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Graft-Versus-Host Disease and Survival after Cord Blood Transplantation for Acute Leukemia: A Comparison of Japanese versus White Populations

Yachiyo Kuwatsuka [1,2,*], Yoshiko Atsuta [3], Mary M. Horowitz [1,4], Jiro Inagaki [5], Junya Kanda [6], Koji Kato [7], Katsuyoshi Koh [8], Mei-Jie Zhang [1,9], Mary Eapen [1,4], for the Center for International Blood and Marrow Transplant Research (CIBMTR), and Donor/Source and GVHD Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT)

[1] *Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[2] *Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[3] *Department of HSCT Data Management and Biostatistics, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[4] *Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Department of Pediatrics, National Kyushu Cancer Center, Fukuoka, Japan*
[6] *Division of Hematology, Saitama Medical Center, Jichi Medical University, Saitama, Japan*
[7] *Department of Hematology and Oncology, Children's Medical Center, Japanese Red Cross, Nagoya First Hospital, Nagoya, Japan*
[8] *Department of Hematology/Oncology, Saitama Children's Medical Center, Saitama, Japan*
[9] *Division of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin*

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A B S T R A C T

An earlier report identified higher risks of acute and chronic graft-versus-host disease (GVHD) in White children compared with the Japanese after HLA-matched sibling transplantations. The current analysis explored whether racial differences are associated with GVHD risks after unrelated umbilical cord blood transplantation. Included are patients of Japanese descent (n = 257) and Whites (n = 260; 168 of 260 received antithymocyte globulin [ATG]). Transplants were performed in the United States or Japan between 2000 and 2009; patients were aged 16 years or younger, had acute leukemia, were in complete remission, and received a myeloablative conditioning regimen. The median ages of the Japanese and Whites who received ATG were younger at 5 years compared with 8 years for Whites who did not receive ATG. In all groups most transplants were mismatched at 1 or 2 HLA loci. Multivariate analysis found no differences in risks of acute GVHD between the Japanese and Whites. However, chronic GVHD was higher in Whites who did not receive ATG compared with the Japanese (hazard ratio, 2.16; $P < .001$), and treatment-related mortality was higher in Whites who received ATG compared with the Japanese (relative risk, 1.81; $P = .01$). Nevertheless, there were no significant differences in overall survival between the 3 groups.

INTRODUCTION

Graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation is associated with significant morbidity and mortality [1]. Acute GVHD risks are higher after HLA-mismatched compared with HLA-matched transplantations and primarily attributed to mismatching at major histocompatibility antigens. On the other hand, donor–recipient mismatching for minor histocompatibility antigens may explain GVHD after HLA-matched transplantations. In an earlier report, Oh et al. [2] compared GVHD and overall survival between different ethnic populations after HLA-matched related bone marrow transplantation for hematologic malignancies. That report, which included children and adults, showed higher acute but not chronic GVHD risks for adult U.S. Whites compared with adults of Japanese descent. However, among children, both acute and chronic GVHD risks were higher in U.S. Whites compared with the Japanese. In that report, the observed differences between the Japanese and Whites were attributed to the relative homogeneity of minor histocompatibility antigens in persons of Japanese descent [3].

Umbilical cord blood (UCB) is less immunogenic, and consequently HLA mismatches that are prohibitive between unrelated adult donors and recipients are considered acceptable up to 2 mismatches when selecting UCB units. The practice of transplanting UCB units (UCBT) that are HLA mismatched to recipients is common in both children and adults worldwide [4-8]. To our knowledge, no published reports explore whether racial differences exist in acute and

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* Correspondence and reprint requests: Yachiyo Kuwatsuka, MD, PhD, Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8560, Japan.
E-mail address: ykuwatsuka@med.nagoya-u.ac.jp (Y. Kuwatsuka).

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chronic GVHD risks after UCBT. Almost all UCB units used in Japan are from cord blood banks in Japan, allowing for a homogeneous cohort of donors. On the other hand, the U.S. population is genetically diverse, and UCB units may have been obtained through either a U.S. or international cord blood bank. Additionally, differences in transplantation strategies exist. In Japan, UCB units generally contain fewer total nucleated cells (TNCs) than in the United States and consider lower resolution HLA match (antigen level) at HLA-A, -B, and -DR. In the United States, HLA matching at the DR locus considers allele-level match. Additionally, antithymocyte globulin (ATG) was routinely included in the transplant preparatory regimen before 2007 in the United States [8,9]. Another key difference between the 2 countries is the co-infusion of 2 UCB units, routine in the United States, for adults. Consequently, the current analysis is limited to younger patients such that the comparison is between appropriately aged patients who were transplanted with a single UCB unit. In this report we compare acute and chronic GVHD and mortality risks after UCBT between Japanese and White children with acute leukemia to test whether the genetic diversity of donors and recipients influenced the likelihood of GVHD.

METHODS

Data Source

Data were obtained from the Center for International Blood and Marrow Transplant Research [10] for U.S. transplants and from the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the Japan Cord Blood Bank Network [11] for Japanese transplants. All U.S. patients provided consent for research participation. Patient consent is not required for registration of the JSHCT because registry data consist of anonymized clinical information. The institutional review board of the National Marrow Donor Program, Medical College of Wisconsin, Nagoya University Graduate School of Medicine, and the Data Management Committees of the JSHCT and the Japan Cord Blood Bank Network approved this study.

Inclusion Criteria

Patients were 16 years old and younger with acute myeloid leukemia or acute lymphoblastic leukemia and in first, second, or third complete remission (CR). All patients received a myeloablative transplant conditioning regimen and were transplanted in Japan or the United States between 2000 and 2009. Excluded were non-Whites transplanted in the United States, transplantations in relapse, prior allogeneic transplantation, infusion of 2 UCB units, or reduced-intensity transplant conditioning regimens. Five hundred seventeen patients were eligible: 257 transplants from Japan, 168 transplants for Whites that included ATG in their transplant regimen, and 92 transplants for Whites without ATG. Units were matched to patients at the antigen level at HLA-A and -B and at the allele level at HLA-DRB1; for the Japanese cohort, this occurred retrospectively.

Outcomes

Acute and chronic GVHD were defined as time to occurrence of GVHD, using standard criteria [12,13]. Treatment-related mortality (TRM) was defined as death without leukemia relapse. Relapse was defined as hematological/morphological recurrence of leukemia. Overall mortality was defined as death from any cause.

Statistical Analysis

To compare the outcomes of interest, Cox proportional hazards models were used to adjust for potential imbalance in baseline characteristics between the 3 treatment groups [14,15]. The main effect term, Japanese versus Whites who received ATG versus Whites who did not receive ATG, was held in all steps of model building regardless of level of significance. Other variables considered were age at transplantation ($\leq$5 versus 6 to 16 years), gender, recipient cytomegalovirus (CMV) serostatus, disease, disease status, TNCs (≤ 3 versus $>3 \times 10^7$/kg), HLA match (6/6 versus 5/6 versus 4/6), transplant preparative regimen (containing total body irradiation [TBI] versus not), GVHD prophylaxis (containing cyclosporine versus tacrolimus), and period (2000 to 2006 versus 2007 to 2009). All variables met the proportionality assumption, and there were no first-order interactions between variables in the final model and the main effect term. The effects of acute and chronic GVHD were also tested for their effect on overall mortality as time-dependent covariates. Results are expressed as hazard ratios (HRs) together with 95% confidence intervals (CIs).

Adjusted cumulative incidences of acute GVHD, chronic GVHD, relapse, and TRM [16] and adjusted probabilities of survival [17] were calculated using the multivariate models, stratified on the 3 treatment groups, and weighted by the pooled sample proportion value for each prognostic factor. SAS version 9.3 (Cary, NC) was used in the analyses.

RESULTS

Table 1 shows characteristics of patients, their diseases, and transplant regimens by the 3 treatment groups: Japanese, Whites who received ATG, and Whites who did not receive ATG. None of the Japanese patients received ATG. The median ages of the Japanese and Whites who received ATG was 5 years, whereas Whites who did not receive ATG were slightly older at 8 years.

There were other differences: Japanese patients were more likely to be CMV seropositive, to be transplanted in first CR, and more likely to receive a UCB unit with TNCs $< 3 \times 10^7$/kg compared with Whites. Median TNC doses were 5.1×10^7/kg (range, 1.3 to 48), 7.4×10^7/kg (range, 1.6 to 50), and 5.7×10^7/kg (range, 1.6 to 21) for Japanese, Whites who received ATG, and Whites who did not receive ATG,

Table 1
Characteristics of Study Patients

	Japanese (n = 257)	White, with ATG (n = 168)	White, no ATG (n = 92)	*P*
Age at transplant, yr				<.0001
≤5	135 (53%)	85 (51%)	25 (27%)	
6-16	122 (47%)	83 (49%)	67 (73%)	
Gender				.73
Female	116 (45%)	81 (48%)	40 (43%)	
Male	141 (55%)	87 (52%)	52 (57%)	
Recipient CMV status				<.0001
Negative	78 (30%)	88 (52%)	43 (47%)	
Positive	115 (45%)	80 (48%)	48 (52%)	
Unknown	64 (25%)	—	1 (1%)	
Disease				<.0001
AML	70 (27%)	88 (52%)	23 (25%)	
ALL	187 (73%)	80 (48%)	69 (75%)	
Disease risk				<.0001
CR1	156 (61%)	61 (36%)	32 (35%)	
CR2/CR3	101 (39%)	107 (64%)	60 (65%)	
Year of transplant				<.0001
2000-2006	174 (68%)	105 (63%)	27 (29%)	
2007-2009	83 (32%)	63 (38%)	65 (71%)	
No. of cryopreserved TNCs $\times 10^7$/kg				<.0001
<3	48 (19%)	4 (2%)	9 (10%)	
≥3	201 (78%)	164 (98%)	83 (90%)	
Unknown	8 (3%)	—	—	
HLA match status (A B; intermediate resolution, DRB1; allele level)				.51
6/6	47 (18%)	42 (25%)	17 (18%)	
5/6	127 (49%)	75 (45%)	47 (51%)	
4/6	83 (32%)	51 (30%)	28 (30%)	
Conditioning regimen				<.0001
Non-TBI	75 (29%)	74 (44%)	8 (9%)	
TBI	182 (71%)	94 (56%)	84 (91%)	
GVHD prophylaxis				<.0001
Cyclosporine containing	122 (47%)	138 (82%)	54 (59%)	
Tacrolimus containing	135 (53%)	30 (18%)	38 (41%)	
Median follow-up of survivors, mo (range)				<.0001
	61 (10-138)	52 (12-123)	36 (13-85)	

CMV indicates cytomegalovirus; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia.