

# Acute Lymphoblastic Leukemia in Elderly Patients: A Single Institution's Experience

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**Background/Aims:** We investigated the clinical characteristics and prognosis of elderly patients with acute lymphoblastic leukemia (ALL).

**Methods:** We reviewed the clinical data, laboratory findings, bone marrow findings, and cytogenetic analysis of elderly patients ( $\geq 60$  years) with ALL, and data of an additional 101 younger adult patients ( $< 60$  years) with ALL were reviewed for comparison.

**Results:** Twenty-six elderly patients ( $\geq 60$  years) and 101 younger adult patients ( $< 60$  years) with ALL were retrospectively enrolled. The median follow-up duration was 6.0 months (range, 0.4 to 113.2) in the elderly patients and 21.7 months (range, 1.0 to 122.7) in the adult patients. In total, 34.6% (9 patients) of the elderly patients and 24.8% (25 patients) of the adult patients had Philadelphia chromosome positive ALL. The overall complete remission (CR) rate was much higher in the younger than in the elderly patients (94.1% vs. 57.7%,  $p < 0.001$ ). The median overall survival (OS) of the younger patients ( $< 60$  years) was 26.3 months, whereas that of the elderly patients ( $\geq 60$  years) was 10.3 months ( $p = 0.003$ ). In the elderly patients with ALL, T cell lineage and the presence of lymphadenopathy were significant prognostic factors for OS in a univariate analysis ( $p = 0.033$  and  $0.041$ , respectively).

**Conclusions:** The outcomes of Korean elderly patients with ALL were poor, and the shorter OS was mainly due to the low CR rate. T-cell lineage and the presence of lymphadenopathy were significant prognostic factors in Korean elderly patients with ALL.

**Keywords:** Leukemia, lymphoid; Aged; Prognosis; Philadelphia chromosome

## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a disease that was thought to incurable in the past. However, ALL entered the era of cure in childhood and the era of prolonged

survival in adults due to the introduction of central nervous system treatment, hematopoietic stem-cell transplantation (HSCT), intensified post-remission therapy, and molecularly targeted therapy such as imatinib mesylate. ALL in elderly patients aged 60 years or older includes

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about 30% of ALL cases excluding pediatric patients [1,2]. The incidence of ALL in elderly patients ( $\geq 65$  years old) is 1.0 to 1.6 per 100,000 patients, which is much higher than that in patients 25-54 years old (0.6 to 0.7 per 100,000) according to the Surveillance Epidemiology and End Results study [3].

The prognosis of elderly patients with ALL is poor, perhaps due to various problems associated with older age such as poor performance status, decreased bone marrow function, and comorbidities. Previous reports demonstrated poor survival in elderly patients with ALL, with complete remission (CR) rates of 45-62%, median overall survival (OS) of 5-7 months, and 5-year survival rates of  $< 10\%$  [4,5]. Furthermore, elderly patients with ALL may not receive novel agents because most clinical trials exclude the elderly.

Although elderly patients with ALL should be considered a fragile and complex population and should be treated carefully based on clinical evidence, reports about the clinical characteristics and prognosis in elderly patients with ALL are insufficient [2,6-11]. No study has been conducted on the clinical features and prognosis of elderly patients with ALL in Korea, though a retrospective study was conducted on elderly patients with acute myelogenous leukemia (AML) [12]. The aim of this study was to investigate the clinical features and outcomes in elderly patients with ALL and to identify prognostic factors compared with younger adult patients, particularly in Korea, which is a rapidly aging society.

## METHODS

### Patients

Patients aged 60 years or more first diagnosed with ALL from January 1998 to December 2007 at Seoul National University Hospital were retrospectively enrolled. To investigate the differences according to age, we additionally enrolled younger adult patients ( $< 60$  years) diagnosed with ALL during the same period at our institution. Patients who did not undergo a bone marrow examination were excluded. The findings of bone marrow aspirates and biopsy specimens including immunophenotyping and cytogenetics as well as clinical and laboratory findings were analyzed. The diagnostic criteria were the French-American-British morphological and cytochemical classification.

Immunophenotyping was performed using flow cytometry and immunohistochemistry, and final diagnosis was classified as early pre B (CD19<sup>+</sup>, HLA-DR<sup>+</sup>, CD10<sup>+</sup>, CD22<sup>+</sup>, CD7<sup>+</sup>, cIg<sup>-</sup>, sIg<sup>-</sup>), common (CD19<sup>+</sup> or CD20<sup>+</sup>, CD10<sup>+</sup>), pre B (cIg<sup>+</sup>), B (sIg<sup>+</sup>), or T (CD7<sup>+</sup>, CD3<sup>+</sup>, CD5<sup>+</sup> or CD2<sup>+</sup>) cell subtype [13]. Karyotyping was performed in 114 patients, and the standard G-banding technique was used in cultured cells aspirated from bone marrow during metaphase. We considered the Philadelphia chromosome (Ph) as positive if it was positive in at least one of three techniques: conventional cytogenetics, fluorescence *in situ* hybridization, or polymerase chain reaction.

### Chemotherapy regimen

The most commonly used regimen for induction therapy was a VPDL regimen of vincristine (1.5 mg/m<sup>2</sup>, D1, 8, 15, and 22), prednisolone (40 mg/m<sup>2</sup> daily, D23-28 and tapering after D1-D22), daunorubicin (45 mg/m<sup>2</sup>, D1-3), L-asparaginase (6000 units/m<sup>2</sup>, D12-21), and a VPD regimen of vincristine (2 mg, D1 and 8), prednisolone (60 mg/m<sup>2</sup>/day, D1-14), daunorubicin (90 mg/m<sup>2</sup>, D1-3) in elderly patients with ALL. The VPD regimen plus imatinib mesylate (600 mg daily) was used in Ph-positive ALL cases after 2002. Post-remission treatment was also analyzed. The VP regimen (vincristine 1.5 mg/m<sup>2</sup> D1 and prednisolone 40 mg/m<sup>2</sup> D1-5) was used in five elderly patients, and the VPD regimen was used in two elderly patients. Maintenance therapy consisted of vincristine, prednisolone, methotrexate, and 6-mercaptopurine.

### Statistics

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and STATA version 11 (Stata Corp., College Station, TX, USA). Pearson's chi-square test for categorical data and Student's *t* test for continuous data were used to compare the elderly patients and younger adult patients.

CR was defined as  $< 5\%$  blasts in bone marrow aspirates. OS was defined as the time from initial diagnosis to death or last follow-up. Leukemia-free survival (LFS) was calculated from CR to the time of relapse or death or last follow-up in those who did not relapse. Non-disease related mortality was defined as death due to graft-versus-host disease, a microbiologically proven infection, a bleeding event, or causes other than leukemia without evidence of leukemia. The datasets from younger adult and elderly

patients were used for the survival analysis. The analysis of prognostic factors for CR rate was performed using the chi-square test for the univariate analysis followed by a multiple logistic regression analysis. Cox's proportional-hazard model was used to identify the prognostic factors for OS and LFS. The survival and cumulative hazards for mortality were estimated by the Kaplan-Meier method. Factors with  $p < 0.20$  in the univariate analysis were included in the multivariate analysis, and a two-sided  $p$  value  $< 0.05$  was considered statistically significant.

### Ethics

This study protocol was reviewed and approved by the

Institutional Review Board of Seoul National University Hospital (IRB no. H-0911-052-301). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed.

## RESULTS

### Patient characteristics

In total, 127 patients with ALL were enrolled including 26 elderly patients ( $\geq 60$  years) and 101 younger adult patients ( $< 60$  years). The median follow-up durations were 6.0 months (range, 0.4 to 113.2) in the elderly patients and

**Table 1. Baseline patient characteristics**

	Adult ALL ( $< 60$ yr, n = 101)	Elderly ALL ( $\geq 60$ yr, n = 26)	<i>p</i> value
Age, yr	30 (15-58)	65 (60-82)	
Male gender	65 (64.4)	17 (65.4)	0.92
Initial findings			
Lymphadenopathy	17 (16.8)	4 (15.4)	1.00
Hepatosplenomegaly	15 (14.9)	1 (3.8)	0.19
Mediastinal mass	6 (5.9)	1 (3.8)	1.00
Weight loss	12 (11.9)	1 (3.8)	0.30
CNS involvement	2 (2.0)	0	1.00
Bleeding	8 (7.9)	0	0.21
Fever	22 (21.8)	3 (11.5)	0.24
History of Malignancy	2 (2.0)	6 (23.1)	0.001
Immunophenotyping			
Unknown	5 (5.0)	1 (3.8)	
T-cell lineage	14 (13.9)	5 (19.2)	0.82
B-cell lineage	82 (81.2)	20 (76.9)	0.82
Early pre B	9 (9.4)	5 (20.0)	
Common B	56 (58.3)	5 (20.0)	
Pre B	11 (11.5)	8 (32.0)	
B	6 (6.3)	2 (8.0)	
Chromosomal abnormalities	51 (50.5)	14 (53.8)	0.80
Unknown	17 (16.8)	3 (11.5)	
Philadelphia chromosome	25 (24.8)	9 (34.6)	0.34
Unknown	2 (2.0)	0	
WBC, / $\mu$ L	12,900 (500-415,000)	7,520 (700-181,200)	0.93 <sup>a</sup>
Hb, g/dL	8.6 (3.9-14.7)	9.6 (5.9-13.1)	0.023 <sup>a</sup>
LDH, IU/L	560 (126-20110)	422 (149-7180)	0.93 <sup>a</sup>

Values are presented as median (range) or number (%).

ALL, acute lymphoblastic leukemia; WBC, white blood cell; Hb, hemoglobin; LDH, lactate dehydrogenase.

<sup>a</sup>Independent *t* test.

21.7 months (range, 1.0 to 122.7) in the younger patients. The median age of the younger patients with ALL was 30 years (range, 15 to 58), whereas that of the elderly patients with ALL was 65 years (range, 60 to 82). No significant differences in the baseline characteristics of the two groups were observed, except in history of malignancy; a larger portion of elderly patients with ALL had a history of malignancy ( $p = 0.001$ ). The composition of ALL subtypes and the frequencies of Ph status were not statistically significant between the two groups. The peripheral blood sample laboratory findings showed more severe anemia

in younger adult patients with ALL than in the elderly patients ( $p = 0.023$ ) (Table 1). Of 26 elderly patients with ALL, abnormal karyotypes were found in 14 (53.8%) (Table 2).

### Induction chemotherapy and initial response

All patients, with the exception of two elderly patients who received supportive care only, received induction chemotherapy. About half of the elderly patients (12 patients, 46.2%) received the VPDL regimen as induction therapy. Five elderly patients (19.2%) were administered the VPD

**Table 2. Cytogenetics of the elderly patients with acute lymphoblastic leukemia**

Patient no	Gender/Age	Immunophenotype	Karyotype
1	M/82	T	Not Available
2	M/75	Early pre B	46,XY[17]
3	F/60	T	46,XX[18]
4	F/66	Common B	46,XX[6]
5	F/74	Early pre B	46,XX[4]
6	M/69	Common B	46,XY[14]
7	M/60	B	46,XY[2]
8	M/66	T	46,XY[13]
9	M/62	T	46,XY[20]
10	M/65	Common B	46,XX,t(9;22)(q34;q11.2)[8]
11	F/69	Unknown	46,XX,t(9;22)(q34;q11), -12, +22, der(22)t(9;22)(q34;q11)[1]/46,XX[19]
12	M/62	Early pre B	46,XY,t(9;22)(q34;q11.2)[6]/45,idm, -12, der(20)t(12;20)(q12;q11.2)[14]
13	M/63	Pre-B	46,XY,t(9;22)(q34;q11)[3]/46,idem, der(9)t(2;9)(q31;p10)[8]/46,XY[7]
14	M/62	B	46,XY,t(8;14)(q24.1;q32.1)/47,sl, +idic(1)(p13),del(17)(p10)[2]/46,XY[1]
15	M/65	Pre B	46,XY,t(8;22)(q24.1;q11),t(14;18)(q32;q21) del(18)(p11.2)[4]/47,sl,+mar[2]/46,XY[1]
16	M/66	Pre B	46,XY,t(9;22)[4]/46,XY[10]
17	F/63	Common B	44~46,XX,t(9;22)(q34;q11.2)[8]
18	M/60	Common B	44,XY,+2[2]-13[11],-20[11],der(22)t(9;22)(q34;q11.2)[11],+mar[11][cp11]
19	M/73	T	46~47, XY,del(6)(q21)[4],del(7)(q22)[5],+20[5][cp5] /46,XY[3]
20	F/67	Pre B	47,XX,t(4;11)(q21;q23),+mar[11]/48,idem,+8[3]/46,XX[2]
21	M/61	Common B	48~49,XY,+8,-20,der(?21)t(20;21)(p11.2;p11),add(22)(q13), +1~4mar[12]/46,XY[8]
22	M/78	Pre B	46, XY[4]
23	M/70	Common B	44~47,XY,+8,der(9;12)(q10;q10)t(9;22)(q34;q11.2),+19[cp3]/46,XY[3]
24	F/65	T	Not available
25	F/62	Common B	66~67,XXX,+X,+1,-2,-3,-4,-5,del(5)(q?33q?35)×2,-7,+8,+9,der(9;21)(q10;q10)×1~2,-12,-13,-15,-16,-17,+19,-20,+21,+22,+mar[22]/46,XX[3]
26	M/64	Early pre B	Not available

**Table 3. Chemotherapy and treatment outcomes**

		Adult ALL ( $< 60$ yr, $n = 101$ )	Elderly ALL ( $\geq 60$ yr, $n = 26$ )	<i>p</i> value
First Induction chemotherapy regimen	VPDL	79 (78.2)	12 (46.2)	0.001
	VPD	9 (8.9)	5 (19.2)	
	Hyper-CVAD	1 (1.0)	1 (3.8)	
	Others	11 (10.9)	6 <sup>a</sup> (23.1)	
	Supportive only		2 (7.7)	
No. of induction	1	91 (90.0)	19 (73.1)	0.007
	2	6 (5.9)	5 (19.2)	
	3	4 (4.0)	0	
Imatinib		14 (13.9)	5 (20.0)	0.54
Post-remission therapy after CR		81 (80.2)	11 <sup>b</sup> (42.3)	$< 0.001$
Cranial prophylaxis		62 (62.0)	6 (23.1)	0.001
HSCT	Conventional	31 (30.7)	0	0.001
	Non-myeloablative	9 (8.9)	2 (9.5)	
CR	CR1	88 (87.1)	13 (50.0)	$< 0.001$
	$\geq$ CR2	7 (6.9)	2 (7.7)	
Leukemia-free survival, mon		13.7 (0.3-122.5)	7.7 (0.8-112.1)	0.95
Early mortality ( $< 3$ mon)		5 (5.0)	7 (26.9)	0.003
Dead		64 (63.4)	14 (53.8)	0.374
	Disease related	48 (47.5)	6 (23.1)	
	Non-disease related	16 (15.8)	10 (38.5)	

Values are presented as median (range) or number (%).

ALL, acute lymphoblastic leukemia; VPDL, vincristine/prednisolone/daunorubicin/L-asparaginase; VPD, vincristine/prednisolone/daunorubicin; CVAD, cyclophosphamide/vincristine/adriamycin/dexamethasone; CR, complete remission; HSCT, hematopoietic stem-cell transplantation.

<sup>a</sup>Two patients treated with VP (vincristine/prednisolone), two patients treated with VPDC, one patient treated with CALGB 9251 regimen, and one patient treated with R-CHOP (rituximab/cyclophosphamide/adriamycin/vincristine/prednisolone).

<sup>b</sup>Seven patients treated with VP based regimen, two patients treated with imatinib only, one patient treated with CALGB 9251 regimen, and one patient who received non-myeloablative stem cell transplantation.

regimen, and one (3.8%) was administered the hyper-CVAD (cyclophosphamide 300 mg/m<sup>2</sup>, D1-3; vincristine 2 mg D4,11; adriamycin 50 mg/m<sup>2</sup> D4; Dexamethasone 40 mg D1-4, D11-14) regimen. The overall CR rate was much higher in the younger adult patients than that in the elderly patients (94.1% vs. 57.7%,  $p < 0.001$ ). Early mortality within 3 months from the start of induction chemotherapy was remarkably higher in the elderly patients (26.9% vs. 5.0%,  $p = 0.003$ ) (Table 3).

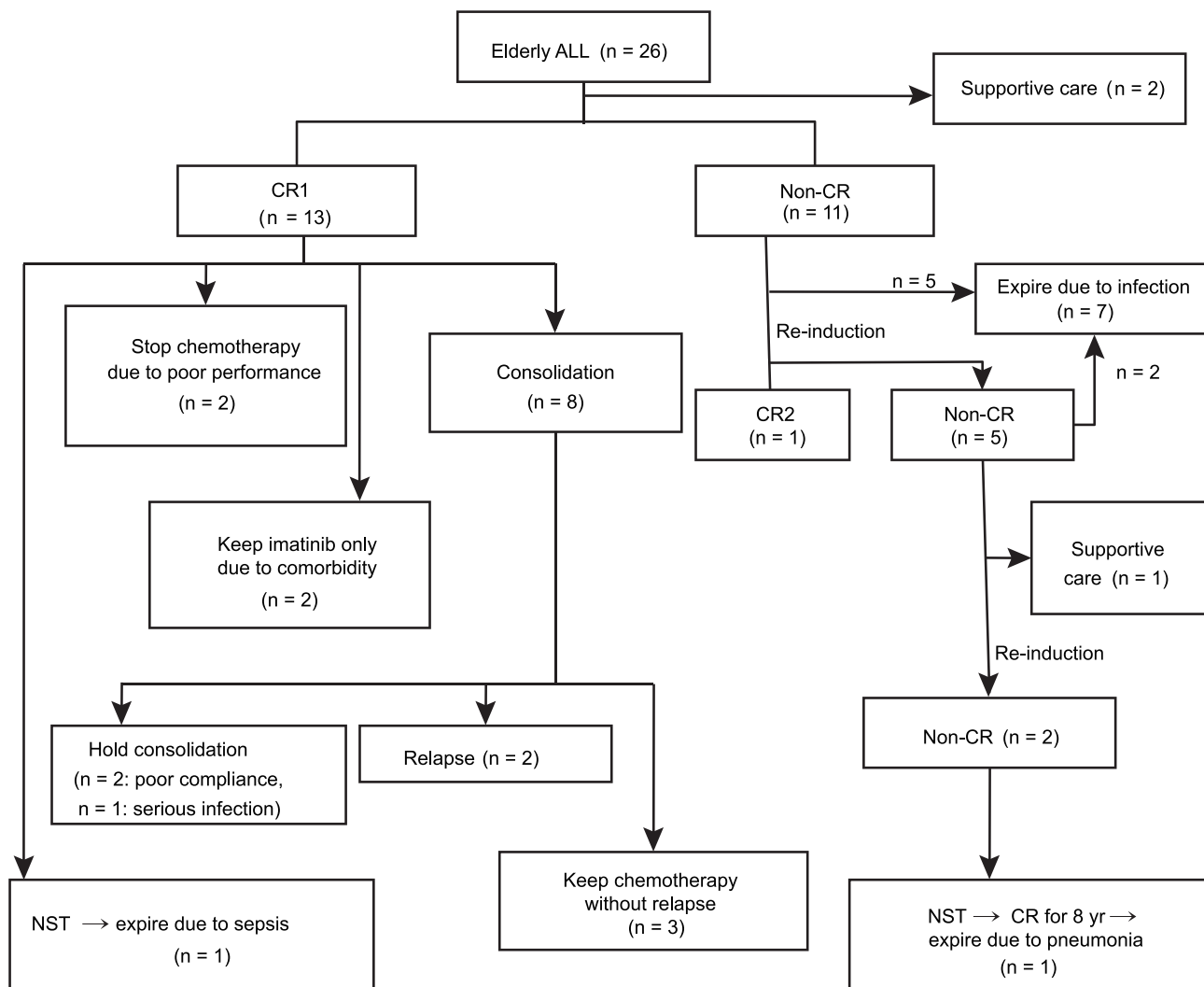
### Post-remission therapy and treatment outcomes

The median number of post-remission consolidation therapy sessions was three (range, 1 to 5) in the elderly patients with ALL. The regimen in the elderly patients was

vincristine and prednisolone in seven patients. Two patients received only imatinib due to severe comorbidities. One patient received the CALGB 9251 regimen, and the other patient received non-myeloablative hematopoietic stem cell transplantation (HSCT) from a matched sibling donor. Of 15 elderly patients who achieved CR, only 11 received post-remission therapy (Fig. 1). The overall non-disease-related mortality rate in the elderly patients was higher than that in the younger adult patients (Table 3, Fig. 2).

### Survival

The median OS of the younger patients was 26.3 months (95% confidence interval [CI], 19.6 to 33.0), whereas that



**Figure 1.** Treatment and outcomes of elderly patients with acute lymphoblastic leukemia (ALL). CR, complete remission; NST, non-myeloablative stem-cell transplantation.

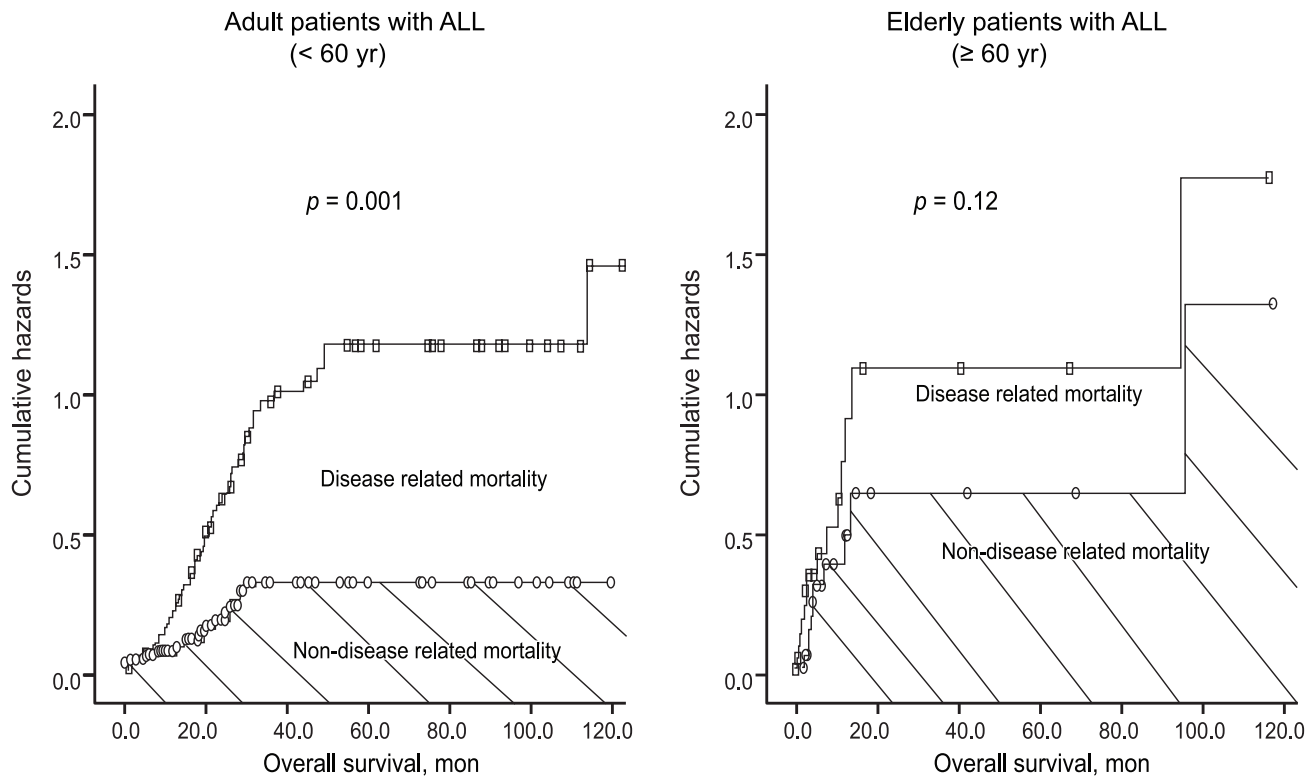
of the elderly patients was 10.3 months (95% CI, 3.5 to 17.2) ( $p = 0.003$ ) (Fig. 3A). The survival difference according to age was not reproduced in the subpopulation of patients with Ph-positive ALL (data not shown), but was consistently found in the patients with Ph-negative ALL (Fig. 3B).

### Survival analysis for elderly patients with ALL

Among the elderly patients, the patients who achieved CR1 (CR after the first induction chemotherapy) showed significantly longer survival compared with those who did not achieve CR1 (median OS, 13.1 months vs. 2.6 months;  $p = 0.001$ ) (Fig. 3C). Furthermore, CR1 was the only independent prognostic factor for OS in elderly patients

with ALL ( $p = 0.001$ ) (data not shown). Although the OS of elderly patients aged 60 to 69 tended to be longer than that of those aged 70 or over, the difference did not reach statistical significance (median OS, 11.2 months vs. 3.7 months;  $p = 0.073$ ) (Fig. 3D).

In the survival analysis using the factors at the initial ALL diagnosis, the probable poor prognostic factors for CR were age  $\geq 70$  years (relative rate of remission [RR], 0.14; 95% CI, 0.013 to 1.45;  $p = 0.098$ ) and leukocytosis ( $\geq 30,000/\mu\text{L}$ ) (RR, 6.00; 95% CI, 0.93 to 38.63;  $p = 0.059$ ). T-cell lineage and the presence of lymphadenopathy were significant factors in poor prognosis for OS in the univariate analysis (hazard ratio [HR], 3.11 and 3.14; 95% CI, 1.14 to 9.34 and 1.01 to 9.99;  $p = 0.033$  and 0.041, respectively).



**Figure 2.** Cumulative hazards of disease related and non-disease-related mortality in younger adult patients (< 60 yr) with acute lymphoblastic leukemia (ALL) and in elderly patients (≥ 60 yr) with ALL ( $p = 0.001$  and  $0.12$ , respectively).

T-cell lineage and Ph-positive status tended to increase the HR for LFS (HR, 8.49 and 4.49; 95% CI, 0.53 to 135.82 and 0.8 to 25.21;  $p = 0.069$  and  $0.064$ , respectively) (Table 4).

### Survival analysis for younger adult patients with ALL

Of 101 younger patients with ALL, 95 (94.1%) achieved CR (Table 3). The remission rate decreased in the younger adult patients with the T-cell lineage (RR, 0.14; 95% CI, 0.025 to 0.78;  $p = 0.025$ ). Leukocytosis ( $\geq 30,000/\mu\text{L}$ ) and Ph status were independent prognostic factors for OS (HR, 1.89 and 1.97; 95% CI, 1.15 to 3.12 and 1.13 to 3.45;  $p = 0.012$  and  $0.017$ , respectively). Leukocytosis was also an independent prognostic factor for LFS (HR, 1.85; 95% CI, 1.09 to 3.13;  $p = 0.022$ ). However, Ph was not a significant predictive factor for LFS ( $p = 0.055$ ) (Tables 5 and 6).

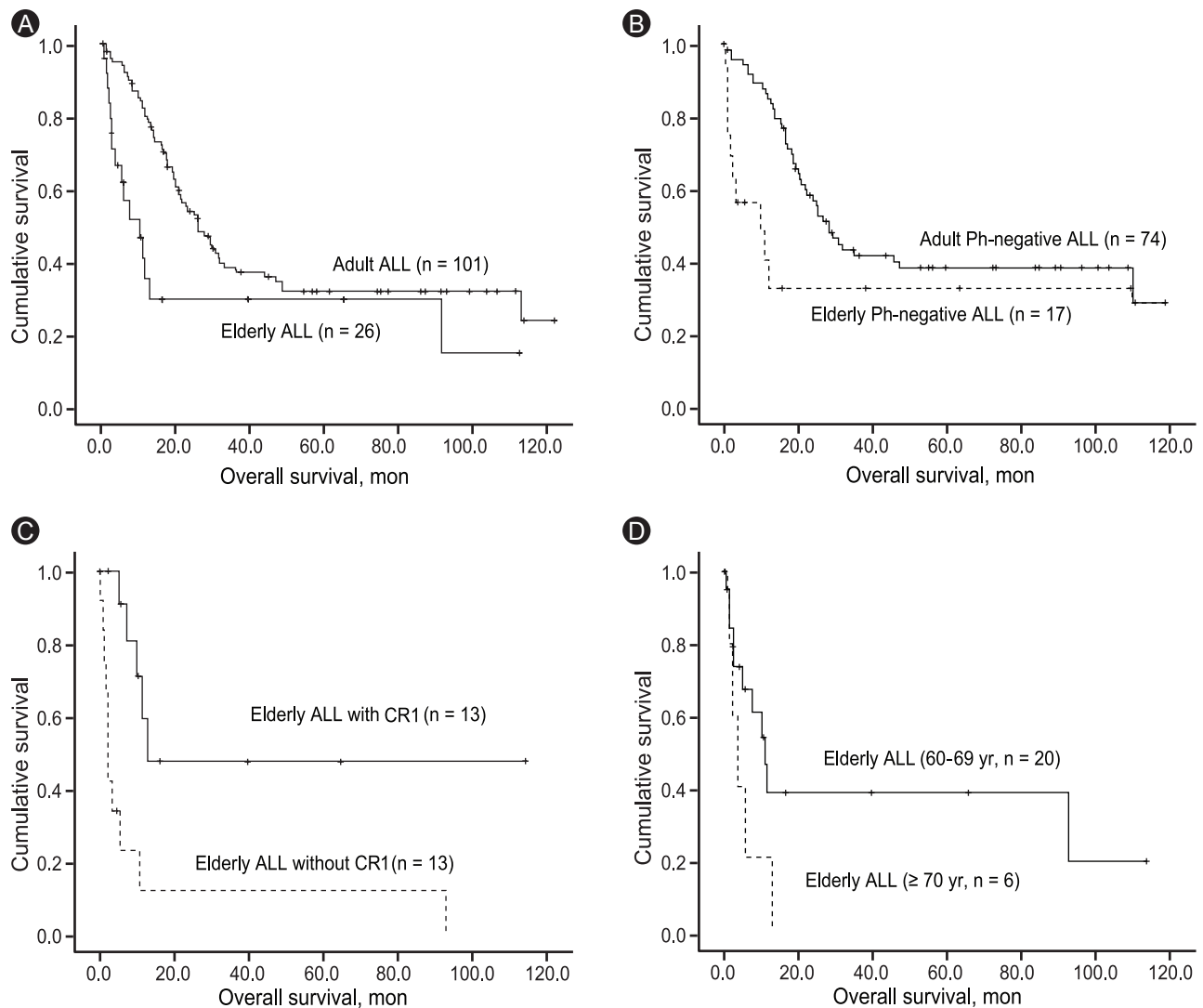
## DISCUSSION

We demonstrated that poor outcomes among Korean el-

derly patients with ALL were associated a low CR rate and poor treatment compliance. The trend toward decreased OS was more profound in patients aged > 70 years than in those aged 60-69 years. Our result also showed that the prognostic factors in the elderly patients with ALL were somewhat different from those in the younger adult patients with ALL. The prognostic factors for OS were T-cell lineage and lymphadenopathy in the elderly patients with ALL, whereas the significant factors for OS were Ph and leukocytosis in adult patients with ALL.

A previous study showed that CR was an important prognostic factor in Korean elderly patients with AML [12].

The low response to chemotherapy in the elderly patients with ALL could be related to several factors. The first factor may be chemotherapy intensity. Intensified combination induction chemotherapy can result in an improvement in the CR proportion, and high dose post-remission methotrexate (MTX) or cytarabine therapy are effective for treating adult ALL [14-16]. However, most elderly patients with ALL in our study could not receive the post-remission therapy after the induction therapy with a standard or reduced dose and also could not be



**Figure 3.** (A) Overall survival (OS) of elderly and younger adult patients with acute lymphoblastic leukemia (ALL). OS of elderly patients with ALL ( $\geq 60$  yr) was shorter than that of younger adult patients with ALL ( $< 60$  yr) (median OS 10.3 mon vs. 26.3 mon, respectively,  $p = 0.003$ ). (B) OS of the elderly and younger adult patients with Philadelphia chromosome (Ph)-negative ALL. OS of the elderly patients with Ph-negative ALL ( $\geq 60$  yr) was shorter than that of adult patients with Ph-negative ALL ( $< 60$  yr) (median OS, 10.3 mon vs. 29.2 mon, respectively,  $p = 0.01$ ). (C) OS according to complete remission in elderly patients with ALL. OS of elderly patients with complete remission was longer than that of elderly patients without complete remission (median OS, 13.1 mon vs. 2.6 mon,  $p = 0.001$ ) (D) OS according to age (60-69 yr vs.  $\geq 70$  yr) in elderly patients with ALL. OS of elderly patients aged 70 years or more was not significantly different from that of the other elderly patients (median OS, 11.2 mon vs. 3.7 mon,  $p = 0.073$ ).

treated with intensified post-remission regimens such as cyclophosphamide or MTX, though they received post-remission therapy. The second factor may be drug resistance mechanisms such as the presence of multidrug resistance gene 1 and multidrug resistance-related protein. The expression of drug resistance is frequent in patients with ALL after induction chemotherapy [17], and it is possible that the expression would be greater in elderly patients with ALL, if the case is analogous to that for AML [18].

Although intensified induction chemotherapy was not introduced, and post-remission therapy was not performed appropriately in most elderly patients with ALL, the survival benefit was definite in the patients who achieved CR. Our study did not show a statistical difference in non-disease-related mortality rates between the elderly and younger adult groups. However, the actual risk of non-disease-related mortality might be significantly higher in the elderly patients considering that only a few patients could receive highly toxic therapy such as HSCT, and our



**Table 4. Univariate analysis for complete remission, overall survival, and leukemia-free survival in elderly patients with ALL ( $\geq 60$  yr) (n = 26)**

	Complete remission			Overall survival			Leukemia-free survival		
	RR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Age $\geq 70$	0.14	0.013-1.45	0.098	2.60	0.88-7.67	0.073	4.48	0.41-49.46	0.18
T-cell lineage	0.22	0.019-2.53	0.23	3.11	1.14-9.34	0.033	8.49	0.53-135.82	0.069
Ph(+)	3.38	0.52-21.73	0.20	1.11	0.40-3.12	0.84	4.49	0.8-25.21	0.064
Lymph adenopathy	0.21	0.018-2.33	0.20	3.14	1.01-9.99	0.041	4.48	0.41-49.46	0.18
Male	0.50	0.09-2.73	0.42	1.80	0.57-5.64	0.31	1.13	0.20-6.26	0.89
Fever	1.67	0.13-21.20	0.69	0.84	0.19-3.72	0.82	0.033	0.00-253.78	0.22
WBC $\geq 30,000/\mu\text{L}$	6.00	0.93-38.63	0.059	0.50	0.17-1.46	0.19	0.99	0.17-5.98	0.99

ALL, acute lymphoblastic leukemia; RR, relative rate of remission; CI, confidence interval; HR, hazard ratio; Ph, Philadelphia chromosome; WBC, white blood cell.

**Table 5. Univariate analysis for complete remission, overall survival, and leukemia-free survival in younger adult patients ( $< 60$  yr) with ALL (n = 101)**

	Complete remission			Overall survival			Leukemia-free survival		
	RR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Male	0.90	0.16-5.15	0.90	1.52	0.91-2.56	0.11	1.31	0.79-2.20	0.30
T-cell lineage	0.14	0.025-0.78	0.025	1.27	0.65-2.50	0.49	1.73	0.85-3.53	0.13
Ph(+) <sup>a</sup>				2.15	1.25-3.72	0.006	1.65	0.93-2.91	0.087
Lymph adenopathy	0.38	0.063-2.23	0.28	1.50	0.78-2.88	0.22	1.04	0.49-2.18	0.93
Fever	0.53	0.091-3.12	0.49	0.90	0.50-1.64	0.73	0.64	0.34-1.24	0.19
Hepatosplenomegaly <sup>a</sup>				0.75	0.35-1.57	0.44	0.72	0.34-1.52	0.39
WBC $\geq 30,000/\mu\text{L}$	1.12	0.19-6.41	0.90	1.86	1.13-3.04	0.014	1.75	1.06-2.89	0.028

ALL, acute lymphoblastic leukemia; RR, relative rate of remission; CI, confidence interval; HR, hazard ratio; Ph, Philadelphia chromosome; WBC, white blood cell.

<sup>a</sup>Could not calculate RR due to the existence of a cell with a count of "0".

results indicated that about half (43.8%) of non-disease-related mortality was related to HSCT in the younger adult patients with ALL.

Our results also showed that the significant prognostic factors in elderly patients with ALL were different from those in younger patients with ALL. T-cell lineage and lymphadenopathy were significant prognostic factors in the elderly patients with ALL, whereas the Ph and leukocytosis were independent prognostic factors in younger adult patients with ALL.

While T-cell lineage ALL is less frequent in elderly patients according to previous studies [2,6,8,11,19], our results showed that T-cell lineage ALL was more frequent in elderly patients. A few studies have reported that pre-B and common B subtypes of ALL are relatively common in elderly patients with ALL [7,19], which was different from

our results. We observed only a small number of B-cell lineage diseases (particularly common B subtype) in Korean elderly patients with ALL.

Our results showed that T-cell lineage was associated with poor survival in elderly patients with ALL (HR for OS, 3.11), which is inconsistent with a previous report showing that T-cell lineage was a positive prognostic factor [20].

Several studies have shown that old age itself is an independent poor prognostic factor in patients with ALL [4,5]. Most studies consider 60 years of age or over as elderly, as in our study [4,10,21,22], but some researchers used different criteria such as 55 or 65 years [1,6]. It is unclear which age criterion appropriately reflects the clinical characteristics of elderly patients. Some evidence suggests that no cutoff point has been identified for the age that best predicts clinical outcomes in elderly patients with

**Table 6. Multivariate analysis for complete remission, overall survival, and leukemia-free survival in adult patients with ALL (< 60 yr) (n = 101)**

	Overall survival			Leukemia-free survival		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Male	1.53	0.89-2.61	0.12	-	-	-
T-cell lineage	-	-	-	1.53	0.74-3.15	0.25
Ph(+)	1.97	1.13-3.45	0.017	1.78	0.99-3.20	0.055
Fever	-	-	-	0.60	0.30-1.20	0.15
WBC ≥ 30,000/μL	1.89	1.15-3.12	0.012	1.85	1.09-3.13	0.022

ALL, acute lymphoblastic leukemia; HR, hazard ratio; CI, confidence interval; Ph, Philadelphia chromosome; WBC, white blood cell.

ALL. Robak et al. [5] showed that clinical outcomes were worse in elderly patients aged 70 years or older compared with those less than 70 years of age, which was consistent with our results.

The Ph-positive status increases with age in patients with ALL [9,23,24], and Ph-positive status was a poor prognostic factor in the pre-imatinib era [25,26]. Ph-positive status is still thought to be an independent poor prognostic factor for survival rather than remission despite the introduction of imatinib for the treatment of Ph-positive ALL [27]. Ph status was an independent prognostic factor for OS in the pooled population as a whole in our study (data not shown), which was consistent with a previous report on a Chinese population [24]. The rate of positive Ph was 34.6% in the elderly patients in our study, which was similar to that in previous studies (26-50%) [28,29].

Population aging is prominent in Asian countries, particularly Korea. According to 2006 data from the Korean National Statistics Office, the proportion of persons aged 65 and older in Korea was 7.9% in 2002 and is expected to climb to 14.4% in 2014, which reflects the most rapid change in population composition in the world [30]. However, no study has been performed on Korean elderly patients with ALL to prepare for the super-aged society in the near future, although a retrospective study has been conducted about elderly patients with AML [12]

Some limitations of this study should be noted. First, the small number of elderly patients enrolled in our study made our results descriptive rather than statistical. Second, the heterogeneity of induction and post-remission therapy due to the nature of a retrospective study was an obstacle to collecting data about the prognostic factors for clinical outcomes. Third, the definition of non-disease-

related mortality is an arguable problem in patients who had died due to infection and cytopenia after induction chemotherapy but did not achieve CR. The definition of non-disease-related mortality is not only disputable in the field of oncology [31] but is also uncertain in the field of hematology.

These factors not only show the limitations of our study but also reflect the difficulties when studying elderly patients with ALL. Despite these limitations, our study is one of the first about Asian elderly patients with ALL. Further well-designed large prospective studies are required to better understand the clinical features and outcomes in Korean elderly patients with ALL.

### Conflict of interest

No potential conflict of interest relevant to this article was reported.

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