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Allogeneic Hematopoietic Stem Cell Transplantation for Adolescents and Young Adults with Acute Myeloid Leukemia

Daisuke Tomizawa [1,*], Shiro Tanaka [2], Tadakazu Kondo [3], Yoshiko Hashii [4], Yasuyuki Arai [3], Kazuko Kudo [5], Takashi Taga [6], Takahiro Fukuda [7], Hiroaki Goto [8], Jiro Inagaki [9], Katsuyoshi Koh [10], Kazuteru Ohashi [11], Yukiyasu Ozawa [12], Masami Inoue [13], Koji Kato [14], Junji Tanaka [15], Yoshiko Atsuta [16,17], Souichi Adachi [18], Hiroyuki Ishida [19]

[1] *Division of Leukemia and Lymphoma, Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan*
[2] *Department of Clinical Biostatistics, Kyoto University, Kyoto, Japan*
[3] *Department of Hematology and Oncology, Kyoto University, Kyoto, Japan*
[4] *Department of Pediatrics, Osaka University, Suita, Japan*
[5] *Department of Pediatrics, Fujita Health University, Toyoake, Japan*
[6] *Department of Pediatrics, Shiga University of Medical Science, Otsu, Japan*
[7] *Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan*
[8] *Division of Hemato-Oncology/Regenerative Medicine, Kanagawa Children's Medical Center, Yokohama, Japan*
[9] *Department of Pediatrics, National Kyushu Cancer Center, Fukuoka, Japan*
[10] *Department of Hematology/Oncology, Saitama Children's Medical Center, Saitama, Japan*
[11] *Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan*
[12] *Department of Hematology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan*
[13] *Department of Hematology/Oncology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan*
[14] *Department of Hematology and Oncology, Children's Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan*
[15] *Department of Hematology, Tokyo Women's Medical University, Tokyo, Japan*
[16] *Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan*
[17] *Department of Healthcare Administration, Nagoya University, Nagoya, Japan*
[18] *Department of Human Health Sciences, Kyoto University, Kyoto, Japan*
[19] *Department of Pediatrics, Kyoto City Hospital, Kyoto, Japan*

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A B S T R A C T

Few reports have focused on adolescent and young adult (AYA) patients with acute myeloid leukemia (AML) treated with hematopoietic stem cell transplantation (HSCT). We performed a retrospective analysis based on data obtained from a Japanese nationwide registration database to compare HSCT outcomes in AYA patients with AML with those in children with AML. An analysis of the 2973 patients with de novo AML who received allogeneic HSCT from 1990 to 2013 showed inferior 5-year overall survival (OS) (54% versus 58%, $P < .01$) and increased treatment-related mortality (TRM) (16% versus 13%, $P = .02$) in AYA patients. Multivariate analysis for both OS and TRM showed a significant negative impact on AYAs. However, the negative impact of older age lost its significance in an additional analysis focusing on 1407 recent transplant recipients with high-resolution HLA typing (2000 to 2013). Finally, we analyzed the impact of transplantation center type on HSCT outcomes in 317 adolescent patients (15 to 18 years old) and found no difference in outcomes between patients treated at a pediatric or an adult hospital. Higher age was a strong predictive factor for inferior OS resulting from increased TRM, which can be eliminated with better donor selection using high-resolution HLA typing.

INTRODUCTION

Acute leukemia is a major type hematological malignancy in both children and adults. However, in children younger than 15 years, acute lymphoblastic leukemia (ALL) predominates. Acute myeloid leukemia (AML) comprises only one-fourth of all leukemia cases in this population and has an incidence of 8 cases per 1,000,000 children [1]. The incidence of AML gradually increases with age; hence, AML is the most

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* Correspondence and reprint requests: Daisuke Tomizawa, MD, PhD, Division of Leukemia and Lymphoma, Children's Cancer Center, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.
E-mail address: tomizawa-d@ncchd.go.jp (D. Tomizawa).

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common type of leukemia in adults. Leukemia is one of the major types of cancer diagnosed in *adolescents and young adults* (AYA) commonly defined as individuals between the ages of 15 and 29 or 39 years [2]. Evidence is increasingly showing the superiority of the pediatric approach for the management of AYA patients with ALL. However, the data on AML are very limited [3] and only a few retrospective studies of AYA patients with AML have compared pediatric and adult approaches [4-9]. Although allogeneic hematopoietic stem cell transplantation (HSCT) is an important curative option for both children and adults with AML, only a few reports have examined the procedure in AYA patients with AML [10,11]. Furthermore, AYA patients, especially adolescents, may undergo transplantation at either a pediatric or an adult transplantation center, depending on their referral pattern, and the differences in practices and attitudes between pediatric and adult physicians might influence HSCT outcomes. We, therefore, conducted a retrospective analysis using data obtained from a national database in Japan.

PATIENTS AND METHODS

Patients

Information was collected from the nationwide HSCT registry of the Japan Society of Hematopoietic Cell Transplantation. The patients were selected according to the following criteria: (1) patients with AML (those with acute promyelocytic leukemia, Down syndrome, and/or secondary AML were excluded); (2) ages 0 to 29 years at the time of transplantation; (3) received their first allogeneic HSCT either in their first or second complete remission (CR), first relapse, or primary induction failure; and (4) between 1990 and 2013. Patients were allocated to either of 2 groups by age at transplantation: patients 15 to 29 years of age were allocated to the *AYA* group while those 0 to 14 years of age were allocated to the *child* group. In addition, patients 15 to 18 years old were specifically defined as *adolescents*. All aspects of the current study were approved by the Transplant Registry Unified Management Program committee of the Japan Society of Hematopoietic Cell Transplantation (number 1-10) and the ethical committee of the National Center for Child Health and Development (number 979).

Statistical Analysis

Analyses in this study were performed in 3 steps: first, the HSCT outcome of the AYA group was compared to that of the child group using data from the total cohort (all transplant recipients from 1990 to 2013); second, the comparative analysis was restricted to recent transplant recipients (2000 to 2013) and cases for which data on high-resolution typing at 6 alleles of HLA A, B, and DRB1 for both the recipient and donor were available; and finally, adolescent patients were extracted from the total cohort and their HSCT outcomes were compared by transplantation center type.

Variables in this study were defined as follows: *low-risk AML cytogenetics* as t(8;21)(q22;q22)/*RUNX1-RUNX1T1* and inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB-MYH11*, *high-risk AML cytogenetics* as monosomy 7, deletions of 5q, t(6;9)(p23;q34)/*DEK-NUP214*, t(16;21)(p11;q22)/*FUS-ERG*, and complex karyotypes (3 or more chromosome abnormalities in the absence of one of the recurring translocations or inversions designated by the World Health Organization's classification). Other abnormalities were defined as *intermediate-risk*. The conditioning regimen was regarded as *myeloablative* (MAC) if the total dose of busulfan exceeded 9 mg/kg (MAC-BU) or the total dose of fractionated total body irradiation (TBI) exceeded 8 Gy (MAC-TBI). Other regimens were defined as *reduced-intensity* [12]. In the first and third steps of the analysis, a donor was regarded as *HLA matched* if all 6 antigens (HLA-A, B, and DR) were identical to the recipient's HLA , whereas other donors were regarded as *HLA mismatched*. However, in the second step of the analysis with high-resolution HLA typing involving the cohort of recent transplant recipients (transplant recipients from 2000 to 2013, hereafter termed *recent recipients*), the following criteria were used: as for a familial donor, an *HLA allele match* was defined as 0 or 1 disparity between the donor and the recipient at 6 loci (HLA-A, B, and DRB1) and an *HLA allele mismatch* was defined as 2 or more disparities; for unrelated donors, a *good HLA allele match* was defined as no disparities, a *partial mismatch* as 1 disparity, and a *mismatch* as 2 or more disparities.

The baseline characteristics and the clinical course of patients were analyzed using the chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. *Disease-free survival* (DFS) was defined as the length of time from the HSCT to the last follow-up or first event (failure to achieve CR, relapse, secondary malignancy, or death from any cause). *Overall survival* (OS) was defined as the length of time from the HSCT to death from any cause. The survival curves for DFS and OS were estimated using the Kaplan-Meier method. The *cumulative incidence of relapse* (RR) was estimated with relapse after the HSCT as the event of interest and death from any cause before relapse and secondary malignant neoplasm as the competing risks. *Treatment-related mortality* (TRM) was estimated with nonleukemia mortality after HSCT as the event of interest and any leukemia mortality, relapse, or secondary malignant neoplasm as competing risks. The cumulative incidence of acute graft-versus-host disease (GVHD) was estimated with acute GVHD as the event of interest, and the cumulative incidence of chronic GVHD was estimated with chronic GVHD as the event of interest for patients who survived 100 days or longer after transplantation. Death and the recurrence of leukemia before development of GVHD were considered competing risks. Cox proportional hazards regression was used to identify the risk factors associated with the DFS and OS rates, and Fine and Gray competing risk regression was used to identify risk factors associated with RR and TRM. Variables including age at HSCT, year at HSCT, AML cytogenetic abnormalities, status at HSCT, donor, conditioning, and GVHD prophylaxis were included in the models. Year at HSCT and GVHD prophylaxis were excluded in the second step of the analysis. Type of HSCT center, AML cytogenetic abnormalities, donor, and conditioning were included for the final step of the analysis. The variables significantly associated with the DFS, OS, RR, and TRM were then identified by a significance level of .05. All *P* values were 2-sided and no statistical adjustment was made for multiple testing. All data analyses were performed by an academic biostatistician using SAS statistical software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

In total, 2977 patients were identified. Four patients were excluded because the dates of the events were incompatible (n = 2) or their survival status was unknown (n = 2). Data on the remaining 2973 patients (the total cohort), comprising 1123 patients in the child group and 1850 in the AYA group, were further analyzed. The patient characteristics of the 2 groups are shown in Table 1. There was a higher percentage of French-American-British classification M0, M1, and M2 morphology in the AYA group while M5 and M7 were less common than in the child group. In addition, the AYA group had a higher percentage of intermediate-risk AML cytogenetic abnormalities and a lower percentage of high-risk AML cytogenetic abnormalities. More patients in the AYA group received HSCT at primary induction failure, had an HLA-matched related or unrelated donor, or underwent MAC-TBI conditioning and GVHD prophylaxis with cyclosporine and methotrexate (MTX). In contrast, a higher percentage of patients in the child group received a transplant from an HLA-mismatched related donor or an unrelated cord blood donor and received MAC-BU or reduced-intensity conditioning and GVHD prophylaxis with tacrolimus plus MTX or MTX only for matched sibling donors. Details of the conditioning regimen used in both cohorts are listed in Supplemental Table S1.

Transplantation Outcomes of the Total Cohort (All Transplant Recipients from 1990 to 2013)

The OS, DFS, RR, and TRM curves of the AYA and the child groups are shown in Figure 1. The 5-year OS and DFS rates were significantly poorer among AYAs than among children at 54% (95% confidence intervals [CI], 51% to 56%) and 58% (95% CI, 55% to 61%) ($P < .01$) and 48% (95% CI, 46% to 51%) and 53% (95% CI, 50% to 56%) ($P = .03$), respectively. Five-year RR did not differ between the 2 groups at 34% (95% CI, 32% to 36%) and 33% (95% CI, 31% to 36%) ($P = .99$), respectively. However, 5-year TRM was significantly higher in AYAs at 16% (95% CI, 14% to 17%) versus 13% (95% CI, 11% to 15%) ($P = .02$) in the child group. When the patients were subdivided into the 0 to 9-year-old, 10 to14-year-old, 15 to 18-year-old, and 19 to 29-year-old age groups, the OS rate decreased while