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Comparison of survival of adolescents and young adults with hematologic malignancies in Osaka, Japan

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ABSTRACT

The survival gap between adolescents and young adults (AYAs) with hematological malignancies persists in many countries. To determine to what extent it does in Japan, we investigated survival and treatment regimens in 211 Japanese AYAs (15–29 years) in the Osaka Cancer Registry diagnosed during 2001–2005 with hematological malignancies, and compared adolescents (15–19 years) with young adults (20–29 years). AYAs with acute lymphoblastic leukemia (ALL) had a poor 5-year survival (44%), particularly young adults (29% vs. 64% in adolescents, $p = 0.01$). Additional investigation for patients with ALL revealed that only 19% of young adults were treated with pediatric treatment regimens compared with 45% of adolescents ($p = 0.05$). Our data indicate that we need to focus on young adults with ALL and to consider establishing appropriate cancer care system and guidelines for them in Japan.

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Adolescents and young adults; hematological malignancies; leukemia; lymphoma; survival

Introduction

In spite of the striking improvement in the survival of children (0–14 years) with hematological malignancies over the past three decades, less improvement has been reported in adolescents and young adults (AYAs).[1–4] The reasons for this difference may include differences in cancer biology and chemotherapy pharmacokinetics, together with a lack of specialist care guidelines, treatment regimens, and clinical trials relevant to AYAs.[2] In the United States, the 5-year survival in 10–16 year-olds diagnosed with acute lymphoblastic leukemia (ALL) diagnosed during 2000–2010 was 75–80%, whereas it was only 45–55% in 18–21 year-olds and even lower, 30–45%, in 21–29 year-olds.[3] In Australia, the 5-year survival from ALL between children (0–14 years), adolescents (15–19 years) and young adults (20–29 years) was 87.5%, 73.6%, and 47.1%, respectively for those diagnosed during 2000–2004.[4] Several retrospective studies have revealed better survival for AYAs with ALL who were treated with pediatric treatment regimens than those who were treated with conventional adult treatment regimens,[5–12] and a recent prospective trial of applying a pediatric regimen to young adults was successful.[13]

While international attention has been focused on hematological malignancies in AYAs, little is known about them in Japan. We therefore investigated survival of Japanese AYAs diagnosed during 2001–2005 with hematological malignancies and compared older adolescents (15–19 years) with young adults (20–29 years) in the cohort. For patients with ALL, we collected additional information about having Philadelphia chromosome (Ph), their treatment regimens, clinical trial enrollment, and use of hematopoietic stem cell transplantation (HSCT).

Patients and methods

Patients

We identified 268 AYA patients (age 15–29) diagnosed with leukemia (ICD-10 code: C91-95) or lymphoma (C81-85, C96) in 2001–2005 from the Osaka Cancer Registry (OCR), which is the population-based cancer registry in Osaka prefecture. Of these, 220 patients were treated in the 33 designated cancer care hospitals from which patients' clinical information was available. Patients who were registered by death certificate only (6 patients, 2.7%) or second malignancy (3 patients, 1.4%) were

excluded, and the remaining 211 patients (adolescents $n = 62$, young adults $n = 149$) were analyzed. In addition to the data from the OCR that included hospital type, we collected information on histological detail and treatment department between July 2012 and December 2012. Active follow-up information on vital status 5 years after diagnosis was collected from OCR. Ten patients (4.7%) were lost to follow-up and were censored at the latest date when they were confirmed alive.

Variables

From the information of treatment departments, medical specialists who treated AYA patients were classified as pediatric oncologists, adult hematologists or others. Hospital types were categorized as designated children's hospital ($n = 1$), representative prefectural cancer center ($n = 1$), university hospital ($n = 5$) and other designated cancer care hospital ($n = 26$). Histologic types were categorized as acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), defined on the basis of the Surveillance, Epidemiology, and End Results (SEER) AYA site recode.[14,15]

Additional investigations

We sent an additional questionnaire to 20 designated cancer care hospitals where identified ALL patients were treated, to obtain information on having Philadelphia chromosome (Ph), their treatment regimens, enrollment in any clinical trials, and use of hematopoietic stem cell transplantation (HSCT) as of October 2013. Pediatric treatment regimens included Japanese clinical trials such as JALSG ALL202-U,[11] JACLS ALL-02,[16] and other published pediatric treatment regimens,[5–10] although the specific name of the treatment regimen was not always available.

Statistical analysis

Basic characteristics of patients and clinical details of ALL patients were compared between adolescents (15–19 years) and young adults (20–29 years), using the Chi-square test. The probability of overall survival (OS) according to histological type was estimated using the Kaplan–Meier method and 5-year OS rates were compared between adolescents and young adults, using the log-rank test. Results were considered to be statistically significant when $p < 0.05$. All statistical analyses were performed using the statistical software package Stata Version 12.1 (Stata, College Station, TX).

This study was approved by the Research Ethics Committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases and the Osaka Medical Center and Research Institute for Maternal and Child Health.

Results

Patient characteristics are shown in Table 1. There were no differences in sex and diagnosis between adolescents and young adults, but there were differences in medical specialists and hospital type. A total of 171 AYA patients (81.0%) were treated by adult hematologists and 12 (5.7%) were treated by pediatric oncologists. The proportion of patients who were treated in a representative prefectural cancer center was higher in young adults (17.5%) than adolescents (6.5%). Almost half of both adolescents and young adults were treated at 26 hospitals rather than the one children's hospital, one representative cancer center or five university hospitals.

Table 2 shows the 5-year OS of AYA patients overall, and of adolescents and young adults separately. The 5-year OS rate was 53.5% [95% confidence interval (CI): 44.2–61.9] for leukemia, and 76.9% (95%CI: 66.2–84.6) for lymphoma. Patients with ALL had the lowest 5-year OS [44.0% (95%CI: 30.1–57.1)] and young adults showed a significantly lower survival than adolescents (Figure 1, 5-year OS: 28.6% vs. 63.6%, log-rank test, $p = 0.012$). The only significant survival gap in patients with hematological malignancies was ALL (Table 2 and Figure 1).

In the additional survey, answers to the questionnaire for ALL patients were obtained from 19 designated cancer care hospitals for 47 cases (94%) (Table 3). One of 20 adolescents (5.0%) and four of 27 young adults (14.8%) were Ph-positive ($p = 0.281$). Only five young adults (18.5%) were treated with pediatric treatment regimens compared with nine adolescents (45.0%) ($p = 0.05$). Fifteen adolescents (75.0%) and 26 young adults (96.0%) were treated by adult hematologists ($p = 0.069$). The proportion of clinical trial enrollment was low in both adolescents (25.0%) and young adults (22.2%). HSCT was performed in 22 young adults (81.5%) compared with nine adolescents (45.0%) ($p = 0.009$).

To explore one potential reason for the survival gap between adolescents and young adults with ALL, we applied the Cox proportional hazards model to estimate the hazard ratio of age group and treatment regimen (Table 4). We did not include the enrollment in clinical trials and use of HSCT in the multivariate model, because it was unclear which treatment regimen were used in clinical trials and patients with HSCT treatment may have caused selection bias in terms of biological prognostic factors or treatment responsibility. In univariate analysis, the group of 20- to 29-year-olds was associated with

Table 1. Characteristics of study subjects.

	All AYAs (15–29 years)		Adolescents (15–19 years)		Young adults (20–29 years)		Adolescents vs. young adults <i>p</i> value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Total patients	211	100.0	62	100.0	149	100.0	
Sex							
Female	95	45.0	27	43.5	68	45.6	0.781
Diagnosis							
Leukemia	125		44		81		0.133
ALL	50	40.0	22	50.0	28	34.6	
AML	41	32.8	13	29.5	28	34.6	
CML	26	20.8	5	11.4	21	25.9	
NOS	8	6.4	4	9.1	4	4.9	
Lymphoma	86		18		68		0.127
HL	26	30.2	5	27.8	21	30.9	
NHL	45	52.3	7	38.9	38	55.9	
NOS	15	17.5	6	33.3	9	13.2	
Medical specialists							
Pediatric oncologists	12	5.7	12	19.3	0	0.0	< 0.001
Adult hematologists	171	81.0	44	71.0	127	85.2	
Unknown/Others	28	13.3	6	9.7	22	14.8	
Hospital type (numbers)							
Children's hospital (1)	3	1.4	3	4.8	0	0.0	0.009
Cancer center (1)	30	14.2	4	6.5	26	17.5	
University hospital (5)	67	31.8	19	30.6	48	32.2	
Other hospital (26)	111	52.6	36	58.1	75	50.3	

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

Table 2. The 5-year overall survival of AYA patients with leukemia or lymphoma.

	All AYAs (15–29 years)			Adolescents (15–19 years)			Young adults (20–29 years)			Adolescents vs. young adults <i>p</i> value
	<i>n</i>	5y-OS (%)	95%CI	N	5y-OS (%)	95%CI	N	5y-OS (%)	95%CI	
Leukemia	125	53.5	44.2–61.9	44	60.7	44.6–73.5	81	49.4	37.8–60.0	0.173
ALL	50	44.0	30.1–57.1	22	63.6	40.3–79.9	28	28.6	13.5–45.6	0.012
AML	41	59.5	42.6–73.0	13	59.8	28.5–81.0	28	59.6	39.0–75.3	0.843
CML	26	73.9	50.9–87.3	5	80.0	20.4–96.9	21	72.2	45.6–87.4	0.727
Lymphoma	86	76.9	66.2–84.6	18	83.3	56.8–94.3	68	75.1	62.6–83.9	0.547
HL	26	100.0	–	5	100.0	–	21	100	–	–
NHL	45	65.2	49.0–77.3	7	71.4	25.8–92.0	38	64.0	46.2–77.3	0.832

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; 5y-OS, 5-year overall survival; CI, confidence interval.

significantly increased risk of death within 5 years in comparison with 15- to 19-year-olds (hazard ratio [HR] 3.40). After the adjustment for treatment regimen, HR in the 20–29 year age group (compared with the 15–19 group) decreased to 2.79, but remained statistically significant ($p=0.03$). The use of treatment regimens other than pediatric was also associated with increased risk of death in comparison with the use of pediatric regimens that was statistically significant in the univariate analysis (HR 3.03, $p<0.05$) but not after the adjustment (HR 2.24, $p=0.15$).

Discussion

In this study, we found that AYAs with ALL had the worst 5-year survival rate (44.0%) among the hematologic malignancies and that there was a significant survival gap between adolescents and young adults (63.6% vs.

28.6%, $p=0.01$). These survival rates are quite lower than that of children (0–14 years) with ALL [5-year OS is 86.3% (95%CI: 80.1–90.7) in 2001–2005, data from OCR]. The poor prognosis of ALL in young adults compared to adolescents may be associated with several factors, including complex pathways to diagnosis, differences in biological characteristics, effect of place of care, treatment regimens, and lower rate of participation in clinical trials.[17,18]

Regarding biological differences, young adults with ALL are reported to have a higher proportion of poor prognostic features, including t(9;22) translocation, hypodiploidy, T-cell immunophenotype, iAMP21, deletion of IKZF1, and Philadelphia chromosome-like ALL, and they are less likely to have favorable hyperdiploidy or t(12;21) translocation, than children and adolescents ALL.[19–22] In our study, only one adolescent and four young adults had Ph-positive ALL. It is unlikely that

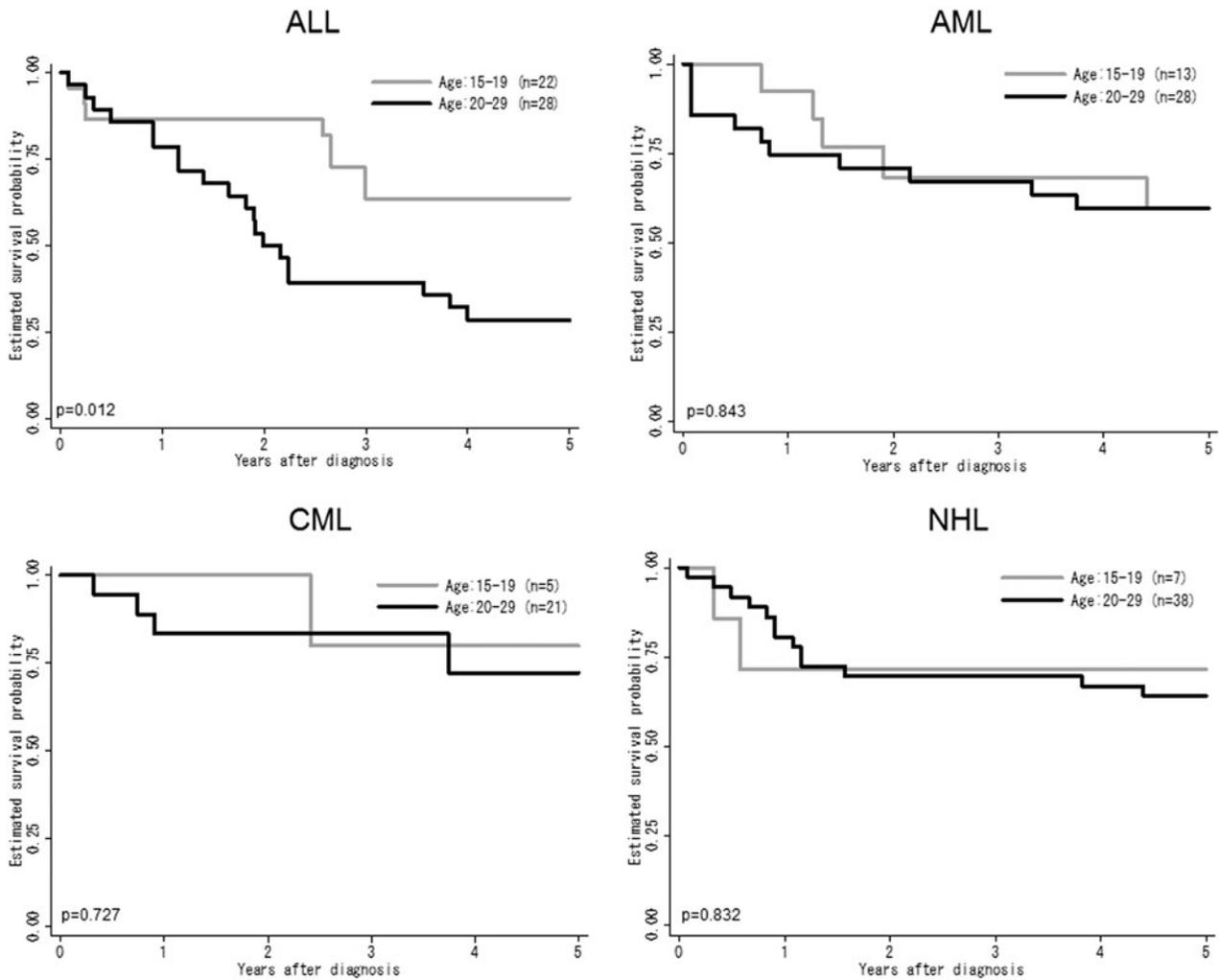


Figure 1. Kaplan-Meier estimates of survival for adolescents and young adults with hematological malignancies, Osaka, 2001–2005. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma.

Table 3. Clinical details of AYA patients with acute lymphoblastic leukemia.

	All AYAs (15–29 years)		Adolescents (15–19 years)		Young adults (20–29 years)		Adolescents vs. young adults <i>p</i> value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Total patients	47	100.0	20	100.0	27	100.0	
Philadelphia chromosome							
Positive	5	10.6	1	5.0	4	14.8	0.281
Negative/Unknown	42	89.4	19	95.0	23	85.2	
Treatment regimen							
Pediatric	14	29.8	9	45.0	5	18.5	0.050
Other than pediatric	33	70.2	11	55.0	22	81.5	
Medical specialists							
Pediatric oncologists	3	6.4	3	15.0	0	0.0	0.069
Adult hematologists	41	87.2	15	75.0	26	96.3	
Unknown/Others	3	6.4	2	10.0	1	3.7	
Clinical trial enrollment							
Enrolled	11	23.4	5	25.0	6	22.2	0.824
Not enrolled	36	76.6	15	75.0	21	77.8	
HSCT							
Treated	31	66.0	9	45.0	22	81.5	0.009
Not treated	16	34.0	11	55.0	5	18.5	

HSCT, hematopoietic stem cell transplantation.

Table 4. Prognostic factors associated with death in AYA patients with acute lymphoblastic leukemia.

	Univariate analysis			Multivariate analysis		
	HR	95%CI	p value	HR	95%CI	p value
Age						
15–19 years	1			1		
20–29 years	3.40	1.35–8.58	0.009	2.79	1.08–7.23	0.034
Treatment regimen						
Pediatric	1			1		
Other than pediatric	3.03	1.04–8.85	0.042	2.24	0.74–6.73	0.152

HR, Hazard ratio; CI, confidence interval.

having Ph is the only factor leading to discrepant outcomes in this population, but other detailed information on biology was not available.

As for difference in treatment regimens, most pediatric treatment regimens deliver higher doses of corticosteroids, vincristine, and asparaginase, and more doses of intrathecal methotrexate, and lower doses of daunorubicin, cytarabine, and etoposide than conventional adult treatment regimens.[3,12] Also, a commonly used adult treatment regimen requires more hospitalization time and is associated with fewer acute toxicities and a significantly greater potential for adverse late effects.[3] Although AYAs showed a survival advantage due to treatment on pediatric regimens, it is not clear if young adults of more than 20 years benefit from pediatric treatment regimens because most studies excluded patients above this age.[12] While our study showed that the HR for mortality decreased from 3.0 to 2.2 after adjusting for age, the risk was still more than two times greater for patients treated with other than pediatric regimen. Further investigation is needed to clarify the effect of treatment regimen on the mortality of young adults, but the HR difference is consistent with that previously reported.[13] The fact that only 4 of the 27 young adult ALL patients had Ph-positive disease underscores the need for better ALL therapy. Also, the fact that 15 of the 20 adolescents with ALL were treated by adult-treating hematologists suggests that it was the treatment and not the treaters that accounts for the survival difference.

As for the effects of HSCT, most of the young adults received HSCT, but its role in AYAs has not been clearly defined [23,24] and HSCT treatment may have caused selection bias in terms of disease status. Therefore, we did not assess their contribution to the survival differences.

The proportion of clinical trial enrollment was low both in adolescents and young adults (25% and 22%) but higher than reported in North America and Europe.[25,26] One reason for the low proportion of young adults treated on clinical trials is the upper age limit of available clinical trials with a pediatric treatment

regimen, which in most cases was between 20 and 24 years,[5,7,11] and in some cases 14–17 years.[6,27] In 2000, the U.S. Children's Oncology Group and the National Cancer Institute launched the Adolescent and Young Adult Initiative.[28] As part of their strategy, they increased the upper age limit for pediatric clinical trials to allow inclusion of older individuals, in some cases up to the age of 50 years.[29] In the UK, the inclusion of young patients with cancer in high-quality randomized trials is embedded in health-care service provision. A systematic analysis of clinical trial enrollment of patients aged 15–24 with cancer in Great Britain showed that their participation rate in clinical trials increased from 18% in 2005 to 26% in 2010.[20]

Since 1974, the Japanese government has subsidized medical expenses for children and adolescents under 18 years of age with cancer and the policy has achieved significant results.[30] However, young adults over 18 years of age diagnosed with cancer do not have additional government assistance. Although it is difficult to clarify the influence of this financial factor on survival, the conventional age limits for governmental financial aid may have to be reviewed because these young adults encounter many psychosocial problems such as school attendance, starting a career or family, or sometimes caring for aging parents, which compromise their treatment adherence.[31,32]

As for effects of place of care, the importance of centralizing AYAs with cancer to specialized cancer centers has been emphasized to improve their clinical trial enrollment and provide appropriate care in the UK and the US.[18,32] Our study did not collect sufficient information about these variables to assess their contribution to the survival differences that we observed.

In our study, there was no survival difference in AML between adolescents and young adults (Figure 1). This lack of difference may reflect a recent general consensus in treatment approach across the age range and less biological heterogeneity.[4,33] Although the better outcomes with pediatric therapy than adult therapy were reported by COG, CALGB and SWOG in 16- to 21-year-olds (10-year survival of 45% ± 6% vs. 34% ± 7%),[34] there are no prospective studies to guide the choice of pediatric-like vs. adult-like treatment approach for AYAs with AML. That our young adults have had a better survival with AML than with ALL when the reverse might have been expected emphasizes the ALL deficiency.

Regarding histologic types other than ALL and AML, young adults with CML and NHL also had poorer survival than adolescents, but without statistical significance (Figure 1). Further investigation of biological or treatment detail for these malignancies may be needed.

This study included almost 80% of AYA patients with hematological malignancies observed in population-based data from OCR in 2001–2005 (220/268 cases). OCR has been operating since 1962, covering the Osaka Prefecture in Japan with its population of 8.8 million (2010 census). It confirms the vital status using linkage to the residential database and the death certificate. Although we limited our patients to those who were treated in designated cancer care hospitals, there were no differences in the distribution of sex, age, diagnosis or survival between these patients and those from OCR (data not shown).

The limitations of our study were the relatively small number of patients and the lack of clinical information such as genomic biology other than having Ph-positive disease, disease response, late complications, and cause of death. The strengths of our study were the use of population-based data with active follow-up, collection of information on diagnostic detail and treatment department, and additional investigation on treatment regimens, clinical trial enrollment and use of HSCT for patients with ALL. Although the pediatric regimen might be partly a contributory factor to the survival gap between adolescents and young adults with ALL, we did not find other factors that explained the gap. A nationwide, population-based study with more clinical information would help identify other factors that account for the survival gap.

In conclusion, survival of patients in Osaka with ALL has been significantly worse in young adults than in adolescents. To overcome this age gap, we recommend the establishment of a more appropriate cancer care system and guidelines in Japan for young adults with hematological malignancies.

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