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울산대학교 의과대학 서울아산병원 소아과학교실

Outcome and Prognostic Factors in Pediatric Precursor T-Cell Acute Lymphoblastic Leukemia: A Single-Center Experience

Eun Sang Rhee, M.D., Hyery Kim, M.D., Sung-Han Kang, M.D., Jae Won Yoo, M.D., Kyung-Nam Koh, M.D., Ph.D., Ho Joon Im, M.D., Ph.D. and Jong Jin Seo, M.D., Ph.D.

Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Background: Precursor T-cell acute lymphoblastic leukemia (T-ALL) has worse prognosis than B-cell ALL. We aimed to evaluate prognostic variables in pediatric T-ALL.

Methods: Medical records of 36 T-ALL patients (27 males and 9 females; median age at diagnosis, 10.6 years) diagnosed and treated at Asan Medical Center from 2001 to 2017 were reviewed. Six patients (16.7%) had early T-cell precursor ALL (ETP-ALL). Most patients received the Children's Cancer Group-1882 (CCG1882) or Korean multicenter high risk ALL (ALL0601) protocols and prophylactic cranial irradiation. Clinical features at presentation, response to therapy, and treatment outcomes were analyzed.

Results: The six patients with ETP-ALL and 17 of 30 with non-ETP-ALL received CCG1882 or ALL0601 chemotherapy. Three patients, including two with ETP-ALL, did not achieve complete remission after induction. Rapid early response during induction was achieved by 26 patients. Five year overall survival (OS) and event free survival (EFS) rates were 71.4% and 70.2%, respectively. ETP-ALL and slow early response during induction were significant adverse prognostic factors, while hyperleukocytosis at diagnosis was not. CCG1882/ALL0601 chemotherapy resulted in superior survival (OS: 78.9%, EFS: 73.3%) compared with CCG1901 chemotherapy (OS: 64.3%, EFS: 64.3%), and patients undergoing prophylactic cranial irradiation had superior EFS to non-radiated patients.

Conclusion: A high risk ALL protocol with intensified post-remission therapy, including prophylactic cranial irradiation, conferred T-ALL survival outcomes comparable with those of Western studies. Further treatment intensification should be considered for patients with ETP-ALL and slow induction responders. Additionally, CNS-directed treatment intensification, without prophylactic cranial irradiation, is needed.

Key Words: Acute lymphoblastic leukemia, Pediatric, Precursor T-cell lymphoblastic leukemia-lymphoma, Survival

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Corresponding Author: Hyery Kim
Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, 88-1 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3373
Fax: +82-2-473-3725
E-mail: taban@hanmail.net
ORCID ID: orcid.org/0000-0003-2852-6832

Introduction

Precursor T-cell acute lymphoblastic leukemia (T-ALL) has been associated with a worse prognosis than other forms of childhood ALL [1,2]. Over recent years, the introduction of intensive, high-dose, multi-agent pulse chemotherapy has improved event free survival (EFS) rates for patients with T-ALL from 15-20% to 50-85%. The outcomes for T-ALL are now reported as comparable to those of children with high risk B-cell ALL (B-ALL) [3-5].

Despite these significant advances, EFS for T-ALL in current trials has plateaued in the range 70-75% [6,7]. In addition, relapsed T-ALL has a dismal prognosis, with reported 3 year EFS rates of <15% [8]. These patients are extremely difficult to salvage, as most have chemotherapy-refractory disease. In this regard, prognostic factors and optimal indications for treatment intensification, including hematopoietic stem cell transplantation (HSCT), in patients with T-ALL require elucidation.

Early T-cell precursor ALL (ETP-ALL) is a recently identified type of T-ALL that may have poor prognosis [9]. ETP-ALL is defined by a unique immunophenotype, expressing T-lineage and myeloid/early progenitor markers, and was initially reported as having distinctive gene expression and cell marker profiles, poor response to chemotherapy, and very high risk of relapse [9-11].

Data from St. Jude Children's Research Hospital and AIEOP trials suggest that ETP-ALL patients respond poorly to current chemotherapeutic approaches [9,11]; however, more recent data from AIEOP-BFM ALL 2000 and UK ALL 2003 suggest that not all of these patients have poor outcomes [12]. AIEOP-BFM ALL 2000 demonstrated that ETP-ALL patients can be classified based on their response to chemotherapy [13]. Given these inconsistent results, the treatment strategy for ETP-ALL is yet to be standardized.

The aim of this study was to determine survival outcomes and identify prognostic variables in pediatric T-ALL, including ETP-ALL, in our treatment setting by reviewing a single institution experience.

Materials and Methods

1) Patients

Children and adolescents younger than 22 years of age who were diagnosed with precursor T-ALL and treated in Asan Medical Center Children's Hospital during March 2001 to March 2017 were included. Data were reviewed retrospectively. ETP-ALL was diagnosed by immunophenotyping and characterized by lack of CD1a and CD8 expression, weak CD5 expression (<75% positive blasts), and expression of one or more of the following myeloid or stem cell antigens on at least 25% of lymphoblasts: CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65 [14]. This study was approved by the Institutional Review Board of Asan Medical Center (S2018-1398-0001).

2) Treatment protocol

Several protocols were used for treatment. During the earlier period, the Pediatric Oncology Group (POG) T-ALL protocol, POG-9404, was used, which comprised vincristine, prednisone, methotrexate (MTX), and mercaptopurine, with one dose per week for a total of 20 weeks of L-asparaginase, and doxorubicin with intrathecal (IT) chemotherapy and cranial irradiation (CRT; 18 Gy) [15]. The duration of therapy was 2 years from the date of documented complete remission (CR). Since November 2002, Children's Cancer Group (CCG)-1901, CCG-1882, or Korean multicenter study of high risk ALL-0601 protocols were used. Patients with extramedullary involvement or lymphomatous features tended to receive the CCG-1901 protocol. The CCG-1882 protocol consisted of the Augmented Berlin-Frankfurt-Münster (BFM) regimen, which employed longer and stronger post-induction intensification [16]. The CCG-1901 protocol was administered as previously reported [17]. Induction phases consisted of five drugs (vincristine, prednisone, L-asparaginase, daunorubicin, and cyclophosphamide). Initial consolidation comprised six-agent chemotherapy combined with 18 Gy of total-brain irradiation. The Korean multicenter study-0601 protocol was designed based on the CCG-1882 protocol (Table 1). After the standard four-drug induction, patients received double interim

Table 1. Details of the Korean multicenter study of high risk acute lymphoblastic leukemia-0601

Phase and drug	Dose	Schedule
Induction, 5 wk		
IT cytarabine	Age-adjusted[a]	Day 0
Vincristine	1.5 mg/m^2 (2 mg max)	Day 0, 7, 14, 21
L-Asparaginase (*Erwinia*)	6,000 U/m^2 (6,000 U/m^2)	9 doses
Daunomycin	25 mg/m^2/d	Day 0, 7, 14, 21
Prednisolone	60 mg/m^2/d	Days 0-27
IT methotrexate	Age-adjusted[b]	Day 7, 28 (add day 14, 28 when CNS2 or CNS3)
Consolidation, 5 wk		
Prednisolone	Taper	Days 0-14
Cyclophosphamide	1,000 mg/m^2	Day 0, 28
Mercaptopurine	50 mg/m^2/d	Days 0-13, 28-41
Cytarabine	75 mg/m^2/d	Days 1-4, 8-11, 15-18, 22-25
Vincristine	1.5 mg/m^2 (2 mg max)	Day 14, 21, 42, 49
L-Asparaginase (*Erwinia*)	6,000 U/m^2 (6,000 U/m^2)	Day 14, 16, 18, 21, 23, 25, 42, 44, 46, 49, 51, 53
IT methotrexate	Age-adjusted[b]	Day 0, 7, 14, 21
1st Interim maintenance (IM), 8 wk		
Vincristine	1.5 mg/m^2 (2 mg max)	Day 0, 10, 20, 30, 40
Methotrexate	100 mg/m^2/dose (initial)	Day 0, 10, 20, 30, 40 escalate by 50 mg/m^2/dose to toxicity
L-Asparaginase (*Erwinia*)	15,000 U/m^2 (25,000 U/m^2)	Day 1, 11, 21, 31, 41
Mercaptopurine	50 mg/m^2/d	Days 0-41
IT methotrexate	Age-adjusted[b]	Day 0, 20
1st Delayed intensification (DI), 7-8 wk		
Dexamethasone	10 mg/m^2/d	Days 0-6, 14-20
Vincristine	1.5 mg/m^2 (2 mg max)	Day 0, 7, 14, 42, 49
Adriamycin	25 mg/m^2/d	Day 0, 7, 14
L-Asparaginase (*Erwinia*)	6,000 U/m^2 (6,000 U/m^2)	6 doses during days 3-14, day 42, 44, 46, 49, 51, 53
Cyclophosphamide	1,000 mg/m^2	Day 28
Mercaptopurine	50 mg/m^2/d	Days 28-41
Cytarabine	75 mg/m^2/d (SQ or IV)	Days 28-31, 35-38
IT methotrexate	Age-adjusted[b]	Day 0, 28, 35
2nd IM, 8 wk	As in "1st IM"	
2nd DI, 8 wk	As in "1st DI"	Daunomycin 25 mg/m^2/d instead of doxorubicin
	SER without CNS3: Prophylactic cranial irradiation (1,200 cGy)[c]	
	CNS3: Craniospinal irradiation (Cranial: 1,800 cGy+Spinal: 6,000 cGy)	
Maintenance, 12 wk/cycle		
Vincristine	1.5 mg/m^2 (2 mg max)	Day 0, 28, 56
Prednisolone	40 mg/m^2/d	Days 0-4, 28-32, 56-60
Mercaptopurine	50 mg/m^2/d	Days 0-83
Methotrexate	20 mg/m^2/dose	Day 7, 14, 21, (28), 35, 42, 49, 56, 63, 70, 77 (omit when IT MTX)
IT methotrexate	Age-adjusted[b]	Day 0 (day 28: until RER #4)
	Patients with testicular disease:	Testicular irradiation (2,400 cGy)[d]

[a]Doses were age-adjusted as follows: age 1 to 1.9 years, 30 mg; age 2 to 2.9 years, 50 mg; age ≥3 years, 70 mg.
[b]Doses were age-adjusted as follows: age 1 to 1.9 years, 8 mg; age 2 to 2.9 years, 10 mg; age ≥3 years, 12 mg.
[c]Radiation was started from day 28 of the secondDI.
[d]Cycles of maintenance therapy were repeated until the total duration of therapy, beginning with the first interim maintenance period, reached 2 years for girls and 3 years for boys.
IV, intravenous; IT, intrathecal; SQ, subcutaneous.

maintenance (IM) and delayed intensification (DI), based on the augmented BFM regimen, and prophylactic CRT (12 Gy) was administered during the second DI phase.

Patients with central nervous system (CNS) disease at diagnosis received two additional IT MTX injections during induction, and CRT (24 Gy in 12 fractions) was ad-

ministered during the second DI. Treatment was continued for 2 years for girls and 3 years for boys, from the first IM to the final maintenance cycle.

3) Statistical analysis

The events considered were relapse at any site, induction failure, death in remission, or a second malignant neoplasm, whichever occurred first. For response evaluation during induction, patients were defined as slow early responders (SER) if the bone marrow (BM) result at 7 days of induction was M3 (BM blasts≥25%) or BM at 14 days was M2 (5%≤BM blasts<25%) or M3, and as rapid early responders (RER) otherwise. Data on patients who did not have an event at the time of analysis were censored in the analysis of EFS at the time of the last contact with them. EFS and overall survival (OS) were estimated using Kaplan-Meier analysis, and the survival differences by treatment groups and variables were analyzed by log-rank test. IBM SPSS Statistics 24.0 software was used for all statistical analyses, and statistical significance was accepted for $P<0.05$.

Results

1) Patient characteristics

A total of 36 patients were reviewed (Table 2). The median follow-up duration was 8.7 years (range, 1.3-17.6 years). Six patients were defined as ETP-ALL. Among the six patients, 2 patients showed lack of CD1a and CD8 expression, weak CD5 expression, and expressed one or more of the myeloid or stem cell antigens (CD117, CD34, HLA-DR, CD13, CD33, CD11b, and/or CD65). One patient fulfilled all the requirements listed above, except that the CD5 expression was 85.7%. Another patient lacked data for

Table 2. Characteristics of the patients (N=36)

Characteristics	Total patients (N=36)	ETP-ALL (N=6)	Non-ETP-ALL (N=30)
Age (yr), median (range)	10.6 (1.6-21.8)	12 (5.6-14.8)	10 (1.6-21.8)
Age group (yr)			
<10	17	2	15
≥10	19	4	15
Sex			
Male	27	4	23
Female	9	2	7
WBC at diagnosis (10^6/L)	24,150 (1,100-530,500)	43,700 (1,800-292,000)	24,150 (1,100-530,500)
<100,000	24	4	20
≥100,000	12	2	10
CNS involvement			
CNS1	35	6	29
CNS2	-	-	-
CNS3	1	-	1
Extramedullary bulky disease			
Not involved	3	-	3
Cervical lymphadenopathy	8	1	7
Mediastinal mass	13	2	11
Data not available	12	3	9
Cytogenetics			
14q11.2 abnormality	4	-	4
11q23 abnormality	3	1	2
Del(6q)	2	-	2
Normal	18	2	16
Hyperdiploidy	2	1	1
Others	6	2	4

ETP-ALL, early T-cell precursor acute lymphoblastic leukemia; WBC, white blood cell; CNS, central nervous system.

the myeloid or stem cell antigens but showed lack of CD1a and CD8 expression. Two patients were not tested for CD1a, however lacked CD8 expression and showed weak CD5 expression. Median age at diagnosis was 10.6 years (range, 1.6-21.8 years). There were 27 male and 9 female patients. Seventeen (47.2%) patients were at least 10 years of age, and 12 (33.3%) had white blood cell (WBC) counts of more than 100,000/μL at diagnosis. Data regarding extramedullary disease were available for 24 patients, and 21 of these 24 showed imaging evidence of extramedullary disease at diagnosis: 13 patients with mediastinal mass, and eight with cervical lymphadenopathy. Only one patient had CNS leukemia and was classified as CNS3. None of the male patients showed testicle involvement at diagnosis.

Regarding cytogenetic features, 18 patients (50%) had normal karyotype, and four (11.1%) had 14q11.2 abnormalities; 11q23 and del(6q) related abnormal karyotypes were found in three and two patients, respectively.

2) Treatment outcome

After induction, 33 patients (91.7%) reached CR, and the other three patients failed to achieve remission. Those three patients received salvage chemotherapy; however, two died of leukemia. The other patient with induction failure underwent unrelated peripheral blood stem cell transplantation (uPBSCT) after CR2, but died of *Acinetobacter baumannii* sepsis on day 38 post-PBSCT.

According to response analysis during induction of the 32 patients, excluding the three induction failures and one patient whose data were not available, 25 patients were SER, and seven were RER. Ten events, including three induction failures, occurred during a median follow-up duration of 8.7 years (range, 1.3-17.6 years). There were four relapse events in the RER group and three in the SER group: isolated BM relapse in three patients (one RER, two SER), isolated CNS relapse in three patients (two RER, one SER), and combined BM and CNS relapse in one RER patient.

Three patients died of disease and another three died of treatment related complications. The cause of treatment related mortality was sepsis during reinduction chemotherapy after relapse in two patients (one *A. baumannii*, one *Candida*), and after uPBSCT in one (*A. baumannii*). There were no secondary malignancies.

In survival analysis, the estimated 5 year OS rate was 71.4±8.4%, and the EFS rate was 70.2±8.0%, for all patients (Fig. 1). Analysis by response during induction demonstrated that the OS of 57.1±18.7% in the SER group was significantly lower than that (83.9±8.8%) in the RER group (P=0.017, Fig. 2A). EFS rates for RER and SER patients were 81.8±8.3% and 57.1±18.7%, respectively, and there was no significant difference between the two groups (P=0.078, Fig. 2B).

OS and EFS were analyzed for patients with ETP-ALL and

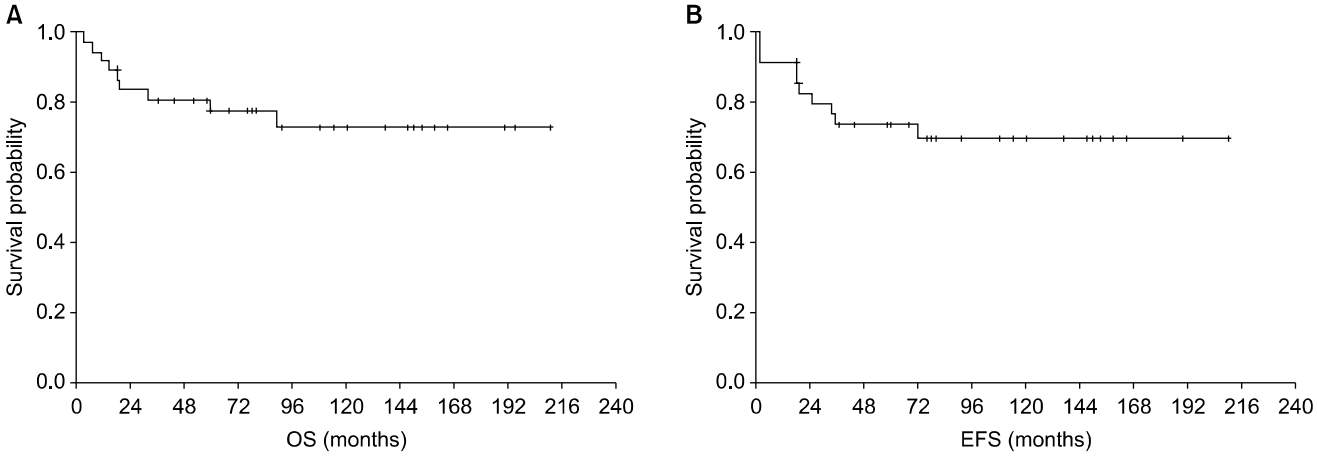

Fig. 1. Overall survival (OS) and event free survival (EFS) rates (N=33). Three of the total 36 patients were not included due to loss of follow up. (A) The estimated 5 year overall survival rate was 71.4±8.4%, and (B) the event free survival rate was 70.2±8.0%.

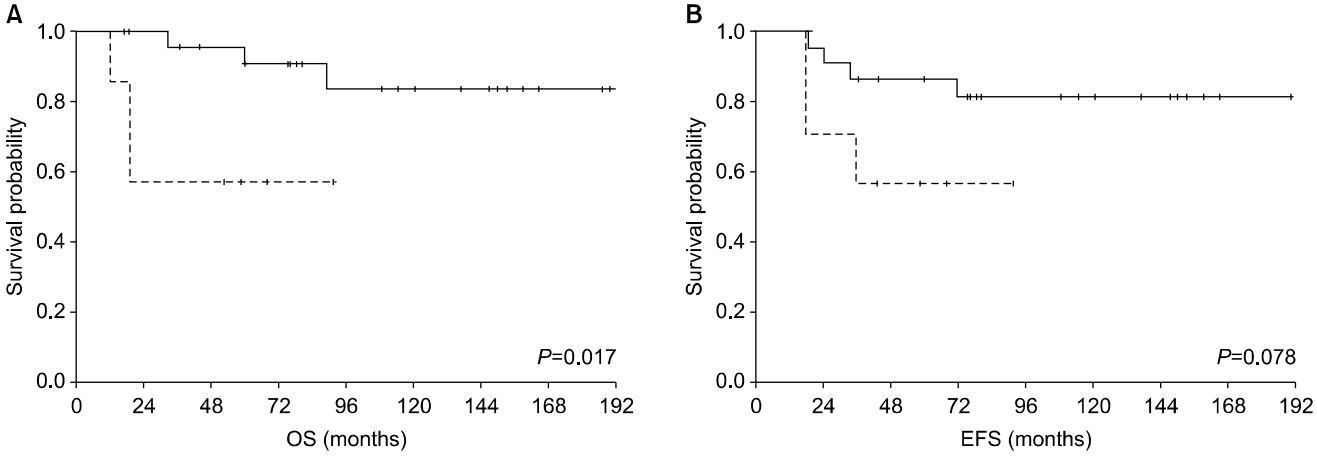

Fig. 2. Overall survival (OS) and event free survival (EFS) rates according to induction response. (A) Overall survival rate of rapid early responders (RER, N=25) was 83.9±8.8%, and that of slow early responders (SER, N=7) was 57.1±18.7%. OS was significantly lower in SER than RER (P=0.017). (B) Event free survival rates of RER and SER were 81.8±8.3% and 57.1±18.7%, respectively, and there was no statistical difference between the two groups (P=0.078). Bold line, RER; dotted line, SER.

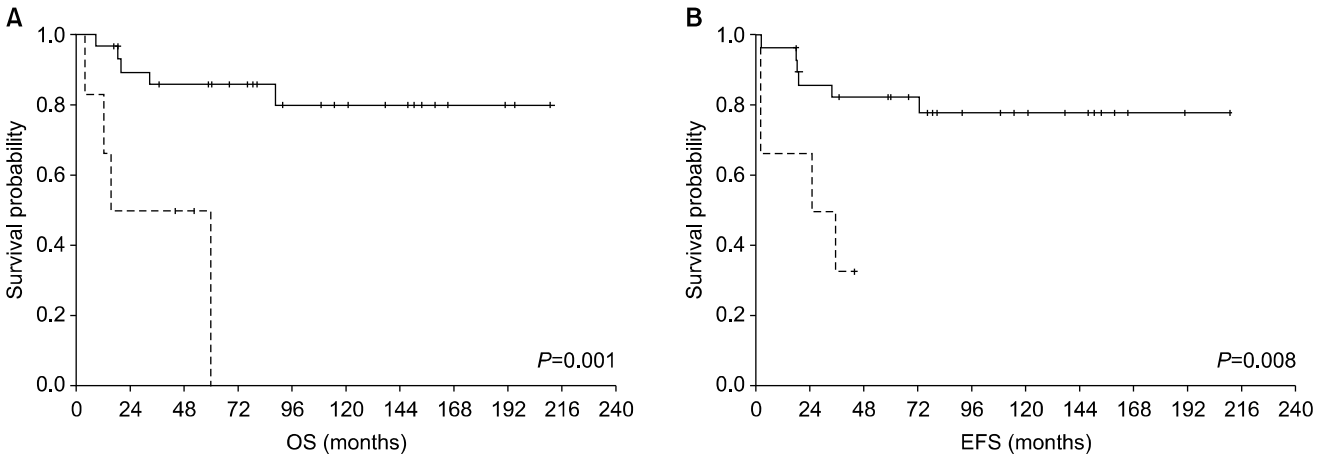

Fig. 3. Overall survival (OS) and event free survival (EFS) rates of patients with early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) and others. (A) The overall survival rate for non-ETP-ALL (N=30) was 80.2±8.2% and that of ETP-ALL (N=6) was 0% (P=0.001). (B) Event free survival rates of non-ETP-ALL and ETP-ALL were 78.2±7.9% and 33.3±19.2%, respectively, and EFS was significantly lower in ETP-ALL than non-ETP-ALL (P=0.008). Bold line, non-ETP-ALL; dotted line, ETP-ALL.

non-ETP-ALL (Fig. 3). OS for patients with non-ETP-ALL (N=30) was 80.2±8.2% and that of patients with ETP-ALL (N=6) was 0% (P=0.001, Fig. 3A). EFS for non-ETP-ALL and ETP-ALL was 78.2±7.9% and 33.3±19.2%, respectively, which was significantly lower for ETP-ALL (P=0.008, Fig. 3B).

3) Outcome of non-early T-cell precursor acute lymphoblastic leukemia

Fig. 4 shows the treatment course and outcomes of 30 non-ETP patients. As induction, 17 patients received ALL-0601 or CCG-1882 regimens, 10 patients received CCG-1901, two patients received POG-9404, and one patient received COG-0331. As a result of induction, 29 patients (96.7%) achieved CR, and 24 among those (82.8%) showed rapid early response. One patient receiving CCG-1901 failed to achieve CR and was administered salvage chemotherapy followed by uPBSCT, but died of *A. baumannii* sepsis. Prophylactic CRT was administered to 25 patients. Five patients relapsed, and CNS relapse occurred in three patients, even after prophylactic CRT. Four patients

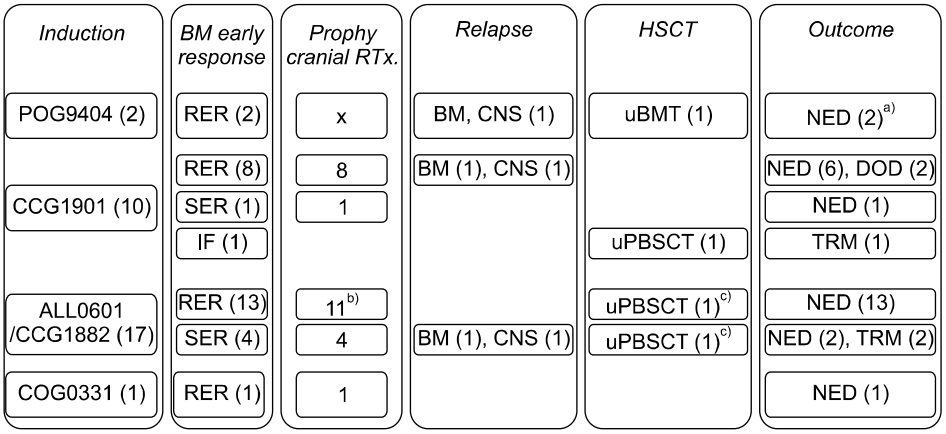

Fig. 4. Treatment results of patients with non-early T-cell precursor acute lymphoblastic leukemia (N=30). [a]Alive for 12 years after unrelated bone marrow transplantation. [b]One patient with CNS3. [c]Alive after unrelated peripheral blood stem cell transplantation following first complete remission. BM, bone marrow; RTx, radiotherapy; HSCT, hematopoietic stem cell transplantation; RER, rapid early responder; SER, slow early responder; IF, induction failure; CNS, central nervous system; uBMT, unrelated bone marrow transplantation; uPBSCT, unrelated peripheral blood stem cell transplantation; NED, no evidence of disease; DOD, died of disease; TRM, treatment related mortality.

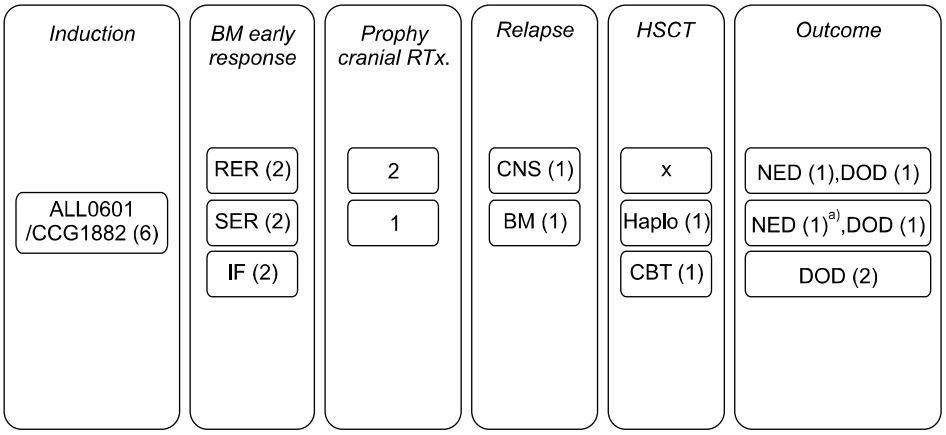

Fig. 5. Treatment results of patients with early T-cell precursor acute lymphoblastic leukemia (N=6). [a]Died of disease after the parents' request to discontinue medical treatment. HSCT, hematopoietic stem cell transplantation; RER, rapid early responder; SER, slow early responder; IF, induction failure; CNS, central nervous system; BM, bone marrow; Haplo, haploidentical stem cell transplantation; CBT, cord blood transplantation; NED, no evidence of disease; DOD, died of disease; TRM, treatment related mortality.

underwent stem cell transplantation; two in the ALL-0601 group received uPBSCT at CR1, and the other two at CR2. Currently, 25 patients (69.4%) are alive with CR status. Analysis according to treatment protocol indicated that patients treated with the ALL-0601 or CCG-1882 protocols had superior EFS than those receiving CCG 1901 (ALL-0601/CCG-1882: 86.7±8.8%, CCG-1901: 64.3±21.0%); however, the difference was not significant (P=0.461).

4) Outcome of early T-cell precursor acute lymphoblastic leukemia

Six patients had ETP immunophenotype disease, and all received the ALL-0601 or CCG-1882 protocols (Fig. 5). Four patients (66.7%) achieved CR at the end of induction, and two of them were RER. Two patients showed persistent disease at the end of induction, and both died of disease; one patient died of relapsed leukemia after umbilical cord blood transplantation at CR2. Relapse occurred in the BM in one

patient, and the CNS in one patient. The patient with isolated BM relapse underwent haploidentical stem cell transplantation after salvage chemotherapy, and was alive at the time of this analysis. The other patient with isolated CNS relapse experienced subsequent BM relapse, and died of refractory disease. Currently, two ETP-ALL patients are alive in CR.

5) Survival analysis according to prognostic factors

Survival differences were analyzed separately according to previously identified prognostic factors (Table 3). Patients with ETP-ALL had significantly inferior survival outcomes with OS 0% and EFS 33.3±19.2%. According to WBC count at diagnosis, most patients had initial WBC counts lower than $50,000\times10^6$/L, with 11 having WBC counts higher than $100,000\times10^6$/L; however, survival outcomes were comparable between the two different WBC count groups. Although data relating to prophylactic CRT were not available for three patients, irradiation did not influence survival outcome. By contrast, early response of the BM during induction was a significant prognostic factor for OS and EFS, as the survival rate of the SER group was only 57.1±18.7%. Type of treatment regimen did not influence survival outcomes. Further analysis using a Cox regression model indicated that none of these factors exerted independent predictive power (data not shown).

Discussion

T-cell lymphoid malignancies have distinct biochemical, immunologic, and clinical features, which set them apart from non-T-lymphoid malignancies. Historically, the diagnosis for patients with T-ALL portended a worse prognosis than for other forms of non-T childhood ALL. Although EFS

Table 3. Survival analysis according to prognostic factors

Factors	No. of patients	OS (%)	*P*	EFS (%)	*P*
ETP vs. non-ETP			0.001		0.008
Non-ETP	30	80.2±8.2		78.2±7.9	
ETP	6	0.0		33.3±19.2	
WBC at diagnosis (10^6/L)			0.142		0.239
<50,000	19	66.7±11.7		72.1±11.1	
50,000-100,000	3	33.3±27.2		33.3±27.2	
≥100,000	11	91.7±8.0		75.0±12.5	
Prophylactic cranial RT			0.074		0.256
Yes	24	82.4±8.1		79.2±8.3	
No	9	55.6±16.6		66.7±15.7	
Data not available	3				
Extramedullary disease			0.599		0.469
No	3	100		100	
Cervical LNs	3	87.5±11.7		87.5±11.7	
Mediastinal mass	13	64.7±14.5		59.2±14.1	
Data not available	12				
BM early response[a]			0.017		0.078
RER	25	83.9±8.8		81.8±8.3	
SER	7	57.1±18.7		57.1±18.7	
Treatment[b]			0.879		0.295
CCG1901	9	64.3±21.0		64.3±21.0	
ALL0601/CCG1882	19	78.9±9.4		73.3±10.2	
POG9404	2	100		50.0±35.4	

[a]One patient with induction failure and one with no available data were excluded from the analysis.
[b]Patients who were given the three most common regimens were analyzed.
OS, overall survival; EFS, event free survival; ETP-ALL, early T-cell precursor acute lymphoblastic leukemia; WBC, white blood cell; RT, radiotherapy; LN, lymph node; BM, bone marrow.

of T-ALL has improved over the decades and the outcomes for this disease are now comparable to those of children with high risk B-ALL, prognostic factors are less clear in patients with T-ALL than in those with B-ALL.

Early treatment response has been reported as an important prognostic factor in T-ALL. Patients with T-ALL with a poor response to the pre-steroid phase and/or no response by the end of induction had a 5 year disease free survival rate of 35% in the BFM 90 trial and 51% in the BFM 95 trial, when treated with chemotherapy alone [18]. The CCG-1882 regimen introduced a longer and stronger BFM regimen for high risk patients with a poor day 7 response to initial induction therapy (SER), who had higher failure rates [19]. This regimen resulted in improvements in both EFS and OS, as the EFS of the SER group was significantly better in the augmented-therapy group than in the standard-therapy group (75.0±3.8% vs. 55.0±4.5%, $P<$ 0.001).

In this study, 19 of 36 patients (52.8%) received CCG-1882 or ALL-0601. In those patients, treatment was intensified for patients who showed slow response (SER) during induction; patients who had M3 BM at day 7 or M2/M3 at day 14 received augmented treatment after induction. In this study, the survival results of the SER group were significantly worse than those of the RER group, even with intensified treatment; however, the number of SER during induction was low, with only seven patients in the SER analysis group compared with 26 in the RER group. Analysis of a larger number of patients with a longer follow-up period will be crucial for proper determination of the effects of intensification in these patients.

In addition to early treatment response, the level of MRD is the single most powerful prognostic factor in childhood ALL [13,20]. While the majority of data suggest that end of induction MRD is the best predictor of outcome in B-ALL, recent data from AIEOP-BFM ALL 2000 strongly suggest that end of consolidation MRD level was a better predictor of adverse outcome in T-ALL, although response at early time points is essential to identify the patients with the best prognosis [20]. In the present study, we could not analyze treatment outcomes according to MRD because only 10 patients were consistently tested for MRD levels, as there were no standard recommendations regarding MRD assessment and treatment modification. The Children's Oncology Group is now undergoing a prospective clinical trial on T-ALL to determine the clinical implications of MRD levels, and the results are awaited.

Another suggested prognostic factor is the maturation stage of T-ALL. Several early studies suggested a relationship between prognosis and T-ALL maturation stage, with precursor T-ALL having a more favorable and ETP-ALL having an inferior outcome [21]; however, the clinical outcome of ETP-ALL patients, compared with other subtypes of T-ALL, remains controversial. This leukemia subtype was originally described as a high risk group associated with poor outcomes [9,22]; however, a later study of children and young adults with ETP-ALL treated on the UKALL 2003 protocol demonstrated that ETP-ALL has an intermediate prognosis, with recent chemotherapy protocols based on MRD-based risk stratification, and does not universally warrant stem cell transplantation in first remission [23]. The reason for the relatively favorable prognosis of ETP-ALL patients in the UKALL 2003 trial is not clear; however, a possible explanation is that treatment intensification for MRD-positive patients may have offset the otherwise inferior outcome of these patients.

In the present study, ETP patients had significantly lower survival rates. Although only six patients were classified as having ETP-ALL, two failed to achieve remission, and two others relapsed after remission. Although allogeneic stem cell transplantation at first remission would not be essential for every ETP-ALL patient, treatment intensification is necessary for ETP-ALL.

T-cell immunophenotype in ALL is a known risk factor for CNS relapse. Thus, a significant majority of patients with T-ALL receive prophylactic CRT to reduce CNS relapse risk, although RER non-CNS3 T-ALL patients did not receive CRT on CCG 1961 [24]. RER patients who did not receive CRT had a higher incidence (7.9%) of CNS relapse than SER T-ALL patients who received prophylactic CRT (0.8%) on CCG-1961 [25]. Although CRT is effective, the usefulness of CRT may be offset by substantial long-term adverse effects, including secondary cancers, irreversible endocrinopathies, and neurocognitive and neurotoxic effects [26]. Also, sev-

eral small group studies have reported that the risk of CNS relapse in T-ALL can be abrogated by early, frequent IT MTX, high-dose MTX (HD-MTX), and increased doses of asparaginases [27]. European Organization for Research and Treatment of Cancer (EORTC) studies eliminated CRT for all *de novo* ALL patients, while including multiple courses of HD-MTX and triple IT chemotherapy (ITT). In the EORTC-58881 study, the 8 year isolated and overall CNS relapse incidence rates in T-ALL patients decreased to 6.8% and 10.9%, respectively, and were subsequently reduced further in the EORTC-58951 study, to 5.3% and 8.5%, respectively [28].

We provided prophylactic CRT to all patients in the CCG-1901 group, and to 18 of 23 patients in the ALL-0601/CCG-1882 groups, regardless of the initial response; however, all CNS relapses occurred in already irradiated patients. None of our protocols included HD-MTX or ITT. Although retrospective, these results suggested that prophylactic CRT alone without CNS oriented intensified chemotherapy cannot lower the risk of CNS relapse. In the ongoing strategy for T-ALL in our center, HD-MTX with ITT will be included instead of prophylactic CRT.

Hyperleukocytosis at diagnosis has been reported as a prognostic marker for inferior survival. According to previous studies, the outcomes of patients with WBC $\geq 200 \times 10^9$/L were significantly worse than those of patients presenting with lower WBC values [29-32]. Hasting *et al.* reported that markedly elevated initial WBC ($>200 \times 10^9$/L) was a significantly worse prognostic factor in 251 patients treated with the CCG-1961 protocol. In that study, augmented therapy benefited T-ALL with hyperleukocytosis over 200×10^9/L, whereas there appeared to be no impact on survival for B-ALL patients with hyperleukocytosis. The results of the present study also indicated that extreme hyperleukocytosis at diagnosis was not a significant prognostic factor for patients with T-ALL. Instead, early treatment response, regardless of WBC count, was the most important factor influencing outcome.

This study has some limitations. The small patient population and the retrospective nature of the study do not allow us to draw any conclusion about prognostic factors in T-ALL. T-ALL is diagnosed less frequently than B-ALL, so that inclusion of large numbers of patients with T-ALL for analysis can be challenging. In addition, there are still controversies concerning the diagnosis of ETP T-ALL, and because diagnosis has only recently been established, some of the patients who were diagnosed as T-ALL earlier did not get tested for all the markers that are helpful in making the diagnosis of ETP T-ALL. Furthermore, the treatment protocols were varied and MRD testing was not included in the treatment scheme. The OS and EFS of T-ALL were reported as 80.4% and 71.3% in the CCG-1961 study (24), and 80.7% and 75.9% in AIEOP-BFM-ALL 2000, respectively [20]. In the present study, OS and EFS were 71.4% and 70.2%, respectively, which are relatively lower than those of international prospective studies. Larger nationwide series with uniform treatment strategies and MRD-based treatment intensification are needed to establish the proper treatment for T-ALL to enhance survival of these patients.

In conclusion, this study shows that a high risk ALL protocol with intensified post-remission therapy, including prophylactic CRT, conferred survival outcomes in T-ALL comparable to those of Western studies. Further treatment intensification should be considered for patients with ETP-ALL and slow induction responders, and CNS-directed treatment intensification without prophylactic CRT is needed.

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