for cancers of lip (SIR 14.28), tonsil (SIR 8.66), oropharynx (SIR 46.70), bone (SIR 23.53), soft tissue (SIR 12.92), and vulva (SIR 18.55) and skin melanoma (SIR 3.04). Lymphoma patients had significantly higher risks of oropharyngeal cancer (SIR 67.35) and skin melanoma (SIR 3.52). Among RIC/NMC recipients, age >50 years was the only independent risk factor for solid cancers (hazard ratio [HR] 3.02, $P < .001$). Among patients ages 40 to 60 years, when adjusted for other factors, there was no difference in cancer risks between RIC/NMC and MAC in leukemia/MDS patients (HR .98, $P = .905$). In lymphoma patients, risks were lower after RIC/NMC (HR .51, $P = .047$). In conclusion, the overall risks of second solid cancers in RIC/NMC recipients are similar to the general population, although there is an increased risk of cancer at some sites. Studies with longer follow-up are needed to realize the complete risks of solid cancers after RIC/NMC AHCT.

INTRODUCTION

It is well established that patients treated with allogeneic hematopoietic cell transplantation (AHCT) using myeloablative conditioning (MAC) are at increased lifelong risk for second solid cancers [1-8]. A latency period of 3 to 5 years occurs before second solid cancers start appearing after AHCT, and most recent large studies have reported cumulative incidence rates of 1% to 2% at 10 years and 3% to 5% at 20 years after transplantation. The incidence of solid malignancies continues to rise with increasing survival after transplantation, and lifelong surveillance is recommended for prevention in AHCT survivors [9]. Important risk factors for these cancers in MAC AHCT recipients include exposure to higher dose of total body irradiation (TBI), younger age at transplantation, use of HLA-mismatched donor, and chronic graft-versus-host disease (GVHD) [1,3,6,7].

The introduction of reduced-intensity conditioning (RIC) and nonmyeloablative conditioning (NMC) regimens over the last decade now allows AHCT to be offered as a treatment option for patients who are otherwise ineligible for transplantation using MAC based on age, performance status, or comorbidities [10-13]. AHCT using RIC/NMC regimens leads to long-term engraftment, exhibits graft-versus-malignancy effect, and results in significantly lower early transplant-related toxicity and mortality [14-18]. However, given the recent introduction of these conditioning regimens, the incidence and risk factors for late complications, including second solid cancers, have not been adequately characterized.

In patients with cancer, less chemotherapy is associated with a decreased probability of second malignancies [19-22]. It is therefore possible that RIC/NMC patients may have a lower probability of developing second solid malignancies compared with patients treated with MAC. On the other hand, lower doses of TBI and chemotherapy may be more carcinogenic than MAC regimens because cells may be damaged but not eliminated. Also, RIC/NMC regimens are typically used in older patients who have a higher baseline cancer risk compared with MAC recipients who tend to be younger in age. Recent data from a single-center study suggest that the risk of second cancers after RIC/NMC may not be diminished compared with MAC [23]. Given the paucity of studies characterizing second cancers in recipients of RIC/NMC transplantation, additional data using large samples are needed to better understand the impact of these potentially devastating late effects.

Using data from an international transplant outcomes registry, the Center for International Blood and Marrow Transplant Research (CIBMTR), we describe the incidence and risk factors for second solid cancers (excluding nonmelanoma skin cancers) after RIC/NMC AHCT for leukemia, myelodysplastic syndrome (MDS), and lymphoma. We also compare the risks of second solid cancers after RIC/NMC AHCT with general population control subjects. Finally, we compare the risks of solid cancers after RIC/NMC and MAC transplantation in a subgroup of patients with the same age at transplantation (40 to 60 years).

METHODS

Data Source

The CIBMTR is a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on HCTs to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) in Minneapolis. Participating centers are required to report all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Data are collected before transplant, 100 days, and 6 months after transplant and annually thereafter or until death. Among other data, all centers contribute data on the development of a new malignancy and causes of death. Observational studies conducted by the CIBMTR are performed under guidance of the Institutional Review Board of the NMDP and are in compliance with all applicable federal regulations pertaining to the protection of human research participants.

Patients

The study included all patients receiving AHCT for acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, MDS, and lymphoma between 1995 and 2006 that were reported to the CIBMTR. We limited our cohort to recipients of peripheral blood stem cell or bone marrow grafts from related or unrelated donors; umbilical cord blood transplant recipients were excluded. Also excluded were patients who had received syngeneic transplants. To avoid bias from inclusion of teams with incomplete follow-up and, consequently incomplete ascertainment of events in the late post-transplant period, we excluded patients from centers with completeness index of follow-up of <80% at 5 years post-transplantation (1179 patients from 68 centers) [24].

Study Definitions and Objectives

Conditioning regimens were defined as MAC, RIC, and NMC using previously defined guidelines [25]. Standard definitions were used for assigning disease status (early, intermediate, or advanced) for patients with acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and MDS [26]. The NMDP classification of HLA-matching status was used for unrelated donor AHCT recipients (well matched, partially matched, or mismatched) [27]. Patients with leukemia/MDS and lymphoma were analyzed separately given the differences in their pretransplant and transplant treatment exposures. The CIBMTR routinely collects data on the occurrence of secondary cancers after AHCT. For this study, when necessary, pathology and physician reports of second cancers were requested from the transplant centers and reviewed centrally at the CIBMTR and tumors reclassified [28].

Statistical Analyses

For comparing groups, we used the chi-square or Fisher's test (as applicable) for categorical variables and Wilcoxon 2-sample test for continuous variables. The cumulative incidence of solid cancers was estimated taking into account the competing risk of death among patients who

Table 1
Characteristics of Adult Patients Receiving RIC/NMC AHCT for AML, ALL, CML, MDS, and Lymphoma between 1995 and 2006 and Reported to the CIBMTR

Characteristics	Leukemia Cohort	Lymphoma Cohort	All Patients
Number of patients	2833	1436	4269
Number of centers	196	148	206
Median age at transplant, yr (range)	54 (<1-79)	49 (8-75)	53 (<1-79)
Age at transplant, yr			
<20	198 (7)	47 (3)	245 (6)
20-39	456 (16)	374 (26)	830 (20)
40-59	1388 (49)	802 (56)	2190 (51)
≥60	791 (28)	213 (14)	1004 (23)
Patient gender			
Male	1597 (56)	907 (63)	2504 (59)
Female	1236 (44)	529 (37)	1765 (41)
Karnofsky score before transplant			
≥80	2309 (82)	1180 (82)	3489 (82)
<80	342 (12)	148 (10)	490 (11)
Missing	182 (6)	108 (8)	290 (7)
Region of teams			
United States	2144 (76)	1295 (90)	3439 (81)
Canada	28 (1)	5 (<1)	33 (1)
Europe	399 (14)	79 (6)	478 (11)
Asia	137 (5)	7 (<1)	144 (3)
Australia/New Zealand	60 (2)	24 (2)	84 (2)
Middle East/Africa	27 (1)	20 (1)	47 (1)
Central/South America	38 (1)	6 (<1)	44 (1)
Disease			
AML	1691 (60)	—	1691 (40)
ALL	235 (8)	—	235 (6)
CML	387 (14)	—	387 (9)
MDS	520 (18)	—	520 (12)
Lymphoma	—	1436 (100)	1436 (34)
Disease risk before transplant*			
Leukemia/MDS early	1195 (42)	—	1195 (28)
Leukemia/MDS intermediate	613 (22)	—	613 (14)
Leukemia/MDS advanced	989 (35)	—	989 (23)
Missing	36 (1)	—	36 (1)
Lymphoma	—	1436 (100)	1436 (34)
Year of transplant			
1995-1998	158 (6)	77 (6)	235 (5)
1999-2002	777 (27)	457 (31)	1224 (29)
2003-2006	1898 (67)	912 (64)	2810 (66)
Median interval from diagnosis to transplant, mo (range)	9 (<1-343)	33 (<1-413)	14 (<1-413)
Interval from diagnosis to transplant, mo			
<6	899 (32)	29 (2)	928 (22)
6-11	816 (29)	142 (10)	958 (23)
≥12	1110 (39)	1256 (88)	2366 (56)
Missing	8 (<1)	9 (<1)	17 (<1)
Conditioning regimen			
TBI + Cy + Flud ± other	106 (4)	20 (1)	126 (3)
TBI + Flud ± other (no Cy)	570 (20)	246 (17)	816 (19)
Bu + Flud ± other	694 (24)	199 (14)	893 (21)
Mel + Flud ± other	631 (22)	309 (22)	940 (22)
Cy + Flud ± other	227 (8)	278 (19)	505 (12)
Other	605 (21)	384 (27)	989 (23)
TBI dose, cGy			
No TBI	2019 (71)	1095 (76)	3114 (73)
≤400	625 (22)	290 (20)	915 (21)
>400	185 (7)	51 (4)	236 (6)
TBI dose missing	4 (<1)	0	4 (<1)
Donor			
HLA-idential sibling	829 (29)	411 (29)	1240 (29)
Other related	99 (3)	38 (3)	137 (3)
Well-matched unrelated	1058 (37)	618 (43)	1676 (39)
Partially matched unrelated	448 (16)	276 (19)	724 (17)
Mismatched unrelated	145 (5)	62 (4)	207 (5)
Unknown degree of match, unrelated	254 (9)	31 (2)	285 (7)
Graft type			
Bone marrow	625 (22)	351 (24)	976 (23)
Peripheral blood stem cells	2208 (78)	1085 (76)	3293 (77)
GVHD prophylaxis			
Ex vivo T cell depletion ± other	88 (3)	34 (1)	112 (3)
FK506 + MMF ± other	421 (15)	269 (19)	690 (16)
FK506 + MTX ± other (except MMF)	595 (21)	433 (30)	1028 (24)
FK506 ± others (except MTX, MMF)	196 (7)	83 (6)	279 (7)
CSA + MMF ± other (except FK506)	719 (25)	298 (21)	1017 (24)

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