Biol Blood Marrow Transplant 25 (2019) 1597–1602

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Allogeneic Stem Cell Transplantation for Acute Lymphoblastic Leukemia in Adolescents and Young Adults

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Article history:
Received 28 February 2019
Accepted 10 April 2019

Key Words:
Acute lymphoblastic leukemia
Adolescent and young adult
Hematologic stem cell transplantation

A B S T R A C T

Hematologic stem cell transplantation (HSCT) is the most potent consolidation therapy for high-risk acute lymphoblastic leukemia (ALL), but their outcomes and complications in adolescent and young adult (AYA) patients remain unclear. We compared outcomes after HSCT for ALL among children (age 1 to 9 years; n = 607), adolescents (age 10 to 19 years; n = 783), and young adults (age 20 to 29 years old, n = 603), based on Japanese nationwide registry data. The 5-year overall survival (OS) rate among AYA patients was worse than that of children, at 64% (95% confidence interval [CI], 60% to 68%). In the AYA, the 5-year treatment-related mortality (TRM) after HSCT was 19% (95% CI, 16% to 22%), significantly higher than that in younger patients. The most common cause of TRM in the AYA was infection. The relapse rate was not different across the 3 age groups. When focusing on older adolescents (age 15 to 19 years), there was no difference in outcomes between those treated in pediatric centers and those treated in adult centers. In conclusion, the AYA had a greater risk of nonrelapse death than younger patients, and infection was the most common cause. Further optimization is required for HSCT in AYAs with ALL.

INTRODUCTION

The prognosis of pediatric acute lymphoblastic leukemia (ALL) has improved dramatically, and recent studies have reported excellent results [1]. Although the survival rate now approaches 90% for childhood ALL overall, the prognosis remains poor in adolescents and young adults (AYAs) [2,3]. ALL commonly exhibits certain unfavorable biological and molecular genetic features in AYAs compared with younger children, including a lower frequency of *ETV6-RUNX1* and high hyperdiploidy and higher frequencies of *BCR-ABL1*, *DUX4* translocation, and positive minimal residual disease after induction therapy [2–4]. There is evidence supporting the superiority of pediatric-inspired intensive chemotherapy for the management of AYA patients with ALL [5]; however, AYA patients are at greater risk of complications, such as pancreatitis, thrombosis, and osteonecrosis, compared with children age <10 years [4].

Financial disclosure: See Acknowledgments on page 1602.
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https://doi.org/10.1016/j.bbmt.2019.04.014
1083-8791/

In addition to improving event-free survival through intensive chemotherapy, hematopoietic stem cell transplantation (HSCT), which allows for high-dose chemotherapy and a graft-versus-leukemia effect, reduces the risk of relapse among extremely high-risk patients, including those with relapsed ALL [6]. However, toxicity of treatment remains a significant problem, with previous studies reporting 10% to 30% transplantation-related mortality (TRM) in AYA patients who underwent HSCT for ALL, mostly due to graft-versus-host disease (GVHD) and infection [7–10].

Information on the efficacy and safety of HSCT for AYA patients with ALL remains limited. One retrospective study showed improvements in survival rates over time with changing HSCT practices and reported similar patterns across center types, despite variations in practice [10]. This study included patients who underwent HSCT between 1990 and 2007, a period marked by changes in the management of AYA patients with ALL influenced by the adoption of HSCT practices. Evaluating trends in practice and its effect on clinical outcomes among this understudied population of ALL patients will help inform future efforts to optimize treatment strategies.

In the present study, using nationwide registry data collected by the Transplant Registry Unified Management Program (TRUMP) system [11] representing a recent 16-year period across Japan, we examined differences in recent clinical outcomes and complications across age groups of patients who underwent HSCT for ALL, as well as the influence of the type of treating institution on outcomes.

METHODS

Patients

A retrospective cohort study was performed using nationally representative registry data from the Japan Society for Hematopoietic Cell Transplantation (JSHCT) [11]. This registry assembles HSCT recipient, donor, and outcomes data for all the HSCTs performed in Japan using a web-based registry system. Information on survival and underlying disease status is updated annually. We included patients with ALL (both B ALL and T ALL) aged 1 to 29 years at the time of transplantation who underwent their first allogeneic HSCT while in complete remission (CR) between January 2000 and December 2015. Among 2465 eligible patients, we excluded those with *BCR-ABL1* translocation-positive tumors (n = 472), because these patients are known to have unique treatment options, including tyrosine kinase inhibitors. We classified the patients into 3 groups based on age at transplantation: children (1 to 9 years; n = 607), adolescents (10 to 19 years, n = 783), and young adults (20 to 29 years, n = 603). Among adolescents, patients aged 15 to 19 years were defined as "older adolescents."

This study was approved by the Ethical Committee of the University of Tokyo Hospital (no. 11361). Written informed consent was obtained from all subjects.

Outcomes

The primary objective of the study was to compare OS, relapse rate (RR), and TRM among children, adolescents, and young adults. Death from any cause was considered an event in the analysis of OS. A patient was considered to have relapsed based on recurrence of disease symptoms and clinical diagnostic confirmation of ALL after HSCT. TRM was defined as death in remission. Information on cause of death was collected through the web-based JSHCT registration system, with clinicians selecting from a list of potential causes. Baseline was defined as the date of transplantation with an observation period that ended at the time of death due to any cause, time of relapse, or time of death during remission for the analysis of OS, RR, and TRM, respectively; last clinical follow-up; or the end of the study period (September 2016).

Covariate Data

All data included in this study were extracted from the JSHCT registry. Donor sources were classified into 4 groups; cord blood, matched related donor with 0 or 1 HLA allele disparity at 6 loci (HLA-A, -B, and -DRB1) between the donor and the recipient, unmatched related donor with ≥2 disparities, and unrelated donor (except for cord blood). As a secondary objective of this study, we evaluated whether the type of transplantation center (pediatric versus adult) was associated with OS, RR, or TRM, focusing on older adolescents (age 15 to 19 years). In general, pediatricians (pediatric hematologists/oncologists) treat their patients in pediatric centers, and hematologists treat their patients in adult centers. There are some centers in which both pediatricians and hematologists treat their patients in parallel, and we excluded those centers in the analysis comparing the 2 types of centers. We divided the HSCT period into 2 categories, 2000-2007 and 2008-2015, to evaluate differences in time period.

Statistical Analysis

Descriptive statistics for patient, disease, and transplantation characteristics were produced for the 3 age groups. We used Fisher's exact tests to compare the proportions of categorical variables in the 3 groups. Survival curves were assessed using the Kaplan-Meier method, and survival estimates were compared with the log-rank test. Probabilities of RR, TRM, and GVHD were estimated using the cumulative incidence function method, taking into account competing risks.

In the subgroup analysis that focused on older adolescents, we compared the characteristics of patients who underwent transplantation at pediatric

Table 1
Patient, Disease, and Transplantation Characteristics of the Entire Cohort by Age Group

Characteristic	Children (1-9 yr) (n = 607)		Adolescents (10-19 yr) (n = 783)		Young Adults (20-29 yr) (n = 603)		*P* Value
HSCT period, n (%)							<.001
2000-2007	359	(59)	420	(54)	281	(47)	
2008-2015	248	(41)	363	(46)	322	(53)	
Sex, n (%)							.045
Male	372	(61)	488	(62)	337	(56)	
Female	235	(39)	294	(38)	266	(44)	
Status at HSCT, n (%)							<.001
First CR	295	(49)	442	(56)	435	(72)	
Second CR or later	312	(51)	333	(43)	163	(27)	
Donor source, n (%)							<.001
Cord blood	207	(34)	150	(19)	114	(19)	
Matched related donor	168	(28)	250	(32)	216	(36)	
Unmatched related donor	35	(21)	38	(15)	22	(10)	
Unrelated donor	197	(32)	345	(44)	251	(42)	
Conditioning, n (%)							<.001
MAC-TBI	455	(75)	670	(86)	517	(86)	
MAC-BU	38	(6.3)	11	(1.4)	10	(1.7)	
RIC or unknown	114	(19)	102	(13)	76	(13)	

MAC indicates myeloablative conditioning; TBI, total body irradiation; BU, busulfan; RIC, reduced-intensity conditioning.
The sums of the individual categories may not add up to totals because of missing data.

centers and those who did so at adult centers. Kaplan-Meier evaluations of OS, RR, TRM, and GVHD were performed as described above. In addition, we used the Cox proportional hazard model for the multivariate evaluation of the effect of transplantation center type and other characteristics on OS and used the Fine-Gray model to evaluate RR, TRM, and GVHD. Covariates that showed evidence of association with transplantation center type were included in the multivariate analysis.

Two-sided P values of $\leq$.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [12], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Patient Characteristics

A total of 1993 patients with ALL were analyzed, and clinical characteristics are shown in Table 1. From 2000-2007 to 2008-2015, transplantation volume decreased by 31% in children, decreased by 14% in adolescents, and increased by 15% in young adults. The proportion of patients in first CR at HSCT was significantly higher in older patients (72% in young adults), whereas approximately one-half of the children who underwent HSCT were in second CR. Children had significantly higher rates of cord blood transplantation and reduced-intensity conditioning.

Outcomes Among the Entire Cohort

The OS, RR, and TRM curves of the 3 age groups are presented in Figure 1. The survival disadvantages of AYAs compared with children were significant (P = .007 and .020, respectively), and the 5-year survival rates of children, adolescents, and young adults were 70% (95% confidence interval [CI], 66% to 74%), 64% (95% CI, 60% to 68%), and 64% (95% CI, 60% to 68%), respectively. Similarly, the TRM was significantly different for adolescents and young adults compared with children (P < .001 and P = .005, respectively), and the mortality rates without relapse at 5 years in the 3 groups were 19% (95% CI, 16% to 22%), 17% (95% CI, 14% to 21%) and 11% (95% CI, 8.8% to 14%), respectively. The incidence of grade III-IV acute GVHD was 5.9% (95% CI, 4.2% to 8.0%) in children, 5.0% (95% CI, 3.6% to 6.7%) in adolescents, and 4.5% (95% CI, 3.0% to 6.3%) in young adults at 30 days, and 8.9% (95% CI, 6.8% to 11%), 9.2% (95% CI, 7.3% to 11%), and 8.0% (95% CI, 6.0% to 10%), respectively, at 100 days. The chronic GVHD curves were significantly different among the 3 age groups (P < .001), with 1-year incidence rates of 24% (95% CI, 21% to 27%) in children, 28% (95% CI, 24% to 31%) in adolescents, and 32% (95% CI, 29% to 36%) in young adults (Supplementary Figure 1). The relapse curves did not show differences among the groups (P = .30), and the RRs at 5 years after transplantation were 25% (95% CI, 21% to 28%) in children, 22% (95% CI, 19% to 25%) in adolescents, and 23% (95% CI, 19% to 27%) in young adults. The curves for GVHD-free, relapse-free survival (GRFS), defined as the absence of grade III-IV acute GVHD, chronic GVHD requiring systemic treatment, relapse, or death, were significantly different among the 3 age groups (P = .006) (Supplementary Figure 1).

Table 2 shows the causes of treatment-related deaths in each group. Sixty-one children (10%), 123 adolescents (16%), and 89 young adults (15%) died without relapse of ALL. The older age groups (adolescents and young adults) tended to have more deaths caused by infection in both acute

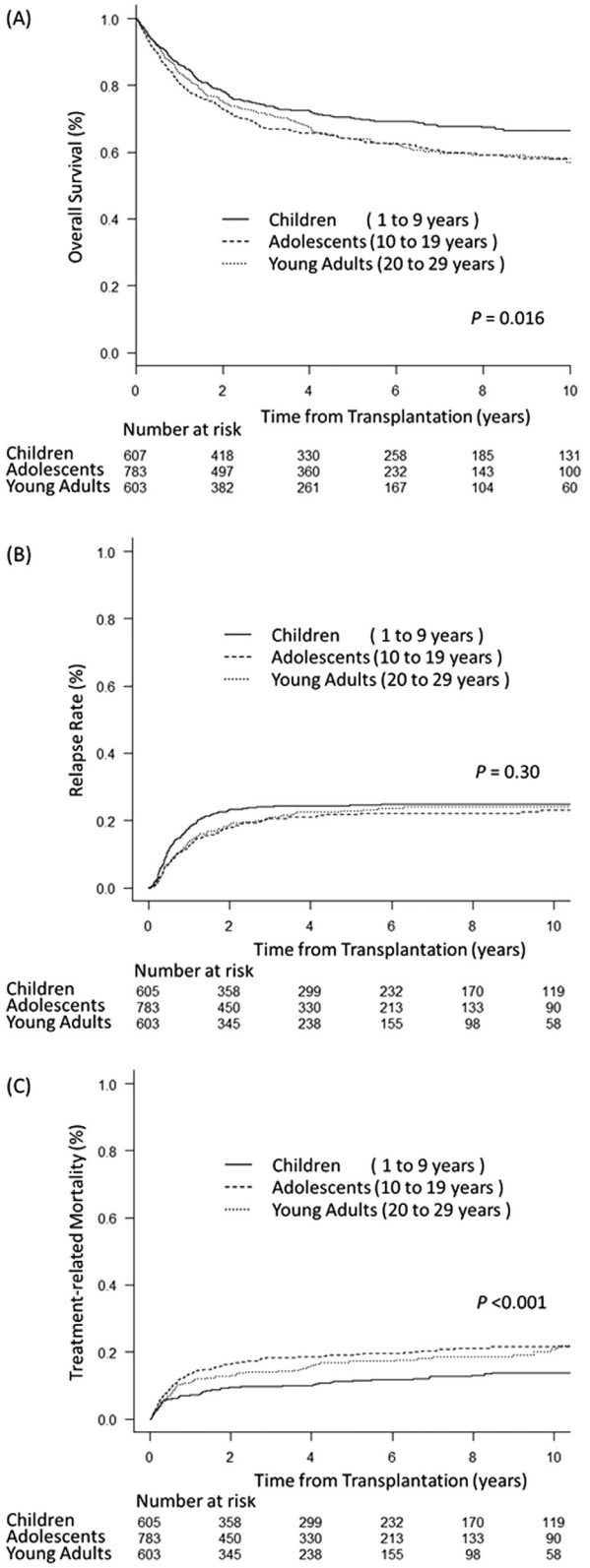

Figure 1. OS (A), RR (B), and TRM (C) of patients receiving HSCT categorized into 3 age groups; children (age 1 to 9 years), adolescents (age 10 to 19 years), and young adults (age 20 to 29 years).

Table 2
Causes of TRM among the Entire Cohort

Causes of TRM	Children (1-9 yr) (n = 61; 10%)		Adolescents (10-19 yr) (n = 120; 15%)		Young Adults (20-29 yr) (n = 89; 15%)	
Acute-phase deaths, ≤100 days since HSCT, n (%)	24	(39)*	45	(37)*	30	(34)*
Rejection	1	(4.2)	4	(8.9)	3	(10)
GVHD	1	(4.2)	4	(8.9)	6	(20)
VOD or TMA	7	(29)	7	(16)	2	(6.7)
Interstitial pneumonia	5	(21)	3	(6.7)	4	(13)
Infection	1	(4.2)	11	(24)	6	(20)
Other†	9	(38)	16	(36)	9	(30)
Chronic-phase deaths, >100 d since HSCT	37	(61)*	77	(63)*	59	(66)*
GVHD	8	(22)	11	(14)	9	(15)
VOD or TMA	4	(11)	0	(0)	4	(6.8)
Interstitial pneumonia	6	(16)	17	(22)	8	(14)
Infection	7	(19)	25	(32)	15	(25)
Second malignancy	5	(14)	5	(6.5)	3	(5.1)
Others†	7	(19)	19	(25)	20	(34)

VOD indicates hepatic veno-occlusive disease; TMA, thrombotic microangiopathy.
* Represents percentage of deaths during acute and chronic phases by age group.
† Others include acute respiratory distress syndrome, organ failure, and unknown causes.

Table 3
Patient, Disease, and Transplantation Characteristics of Older Adolescents (Age 15 to 19 Years) by Clinical Center Type

Characteristic	Pediatric Center (n = 132)		Adult Center (n = 237)		*P* Value
HSCT period, n (%)					.59
2000-2007	71	(54)	135	(57)	
2008-2015	61	(46)	102	(43)	
Sex, n (%)					.82
Male	88	(67)	162	(68)	
Female	44	(33)	75	(32)	
Status at HSCT, n (%)					<.001
First CR	67	(51)	173	(73)	
Second CR or later	65	(49)	58	(24)	
Donor source, n (%)					.92
Cord blood	23	(17)	35	(15)	
Matched related donor	45	(34)	81	(34)	
Unmatched related donor	5	(3.8)	10	(4.2)	
Unrelated donor	59	(45)	111	(47)	
Conditioning, n (%)					.043
MAC-TBI	114	(86)	198	(84)	
MAC-BU	4	(3.0)	1	(.4)	
RIC or unknown	14	(11)	38	(16)	

The sums of the individual categories might not add up to the total because of missing data.

(≤100 days from HSCT) and chronic (>100 days) phases (23% and 29%, respectively) compared with children, which was the most common cause of treatment-related death in these age groups.

Differences in Outcomes of Older Adolescents by Type of Center

Table 3 presents transplantation characteristics for the older adolescent patients (age 15 to 19 years) who underwent HSCT, focusing on differences by type of transplantation center (pediatric or adult center). This analysis included 132 older adolescents who underwent transplantation at pediatric centers and 237 who did so at adult centers. The proportion of patients in first CR was significantly lower in the pediatric centers, consistent with the lower rate of first CR in children compared with young adults in the analysis of the entire cohort (Table 1).

The OS, RR, and TRM curves for older adolescents treated in pediatric centers versus adult centers are presented in Figure 2. No evidence of significant differences in OS, RR, or TRM by transplantation center type can be seen. In pediatric centers and adult centers, respectively, the 5-year OS was 61% (95% CI, 52% to 69%) and 66% (95% CI, 60% to 73%), the 5-year RR was 23% (95% CI, 16% to 31%) and 22% (95% CI, 17% to 28%), and TRM was 22% (95% CI, 16% to 30%) and 16% (95% CI, 12% to 21%). The rate of grade III-IV acute GVHD was 6.1% (95% CI, 2.8% to 11%) in the pediatric centers and 4.2% (95% CI, 2.2% to 7.3%) in the adult centers at 30 days, and 11% (95% CI, 6.7% to 18%) and 8.4% (95% CI, 5.3% to 12%), respectively, at 100 days. The rate of chronic GVHD at 1 year was 25% (95% CI, 17% to

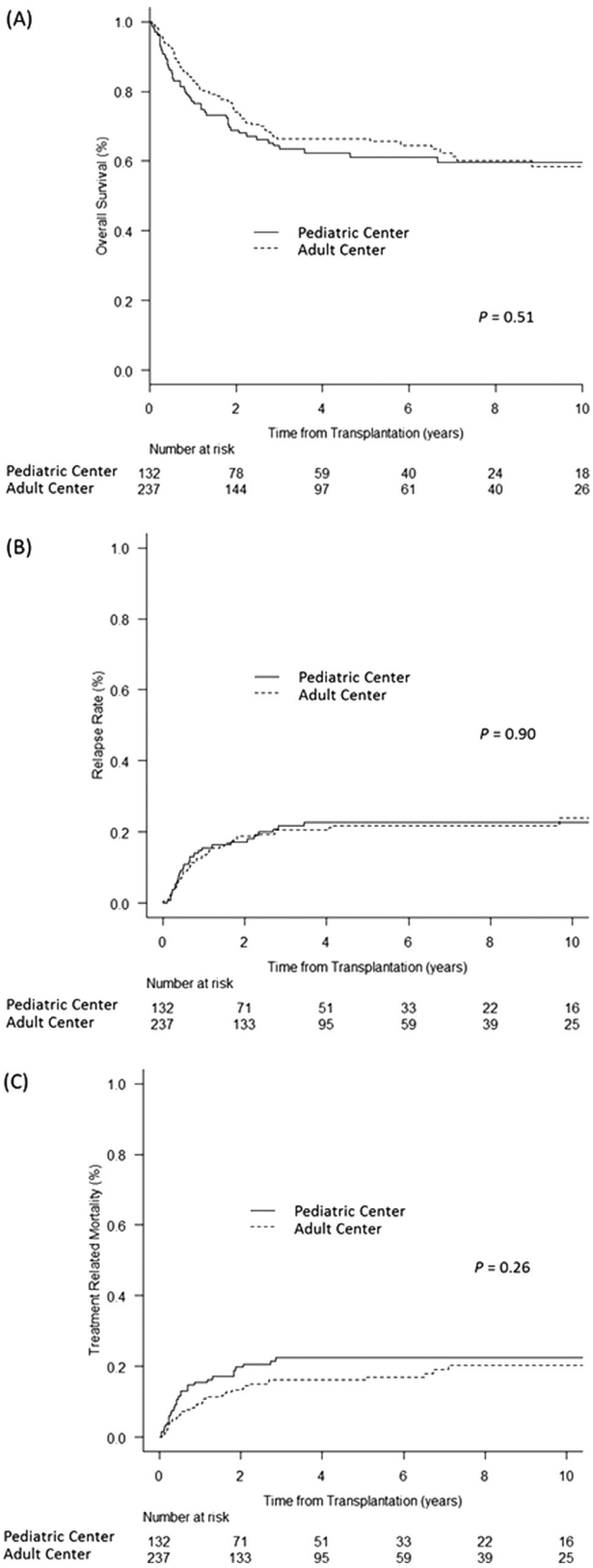

Figure 2. OS (A), RR (B), and TRM (C) of older adolescents (age 15 to 19 years) receiving HSCT categorized by treatment at a pediatric center or an adult center.

32%) in the pediatric centers and 31% (95% CI, 25% to 37%) in the adult centers (Supplementary Figure 2). The GRFS curves for the 2 center types are also shown in Supplementary Figure 2. Multivariate analysis for OS, RR, and TRM showed no differences between the 2 center types, but statistically significant worse outcomes were observed for patients who underwent HSCT in second CR or later compared with those who underwent HSCT in first CR (Supplementary Table 1). Among older adolescents, the incidence curves of TRM by first CR or second CR showed statistically significant differences ($P = .0036$; Supplementary Figure 3).

Twenty-two patients (17%) in pediatric centers and 31 (13%) in adult centers died without relapse of ALL. The rate of acute deaths was higher in the pediatric centers (36% and 26%, respectively). Our small sample size precluded the ability to perform statistical evaluations, but acute death due to infection appeared to be relatively common for patients treated in pediatric centers, whereas death due to GVHD was rare in these patients (Supplementary Table 2).

DISCUSSION

This comparison of outcomes and complications after HSCT for ALL in AYA patients and children using a nationwide registry database in Japan confirms significantly worse survival and a higher risk of TRM, especially caused by infection, in AYAs compared with children. When focusing on older adolescents, there was no significant difference in outcomes by center type (pediatric or adult center) after adjusting for patients' disease status and conditioning.

Previous studies have demonstrated improved outcomes when administering pediatric-based chemotherapy for AYAs with ALL [5]. Many adult centers had previously conducted HSCT as upfront therapy for AYAs with ALL, but evidence showing the superiority of pediatric protocols has established that the routine use of allogenic HSCT provides no gains in prognosis. Currently, few reports are available examining outcomes after HSCT [6] and common treatment complications in AYA patients, and some studies have shown evidence of increased hematologic toxicity and infections among those receiving pediatric-inspired chemotherapy [13]. Similar to the only previous report focusing on outcomes of AYAs with ALL after transplantation (2002 to 2007, in the United States) [10], our data show no statistically significant difference in outcomes between pediatric centers and adult centers.

Our analysis suggests that there are likely unique characteristics of AYA patients, as evidenced by their higher risk of nonrelapse death. It is noteworthy that infection was the main cause of nonrelapse death in adolescents, at a higher rate in pediatric centers compared with adult centers. One factor that may be driving this observation is the differences in patient characteristics between center types, such as disease status at HSCT. A higher proportion of patients in the pediatric centers underwent HSCT at second CR or later. In general, such patients are treated for longer periods, leading to a more fragile immune system and, in turn, increased use of more aggressive conditioning regimens. Another possible factor may be differences in supportive therapy between the 2 types of centers. For example, the use of prophylactic antibiotics around transplantation is not uniform among centers or clinicians [14], and such a disparity might be critical for adolescents. In

contrast, the frequency of GVHD-related mortality appeared to differ between pediatric and adult centers, possibly related to differences in immunosuppressive therapy. Considering the above, adult-inspired use of prophylactic antibiotics and pediatric-inspired immunosuppressive therapy or any other special strategies may improve the outcomes of this age group.

Interestingly, there was no difference in relapse risk between the 2 center types, despite the larger proportion of HSCT recipients in second CR or later in pediatric centers. Further studies are needed to clarify the optimal scenario for transplantation, appropriate conditioning regimen, and supportive treatment. Collaboration between pediatric and adult study groups is essential to develop better treatment strategies for AYA patients with ALL.

Several limitations of this study should be acknowledged. First, our analysis was retrospective with registry-based data and included only the patients who underwent HSCT. The role and decision making process of transplantation in the treatment of ALL are not yet standardized in Japan between pediatric centers and adult centers, and thus our analysis of center type may have been affected by confounding. For example, it is possible that patients treated in pediatric centers may have been more likely than patients treated in adult centers to be in worse condition after long-duration chemotherapy or adverse prognostic features at the time of transplantation. Second, data on pre-HSCT therapy or supportive therapy around transplantation were not available, and thus we were not able to consider them as possible covariates for adjustment, particularly in the analysis of TRM. Third, data on minimal residual disease or high-risk cytogenetics, known to be one of the most important prognostic factors in ALL, was not available, precluding our ability to consider it as a covariate for adjustment or subgroup analyses to evaluate potential differential effects across clinical subtypes. Finally, the data collected on the cause of death were not standardized across providers and institutions, and thus the reported distribution of causes of death may be affected by some misclassification.

In summary, we have performed a retrospective analysis using a nationwide cohort of AYA patients with ALL to compare outcomes after HSCT. Although there was no difference in RR among the 3 age groups, adolescents had a higher risk of nonrelapse death than younger patients, with infection the main problem. In addition, the prognosis did not appear to differ between older adolescents treated at pediatric centers and those treated at adult centers.

ACKNOWLEDGMENTS

The authors thank all the staff at participating hospitals and centers who provided valuable clinical data for the JSHCT registry, as well as Aurelie Piedvache for advising on statistical methods.

Financial disclosure: This work was supported in part by a Research Grant for Allergic Disease and Immunology from the Japanese Ministry of Health, Labor, and Welfare (to Y.A.), and research grants from the National Center for Child Health and Development (28-5 and 29-8; to M.K.).

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.04.014.

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