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Outcome of Recurrent or Refractory Acute Lymphoblastic Leukemia in Infants With *MLL* Gene Rearrangements: A Report From the Japan Infant Leukemia Study Group

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Background. Despite the poor outcome of recurrent or refractory acute lymphoblastic leukemia (ALL) in infants with *MLL* gene rearrangement, few studies have focused on this specific group. We conducted a retrospective analysis of infants with recurrent or refractory ALL from two previous consecutive Japanese studies to clarify the characteristics and prognostic factors among these patients ***Procedure.*** All recurrent or refractory ALL infants with *MLL* gene rearrangement (MLL-R) who were registered in two consecutive Japanese nation-wide multicentric trials (MLL96 and MLL98; between 1995 and 2001) were eligible for the study. ***Results.*** Among 80 MLL-R ALL infants, 34 cases of recurrence and 5 induction failures occurred. The median duration of first remission was 5 months (range, 0–28 months). All patients underwent various salvage chemotherapies; remission was achieved in 40.5% (15/37). A total of 23 patients received subsequent hematopoietic stem cell transplantations (HSCT): 9 in remission, 12 without remission, and 2 with unknown status. With median follow-up period of 5.5 years, the 5-year overall survival (OS) rate after the second-line treatment was 25.6% ± 6.9%. Young age (<3 months) and central nervous system involvement at initial diagnosis were associated with poor outcome; however, failure to achieve remission after salvage therapy was the sole independent poor prognostic factor in multivariate analysis ($P = 0.01$). ***Conclusions.*** The prognosis of infants with recurrent or refractory MLL-R ALL is extremely poor despite alternative treatments including HSCT; therefore, it is necessary to develop novel treatment strategies. Pediatr Blood Cancer 2009;52:808–813.

Key words: infant acute lymphoblastic leukemia; *MLL* gene; recurrent; refractory

INTRODUCTION

The outcome of acute lymphoblastic leukemia (ALL) in infants of less than 12 months of age with *MLL* gene rearrangement remains poor, with recently published long-term event-free survival (EFS) rates of 22–54% [1–4]. More than 50–60% of newly diagnosed cases develop recurrent or refractory disease during or following treatment; however, few reports have focused on the clinical course and outcome of these specific groups. The results of a small number of studies with few cases suggest that the outcomes of recurrent or refractory ALL infants with *MLL* gene rearrangement are dismal and rarely rescued [2,4].

The Japan Infant Leukemia Study Group conducted three consecutive series of nationwide clinical studies for newly diagnosed ALL in infants (the MLL96, MLL98, and MLL03 studies) [5,6]. In the present report, we analyzed the outcome of 39 recurrent or refractory ALL infants with *MLL* gene rearrangement who were registered in either of the first two studies (MLL96 and MLL98), to clarify the characteristics and prognostic factors in this group.

METHODS

Patients

We analyzed the data regarding all consecutive recurrence and induction failures that occurred in two consecutive studies for newly diagnosed infant ALL (the MLL96 and MLL98 studies). Of the 80 ALL infants with *MLL* gene rearrangements (MLL-R) who registered in these two studies between December 1995 and December 2001, 34 relapsed and 5 were resistant to induction chemotherapy (induction failure). Patient characteristics are listed in Table I.

Informed consent, provided according to the Declaration of Helsinki, was obtained from the patients' guardians on registration of the two studies. The rearrangement of an *MLL* gene in each patient was determined by Southern blot analysis and/or split-signal fluorescence *in situ* hybridization (FISH), as described previously [5–7].

First-Line Treatment

Details of the therapeutic regimens used in the MLL96 and MLL98 studies are described elsewhere [5–7]. Briefly, MLL-R ALL infants received induction therapy and three courses of postremission intensification therapy followed by allogeneic hematopoietic stem cell transplantation (HSCT) during the first remission, whenever 5/6 or 6/6 HLA-matched related donor, 6/6-matched unrelated donor, or 4 to 6/6-matched unrelated cord blood donor was available. The protocol-specified conditioning regimen comprised either total-body irradiation (TBI; 12 Gy in six fractions, twice daily on days −7 to −5) or busulfan (BU; 35 mg/m^2/dose

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TABLE I. Main Characteristics of 39 Patients With Recurrent/Refractory Infant ALL and *MLL* Gene Rearrangements

	Induction failure	Relapse pre-HSCT	Relapse post-HSCT	Total
Total no. of patients	5	21	13	39
Age at onset, months				
<3	2	9	1	12
3 to <6	1	8	6	15
≥6	2	4	6	12
Sex				
Male	4	9	4	17
Female	1	12	9	22
WBC count at onset, $\times 10^9$/L				
<100	2	4	4	10
100 to <300	1	9	5	15
≥300	2	8	4	14
CNS disease at onset				
Positive	2	4	2	8
Traumatic tap	0	0	1	1
Negative	3	12	9	24
Unknown	0	5	1	6
Karyotype[a]				
t(4;11)(q21;q23)	1	14	7	22
t(11;19)(q23;p13)	1	1	3	5
t(9;11)(p22;q23)	2	0	2	4
Other 11q23	0	2	1	3
No11q23 abnormalities	1	2	0	3
Unknown	0	2	0	2
First-line treatment				
MLL96	4	13	6	23
MLL98	1	8	7	16
Time to relapse				
Median, months	—	3 (0–22)	12 (4–28)	5 (0–28)
Relapse < 12 months	—	19	6	25
Relapse ≥ 12 months	—	2	7	9
Site of relapse				
Bone marrow	—	20	10	30
Combined BM/CNS	—	1	0	1
CNS	—	0	2	2
Testicular	—	0	1	1

ALL, acute lymphoblastic leukemia; BM, bone marrow; CNS, central nervous system; HSCT, hematopoietic stem cell transplantation; WBC, white blood cells. [a]All patients were confirmed as *MLL* rearranged by Southern blotting and/or split-signal fluorescence *in situ* hybridization (FISH), including three cases with no 11q23 abnormalities and two unknown cases by normal karyotypic analysis.

orally, 4 times a day on days −8 to −5) with a combination of etoposide (60 mg/kg intravenously on day −4) and cyclophosphamide (60 mg/kg intravenously on days −3 and −2).

Second-Line Treatment

Second-line treatment differed among the patients because the choice of treatment for recurrence or induction failure varied among the hospitals. Table II provides an outline of second-line treatment regimens used for these patients. Indication of subsequent HSCT was also determined according to the choice of each institution.

Evaluation of Late Effects

Late effects were also analyzed, including cardiac, pulmonary, renal, endocrine, dental, orthopedic, dermatologic, ophthalmologic, auditory, psychological, growth and development, and occurrence of secondary malignancies. Medical records regarding these issues were reviewed by each physician in the participating centers; these data were collected via a questionnaire sent to each participating center.

Statistical Considerations

Overall survival (OS) rate was estimated using the Kaplan–Meier method and standard errors (SEs) were estimated using the Greenwood formula; these were then compared using the log-rank test. Confidence intervals (CIs) were computed with a 95% confidence level. A Cox regression model was used for multivariate analysis. *P* values, when cited, are two-sided, with a value of 0.05 or less taken to indicate statistical significance.

TABLE II. Second-Line Chemotherapy Regimens Used for 39 Patients With Recurrent/Refractory Infant ALL and *MLL* Gene Rearrangements

Second-line chemotherapy regimen	No. of patients received	No. of patients achieved CR	No. of patients alive in CCR
AML-oriented	11	4	4
Ara-C civ/MIT/VP-16/TIT	7	3	3
Ara-C civ/IDA/VP-16	1	0	0
HDCA/MIT/VP-16/TIT	2	1	1
HDCA	1	0	0
ALL-oriented	11	7	2
VCR/PSL/L-asp/DRB/TIT	3	3	1
VCR/Dexa/PSL/L-asp/pirarubicin/IT-MTX	2	1	0
VCR/PSL/L-asp/MIT	1	1	1
VCR/Dexa/L-asp/IFO/VP-16/HD-MTX/TIT	1	1	0
VCR/Dexa/CPM/HD\MTX/TIT	1	0	0
VCR/L-asp/IFO	1	0	0
HD-MTX	1	1	0
VCR/PSL	1	0	0
AML/ALL-hybrid	5	3	2
Ara-C/pirarubicin/VP-16/PSL/L-asp/TIT	3	1	1
Ara-C/DXR/VP-16/VCR/Dexa/CPM/TIT	1	1	0
HDCA/DRB/VCR/PSL/L-asp/CPM/TIT	1	1	1
Others	2	0	0
BHAC-AMP	1	0	0
CXR/TIT	1	0	0
No (HSCT on disease)	1	0	0
N/A	9	2	2

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Ara-C civ, continuous intravenous infusion of cytarabine; BHAC-AMP, combination of enocitabine/6-mercaptopurine/predonisone/aclarubicin; CCR, continuous complete remission; CPM, cyclophosphamide; CR, complete remission; CXR, cranial radiation; Dexa, dexamethasone; DRB, daunorubicin; DXR, doxorubicin; HDCA, high-dose cytarabine; HD-MTX, high-dose methotrexate; HSCT, hematopoietic stem cell transplantation; IDA, idarubicin; IFO, ifosfamide; IT-MTX, intrathecal methotrexate; L-asp, L-asparaginase; MIT, mitoxantrone; N/A, data not available; PSL, prednisone; TIT, triple intrathecal therapy; VCR, vincristine; VP-16, etoposide.

RESULTS

Outcome and Survival of Relapsed/Refractory Infant ALL With *MLL* Gene Rearrangements

Figure 1 summarizes the outcomes of 39 infants with recurrent or refractory MLL-R ALL. Among the 39 patients, 5 were refractory to induction chemotherapy (induction failure) and 34 relapsed, of which 21 occurred before HSCT in first remission (CR1) and 13 occurred after HSCT in CR1. The source of donor for these 13 infants was bone marrow transplantation (BMT) from related donor (R-BMT) in 3, peripheral blood stem cell transplantation from related donor (R-PBSCT) in 1, BMT from unrelated donor (U-BMT) in 2, unrelated cord blood transplantation (U-CBT) in 6, and autologous HSCT in 1. The median duration of CR1 in all 34 recurrent ALL infants was 5 months (range, 0–28 months).

Of the five infants with refractory ALL, two achieved the first complete remission by AML-type induction chemotherapy: one continued conventional AML-type chemotherapy alone and is alive in remission with a follow-up period of 4 years; the other received U-CBT in CR1 and had relapse in bone marrow (BM) 6 months later, but was rescued by a second transplantation (U-BMT) and is now in CR2 with a follow-up period of 3 years. The remaining three patients never achieved CR: one received AML-type induction chemotherapy; one received BHAC-AMP (combination of enocitabine, mercaptopurine, prednisone, and aclarubicin); and one received the "Phase A" intensification course of MLL96 (combination of cytarabine, etoposide, pirarubicin, prednisone, L-asparaginase, and triple intrathecal therapy). Of these three patients, one received R-BMT but died of interstitial pneumonia; the other two patients died of progressive disease.

Among the 34 patients with recurrence, 32 were evaluable for response: 13 (38.2%) achieved CR2 with various re-induction chemotherapies (Table II). Subsequently, 8 of these 13 patients underwent HSCT (R-PBSCT in 2, R-BMT in 1, U-BMT in 3, and U-CBT in 2); the other 5 patients relapsed and eventually died of progressive disease. Five of the 8 patients undergoing HSCT in CR2 are alive in remission with a median follow-up period of 8 years (range, 3–10 years); 2 experienced a second relapse, and 1 died of veno-occlusive disease (VOD); of the two patients with second relapse after HSCT in CR2, one is alive in CR3 (follow-up period, 3 years) and the other died of progressive disease.

Among the remaining 19 patients who did not achieve CR2, 11 patients underwent HSCT without remission: R-BMT in 2, R-PBSCT in 2, U-BMT in 4, and U-CBT in 3. Of the 11 patients, 2 patients are alive in CR2 with follow-up periods of 5 and 8 years, 3 died of HSCT-related severe infectious complications, and 6 relapsed and died of progressive disease. The remaining 8 patients without CR2 died of progressive disease, with a median period of 6.5 months. Both of the patients who were not evaluable for response

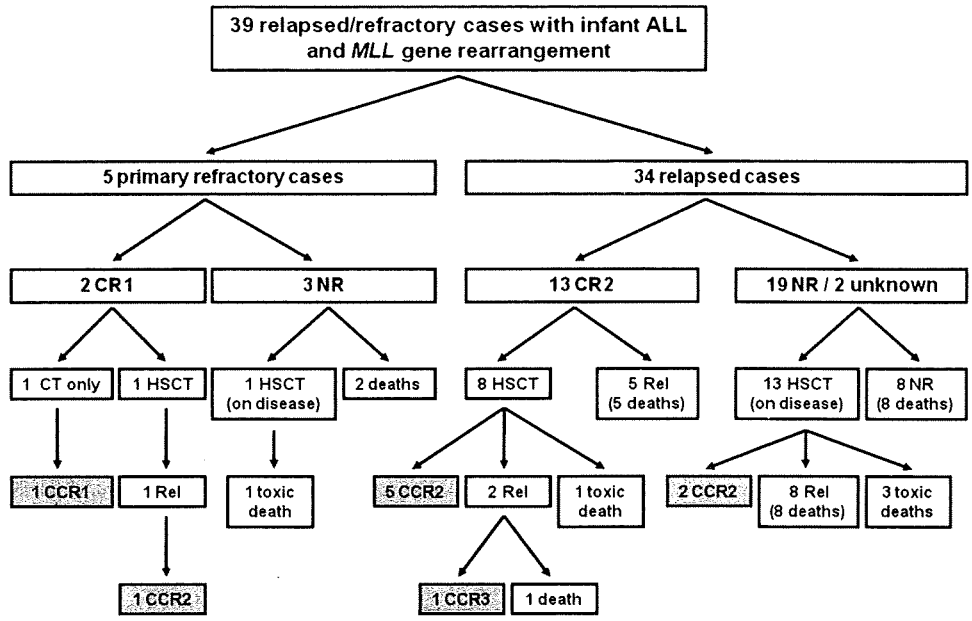

Fig. 1. Summary of outcome in patients with recurrent/refractory infant ALL and *MLL* gene rearrangements. CCR, continuous complete remission; CR, complete remission; CT, chemotherapy; HSCT, hematopoietic stem cell transplantation; NR, no response; Rel, relapse.

underwent HSCT but relapsed and died, one of progressive disease and one of bronchiolitis obliterans (BO).

The overall induction rate by second-line chemotherapy was 40.5% (15/37), and the 5-year OS rate in the whole cohort was 25.6% ± SE 6.9% (Fig. 2).

Prognostic Factors

Univariate analysis revealed three factors associated with a higher risk of failure: age less than 3 months at initial diagnosis, central nervous system (CNS) involvement at initial diagnosis (defined as more than 5 cells/mm^3 with recognizable blasts in cerebrospinal fluid), and induction failure by second-line chemotherapy (Table III). Differences in CR rate by second-line chemotherapy or survival rate were not observed between infants that

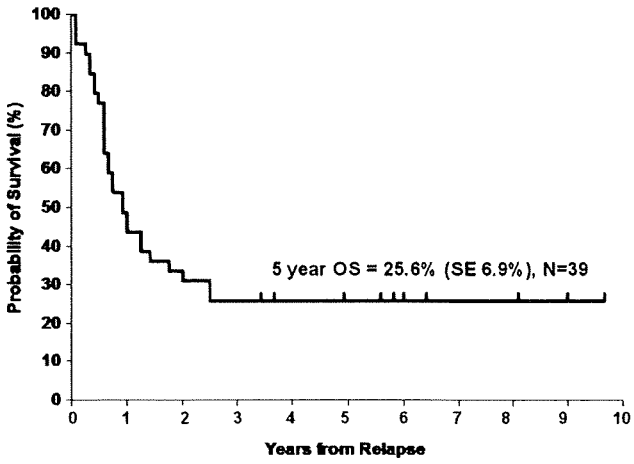

Fig. 2. Overall survival for patients with recurrent/refractory infant ALL and *MLL* gene rearrangements.

TABLE III. Five-Year Survival Rates by Selected Prognostic Features for 39 Cases of Recurrent/Refractory Infant ALL

	No. of patients	5-year OS, % (SE)	*P* value
Age at onset, months			
<3	12	16.7 (10.7)	0.03
≥3	27	29.6 (8.7)	
WBC count at onset, $\times 10^9$/L			
<300	25	24.0 (8.5)	0.54
≥300	14	28.5 (12.0)	
CNS disease at onset			
Positive	8	12.5 (11.6)	0.04
Negative	25	36.0 (9.6)	
Karyotype			
t(4;11)(q21;q23)	22	22.7 (8.9)	0.54
Others	17	29.4 (11.1)	
Duration of CR1[a]			
<12 months	25	16.0 (7.3)	0.06
≥12 months	9	44.4 (16.5)	
Relapse site[a]			
Bone marrow involved	31	28.1 (7.9)	0.55
Isolated extramedullary	3	0.0 (0.0)	
History of prior HSCT[a]			
Yes	13	21.4 (11.9)	0.47
No	21	25.0 (9.6)	
Response to second-line therapy			
CR	15	53.3 (12.8)	0.001
No CR	22	9.0 (6.1)	

BU, busulfan; CNS, central nervous system; CR, complete remission; HSCT, hematopoietic stem cell transplantation; OS, overall survival; SE, standard error; TBI, total-body irradiation; WBC, white blood cells.
[a]Relapsed patients only (five refractory patients excluded).

TABLE IV. Multivariate Analysis of Prognostic Factors in Infants With Recurrent/Refractory ALL

	Parameter estimates	Risk ratio (95% CI)	*P* value
Age at initial diagnosis, less than 3 months	0.453	1.573 (0.665–3.715)	0.301
CNS leukemia at initial diagnosis	0.584	1.794 (0.708–4.546)	0.217
Time to first event, less than 12 months	0.566	1.762 (0.621–5.002)	0.286
Failure to achieve CR after second-line therapy	1.230	3.422 (1.339–8.746)	0.010

CI, confidence interval; CNS, central nervous system; CR, complete remission.

relapsed before and after HSCT. Multivariate analysis revealed induction failure as the only significant prognostic factor (Table IV).

Long-Term Complications in the 10 Surviving Patients

Data regarding long-term complications were analyzed in 9 of the 10 survivors. The median age of the 9 patients at analysis was 6.5 years (range, 4.8–11.0 years). All had received HSCT and 4 were transplanted twice. Eight patients had received TBI-based conditioning regimen, while 1 had received BU-based conditioning regimen.

In these 9 patients, chronic GVHD was observed in 5 (extensive type in 4 and limited type in 1), hypothyroidism in 2, short stature (defined as a height standard deviation [SD] score below −2.0) in 8, skin abnormalities (alopecia, scleroderma, hypopigmentation) in 4, fasciitis in 1, ophthalmologic complications (dry eye, corneal opacity, retinal vasculitis) in 4, pulmonary complications (interstitial pneumonia, bronchiolitis obliterans) in 2, chronic diarrhea with malnutrition in 1, dental abnormalities in 4, and neurocognitive deficits (learning disability, intelligence impairment, autism) in 2. There were no patients with secondary malignancy or symptomatic chronic heart failure. Pubertal development could not be evaluated because all study patients were younger than 12 years old and had not entered puberty at the time of analysis.

DISCUSSION

Relapses are relatively frequent events in ALL infants with *MLL* gene rearrangement, despite intensive chemotherapy with or without HSCT [1–7]. Most previous studies report only a small difference between OS and EFS rates, indicating a dismal prognosis for relapsed or refractory cases in infant ALL. The present study found a response rate of 40.5% with second-line chemotherapy and a 5-year OS rate of 25.6% despite receiving HSCT, which is far from satisfactory.

The high chemotherapeutic-resistance of infant ALL cells is well described elsewhere. For example, Pieters et al. [8,9] demonstrated that infant ALL cells were more resistant in vitro to prednisone and L-asparaginase than those from older children. This result is supported by the finding that in comparison with older children, infants with ALL commonly show a poor response to prednisone [1]. In relapsed infant ALL patients, the high CR rate of 90–95% after induction therapy but high early relapse rate of 30–50% after remission also indicate the presence of a more resistant leukemic clone [5]. This might be explained by infant ALL cells rapidly acquiring additional resistance or by the selection of a more resistant leukemic clone that resided as a minor subclone at diagnosis, both presumably occurring during initial chemotherapy [10–12]. Although the exact mechanism associated with the resistance of ALL cells to chemotherapy remains unknown, there is no doubt that the recurrent or refractory infant ALL cells become highly resistant, thereby leading to the dismal outcome in these patients.

In the present study, we investigated various prognostic factors in recurrent or refractory infant ALL. Young age (<3 months of age) and CNS involvement at initial diagnosis confer a high risk of treatment failure in newly diagnosed ALL infants with *MLL* gene rearrangements, and can be regarded as surrogates of treatment resistance. Of note, univariate analysis revealed that infants with these factors harbor poorer prognosis compared with those without, even in recurrent or refractory infant ALL.

Two important prognostic factors have been established in recurrent or refractory childhood ALL [13–18]: duration of first remission and site of relapse. In the present study, however, we found that these factors had no prognostic impact among recurrent and refractory ALL infants. In the relapsed ALL studies of the BFM group (ALL-REZ studies), three factors (time point of relapse, site of relapse, and immunophenotype of leukemic cells) were used to classify each patient into four groups: from the S1 group (late and isolated medullary relapse) having the best prognosis, to the S4 group (very early and isolated BM relapse) having the worst prognosis [14]. When we classify the 34 relapsed patients in the present study according to this system, there are no patients in the S1 group, 6 in S2, 1 in S3, and 27 in S4. Thus, 79.4% (27/34) of the recurrent ALL infants are assigned to the group with the worst prognosis.

An important finding of the present study is that the achievement of further remission by second-line chemotherapy is clearly associated with an improved prognosis in recurrent or refractory ALL infants: a greater than 50% chance of survival can be obtained if CR is achieved. Therefore, to improve the outcome of recurrent or refractory infant ALL, it is necessary to find a means of improving the salvage therapy and increasing the CR rate.

In the present study, AML-oriented or AML/ALL-hybrid chemotherapy was successful in some infants with refractory ALL, with 6 of 16 patients in continuous CR (Table II). It has been demonstrated that infant ALL cells are more sensitive to cytarabine *in vitro* than those of older children, and that a subgroup may benefit from regimens that include intensive use of cytarabine, followed by HSCT [3,8,9]. Although some cases may benefit from this approach and obtain a chance of long-term survival, most would suffer from some kind of late complications as illustrated in the current report. Taking into account the vulnerability of infants and the highly intensive nature of therapy for *MLL*-rearranged ALL, there exists a clear need for the development of novel therapeutic modalities.

Gene expression profiling has led to the identification of several potential therapeutic targets based on the unique biology of *MLL*-rearranged infant ALL. Among these, inhibition of FLT3, a tyrosine kinase receptor, is currently being tested in a clinical trial [19–21].

Considering the poor outcome associated with relapsed/refractory infant ALL, these patients would benefit from the early clinical development of novel agents.

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Retrospective Analysis of Non-Anaplastic Peripheral T-Cell Lymphoma in Pediatric Patients in Japan

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Background. Reports of non-anaplastic peripheral T-cell lymphoma (PTCL) in pediatric patients are relatively rare. ***Procedure.*** We performed a retrospective analysis in patients with PTCL over an 18-year period (1991–2008). ***Results.*** We could analyze clinical data in 21 patients with non-anaplastic PTCL; 10 were female and 10 male. Median age of onset was 11 years (range: 1–21 years). There were nine patients with PTCL, not otherwise specified (PTCL-NOS); ten with extranodal NK/T-cell lymphoma, nasal type; one with angioimmunoblastic T-cell lymphoma; and one with subcutaneous panniculitis-like T-cell lymphoma. Initial lesions involved cervical lymph nodes in five patients, and the skin in five patients. In five patients, hemophagocytic syndrome (HPS) was the initial clinical feature. There were 12 patients with advanced stage disease (stages III and IV). Chemotherapy and radiation was administered in 18 and 2 patients, respectively. Among the two patients who did not receive chemotherapy and radiation, one patient died while being treated for HPS but another improved spontaneously. Although 5 patients relapsed, 18 of 21 patients remained alive without disease at last follow-up. Five-year overall survival rate was 85.2%. ***Conclusions.*** Generally, the outcome results of conventional chemotherapy for high-risk PTCL are poor in adult patients. However, the excellent results in our study suggest that PTCL of childhood is quite different from that of adulthood. Although this study is first report about PTCL of Asian children, the number of patients was small in this study. Larger studies are needed to confirm these findings. Pediatr Blood Cancer 2010;54:212–215. © 2009 Wiley-Liss, Inc.

Key words: child; peripheral T-cell lymphoma

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare diseases, usually demonstrating clinical aggressiveness [1]. Because of difficulty and variability in diagnosis, improvements in diagnostic technology, and changing classification systems over time, the interpretation of studies is complicated. In addition, the response to current treatments and long-term outcome are generally poor [2–6]. Reports of non-anaplastic PTCL in pediatric patients are relatively rare [7–11]. Moreover, although geographic variation has been well documented, this may reflect exposure to specific pathogenic viruses, such as Epstein Barr (EB) virus and human T-cell leukemia virus-1 in Asian countries. There are no reports about child PTCL from Asia. We therefore performed a retrospective analysis of patients with PTCL over an 18-year period (1991–2008).

METHODS

We performed this retrospective analysis as the lymphoma committee of the Japan Leukemia and Lymphoma Study Group (JPLSG). Data were obtained from the Japan Association of Childhood Leukemia Study (JACLS), Tokyo Children's Cancer Study Group (TCCSG), Japanese Children's Cancer and Leukemia Study Group (JCCLSG), and Kyushu-Yamaguchi Children's Cancer and Leukemia Study Group (KYCCSG). In the 18-year study period, 55 patients were registered as having PTCL or NK/T lymphoma including blastic NK lymphoma and myeloid/NK lymphoma. Clinical data for 21 patients with non-anaplastic PTCL after excluding 34 patients with blastic NK lymphoma and myeloid/NK lymphoma were analyzed.

Pathologic diagnoses were confirmed by central review in 9 of 21 patients. Central review was performed using WHO classification. For the other 12 children, histopathology was performed at the treating center only and confirmed from a copy of the pathology report. In almost all reports, immunophenotyping such as CD79a, CD20, CD3, CD43, TdT, and MPO was included.

The presence of an association with EB virus was determined by detection of EB virus genome in white blood cells or plasma, or the detection of this virus in histological material by EB virus encoded small RNA (EBER) in situ hybridization [12].

Statistical Analyses

Analysis of overall survival was performed using the Kaplan–Meier method, with differences compared by log-rank test. Differences between groups were analyzed using a Fisher exact test and a Mann–Whitney *U*-test. Statistical analyses were

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performed using Dr. SPSS II for Windows (release 11.0.1J, SPSS Japan, Inc.).

RESULTS

In the 18-year study period, we were able to analyze clinical data from 21 patients with non-anaplastic PTCL (Table I). Because 1,711 child and adolescent patients with non-Hodgkin lymphoma were registered in the 18-year period, the proportion of NHL classified as PTCL was 1.2%. Of the 21 patients, 10 were male and 11 were female. Median age of onset was 11 years (range: 1–21 years). There were nine patients with PTCL not otherwise specified (PTCL-NOS); ten with extranodal NK/T-cell lymphoma, nasal type; one with angioimmunoblastic T-cell lymphoma; and one with subcutaneous panniculitis-like T-cell lymphoma. Initial lesions involved the cervical lymph nodes in five patients, and the skin in five patients. In five patients, hemophagocytic syndrome (HPS) was the initial clinical feature. With regard to stage of disease at diagnosis, eight patients were at stages I and II, six were at stage III, and six were at stage IV; this information was not available for one patient. Chemotherapy and radiation were administered in 18 and 2 patients, respectively. Two patients received no treatment. Treatment for PTCL was not consistent in this study. Eight patients received a T-cell lymphoma/leukemia regimen, and four received a B cell lymphoma/leukemia regimen. Among the two patients who did not receive chemotherapy and radiation, one patient died while undergoing treatment for HPS and another improved spontaneously. In the latter patient (patient 5), the initial clinical features were fever, cervical lymphadenopathy, and pancytopenia. He was diagnosed with HPS from laboratory data and bone marrow aspiration. Lymph node biopsy revealed PTCL and there was positive staining on EBER in situ hybridization. However, after several days, the fever abated and laboratory data improved. He received no chemotherapy at the request of his parents and remained disease-free at last follow-up, 9 months after onset.

Eleven patients received stem cell transplantation. Of these, two received an autologous peripheral blood stem cell transplant (PBSCT), five received a related bone marrow transplant (BMT), two received a related PBSCT, two received an unrelated cord blood stem cell transplant (CBSCT), and one received an unrelated BMT. Although 5 patients relapsed, 17 of the 21 patients were alive without disease at last follow-up, giving an overall 5-year survival rate of 85.2% (Fig. 1). Causes of death for the three patients who succumbed to their disease were HPS, progression of disease and complications of stem cell transplantation. Ten of the 21 patients had PTCL associated with EB virus. Compared with patients with extranodal NK/T lymphoma, nasal type, those with PTCL-NOS were younger (median 7 years vs. 15.5 years, $P < 0.05$) and had a lower relapse rate (11% vs. 40%). However, gender (male/female; 5/4 vs. 4/6), proportion with advanced stage disease (56% vs. 60%), survival rate (87.5% vs. 80.0%) and association with EB virus (44% vs. 60%) were similar and statistically non-significant differences.

DISCUSSION

Peripheral NK/T-cell neoplasms are an uncommon group of diseases that show distinct racial and geographic variation. The prognostic significance of the T-cell phenotype has been clearly defined in recent studies by using modern lymphoma classification systems. Anaplastic large cell lymphoma, not rare in childhood, is another type of PTCL. Results of conventional chemotherapy for high-risk PTCL are poor compared with those for their aggressive B-cell counterparts in adult patients.

However, although case reports of pediatric PTCL are sometimes seen [7,10,11], large case series are very rare. The only two such case series published are a report from the United Kingdom [8] and the Children's Oncology Group (COG) Study [9]. In the UK series, 25 cases were identified, 44% of children died and 5-year survival rate was 59%. On the other hand, in the 20 patients in the COG series, 5-year survival rate was 90% in patients with localized disease and 50% in those with advanced disease. In the present study, 21 patients with PTCL were identified; these included 9 with PTCL-NOS; 10 with extranodal NK/T-cell lymphoma, nasal type; 1 with angioimmunoblastic T-cell lymphoma; and 1 with subcutaneous panniculitis-like T-cell lymphoma. Surprisingly, although 57% of patients had advanced stage disease and five patients relapsed after chemotherapy, the 5-year survival rate was 85.2%. However, treatment for PTCL was not consistent in this study. Eight patients received a regimen for T-cell lymphoma/leukemia, and four patients received a B cell lymphoma/leukemia regimen. Moreover, in one patient, symptoms improved spontaneously, and this has not previously been reported. Although five patients had relapse, four patients remained disease free at last follow-up and only two patients had undergone stem cell transplantation. Our study suggests that in the present population, PTCL in childhood does not have a poor outcome compared to adult with PTCL. This reason is not clear. However, the role of stem cell transplantation might be important. Stem cell transplantation had been undergone in eight patients with first complete response or partial response, one patient with progressive disease and two patients after relapse. After stem cell transplantation, only two patients died and nine patients are surviving without relapse.

Many cases of extranodal NK/T-cell lymphoma, nasal type were seen in this study compared with previous reports. Moreover, patients with this type of lymphoma were older at initial presentation than those with PTCL-NOS. Extranodal NK/T-cell lymphoma, nasal type is mostly confined to East Asia, and it predominantly occurs in the nasal or paranasal areas and less frequently in the skin. Most of the tumors show NK-cell phenotypes, although T-cell phenotypes are occasionally seen. The EB virus genome can usually be detected in lymphoma cells. Disease was associated with EB virus in 65% of patients with extranodal NK/T-cell lymphoma, nasal type compared with 50% of patients with PTCL-NOS. Suwiwat et al. [13] detected cell-free EBV DNA in 32/38 (84%) of adult PTCL patients, but failed to find EBV in controls. Rates of EB virus were higher in that report than in our study, possibly because Suwiwat et al. examined adults rather than children. However, we found EB virus in three of four patients who had HPS as the initial clinical feature. EB virus associated with HPS is sometimes seen in childhood, and some of these patients might also have PTCL. T-cell lymphoma-associated hemophagocytic syndrome (T-LAHS) has been frequently reported in Asian countries and is considered to have an extremely poor prognosis. Tong et al. [14] retrospectively analyzed the records of 113 patients with aggressive T-cell lymphoma, of which 28 had LAHS. The therapeutic results of chemotherapy alone or in combination with other modalities were discouraging for T-LAHS and the survival time for most patients was no more than 1 year. In the present study, unlike in other reports, three of four patients with HPS remained disease-free at last follow-up.

TABLE I. Clinical Characteristics and Outcomes for 21 Patients With Peripheral T-Cell Lymphoma

	Age	Gender	Diagnosis	Initial lesion	Stage	Treatment	Response	Relapse	Transplantation	Association of EB virus	Survival time (months)
1	6	M	PTCL-NOS	Liver, spleen	4	JACLS NHL98ER	PR	N	Y	N	68+
2	4	F	PTCL-NOS	HPS	4	ALL (T)	CR	N	N	Y	60+
3	16	M	PTCL-NOS	Cervical	3	BFM NHL-T	PR	N	Y	N	36+
4	5	F	PTCL-NOS	Skin	1	JACLS NHL98T	CR	N	N	N	12+
5	7	M	PTCL-NOS	Cervical, HPS	1	None		N	N	Y	9+
6	9	M	PTCL-NOS	Cervical, spleen	3	TCCSG NHLT01	CR	N	N	ND	57+
7	11	F	PCTL-NOS	Cervical	1	T-LBL	CR	Y	Y	N	12
8	1	F	PTCL-NOS	HPS		VP16 + DEX	CR	N	Y	Y	30+
9	12	M	PTCL-NOS	Submandibular	3	CHOP	PR	N	Y	Y	30+
10	14	F	Subcutaneous panniculitis-like	Skin	2	Steroid	CR	N	Y	N	8+
11	14	M	AITL	Cervical	4	JACLS NHL98T	CR	N	N	N	96+
12	17	M	Extranodal NK/T nasal type	Adrenal grand, HPS	3	None		N	N	N	0
13	14	F	Extranodal NK/T nasal type	Skin	4	93mix	CR	N	Y	N	132+
14	21	F	Extranodal NK/T nasal type	Sinusoidal	4	HLH94	CR	Y	N	Y	30+
15	10	F	Extranodal NK/T nasal type	Orbit, breast	3	DeVIC	PD	Y	Y	N	36+
16	18	F	Extranodal NK/T nasal type	Nasal sinus, kidney, ovary	4	ALL (B)	PD	N	Y	Y	5
17	11	M	Extranodal NK/T nasal type	Skin	3	TCCSG NHL B96-04	CR	N	N	N	107+
18	18	M	Extranodal NK/T nasal type	Nasopharynx	2	Radiation	CR	Y	N	Y	105+
19	8	F	Extranodal NK/T nasal type	Skin	1	CCLSG NHL960LB	CR	N	N	Y	94+
20	10	M	Extranodal NK/T nasal type	Nasal sinus	1	DeVIC + radiation	CR	Y	Y	Y	45+
21	18	F	Extranodal NK/T nasal type	Nasal sinus, HPS	2	CHOP	PR	N	Y	Y	147+

PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; HPS, hemophagocytic syndrome; CR, complete response, PR, partial response; PD, progressive disease; Y, yes; N, no; ND, no data. The drugs contained in remission introduction of each treatment is as follows: JACLS NHL98ER, vincristine (VCR), pirarubicin (THP-ADR), cyclophosphamide (CPM), L-asparaginase (L-asp), dexamethasone (DEX), prednisolone (PSL), JACLS NHL98T, VCR, CPM, adriamycin (ADR), L-asp, PSL, TCCSG NHLT01, VCR, CPM, ADR, L-asp, THPADR, PSL, CHOP: CPM, ADR, VCR, PSL, HLH94: etoposide (VP16), DEX, cyclosporine, DeVIC: DEX, ifosfamide, carboplatinum, VP16, TCCSG NHL B96-04: CPM, VP16, methotrexate (MTX), PSL, CCLSG NHL960LB: CPM, VCR, PRD, ADR, MTX.

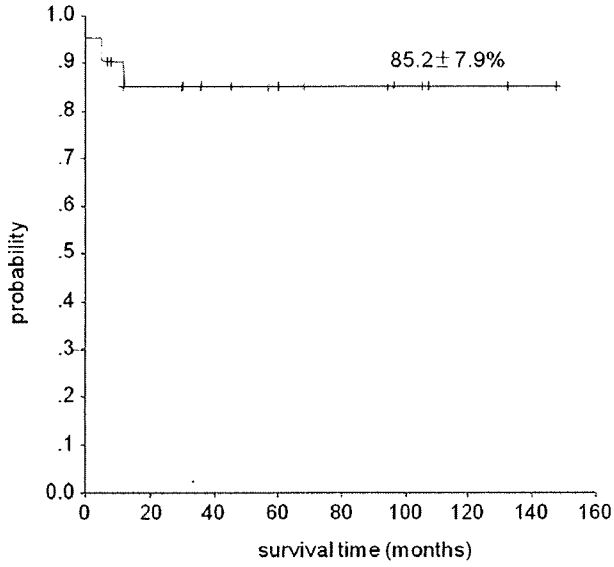

Fig. 1. Survival rate of patients with peripheral T-cell lymphoma. Five-year survival rate was 85.2%.

The findings of the present study differ from those of past reports of PTCL that included adults and children. However, the present study examined only a small number of patients. Larger studies are needed to confirm these findings.

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EDUCATIONAL REPORT

Long-term results of the Japanese Childhood Cancer and Leukemia Study Group studies 811, 841, 874 and 911 on childhood acute lymphoblastic leukemia

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We analyzed the long-term outcomes of 1021 patients with acute lymphoblastic leukemia (ALL), enrolled in four successive clinical trials (ALL811, ALL841, ALL874 and ALL911) between 1981 and 1993. All patients received risk-adopted therapy according to leukocyte count and age at the time of diagnosis. The median follow-up durations of the four studies were 17.8 years in ALL811, 15.5 years in ALL841, 11.9 years in ALL874 and 15.8 years in ALL911. Patients' event-free survival (EFS) and overall survival (OS) rates at 12 years were 41.0 and 54.3% in ALL811, 50.2 and 60.2% in ALL841, 57.3 and 64.7% in ALL874, and 63.4 and 71.7% in ALL911, respectively. Thus, cure can become a reality for about 70% of children with ALL. There is, however, still a significant difference in survival outcomes according to risk group. Late effects were observed in 70 patients out of 834 (8.4%); hepatitis and short stature were most commonly reported. Reduction of late adverse effects for all patients and development of new treatment strategies for very-high-risk patients are major issues for upcoming trials to address.
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Keywords: childhood; acute lymphoblastic leukemia; long-term outcome

Introduction

The therapeutic experience of acute lymphoblastic leukemia (ALL) is one of the true success stories of modern clinical oncology. Incremental advances in treatment success span a 50-year period during which ALL has progressed from a uniformly fatal disease to an illness with an overall cure rate of 75–85%.[1–4] This extraordinary progress has resulted from advances in treatment beginning with the identification of effective single-agent chemotherapy in the late 1940s, followed by development of combination and maintenance chemotherapy and introduction of central nervous system (CNS) preventive therapy in the 1960s. Tailoring therapy according to risk factors, followed by more intensified chemotherapy with improvements in supportive care, further increased the cure rate from the 1980s through early 1990s. On the other hand, late adverse effects have become an important issue disturbing the quality of life of long-term survivors.

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For over 25 years, we have conducted successive clinical trials (ALL811, ALL841, ALL874, ALL911, ALL941 and ALL2000) on children with ALL, and have achieved consistent improvement in treatment outcomes.[5–12] Here, we show long-term outcomes of patients treated from the early 1980s through the mid 1990s (ALL811, ALL841, ALL874 and ALL911), and also discuss late adverse effects.

Materials and methods

Patients

A total of 1021 untreated ALL patients below 18 years of age were registered to participate in a series of Japanese Childhood Cancer and Leukemia Study Group (JCCLSG) trials (ALL811, ALL841, ALL874 and ALL911) conducted in 21 hospitals, all of which were members of the JCCLSG. Written informed consent was provided by patients or legal guardians before treatment. ALL diagnoses were based on cytomorphology (FAB criteria, L1/L2) and cytochemistry when ≧25% lymphoblastic cells were present in bone marrow samples. Flow-cytometric immunophenotyping was performed only for patients in the ALL911 studies at the central laboratory (Aichi Medical University), but was not mandatory. Based on age and leukocyte count at diagnosis,[6] patients were stratified into one of the following groups: low-risk (LR), intermediate-risk (IR) or high-risk (HR). In ALL811, patients in the LR or IR group were defined as the standard-risk (SR) group.[7] Of HR patients in ALL911, cases with initial leukocyte count greater than 100×10^9/l were further stratified into a 'high-high-risk' (HHR) group (Table 1).

Treatment protocols

Details of treatment protocols have been described in earlier publications.[7–10] An outline of treatment regimens in the protocols and detailed therapy schedules, including drug dosage, are provided in Tables 2 and 3, respectively.

ALL811. The main aim of the S811 protocol was a randomized control study of two different maintenance chemotherapies.[7] SR patients received a two-drug (VP) induction therapy consisting of vincristine (VCR) and prednisolone (PSL). After achieving complete remission, they were randomized to either arm-A, consisting of intermittent cyclic administration of four drugs (VPM-M regimen), VCR, PSL, 6-mercaptopurine (6MP) and intermediate-dose methotrexate (MTX), or arm-B, consisting of

continuous low-dose MTX and 6MP combined with VP pulse. HR patients were randomly assigned to the H811A or H811B arms to compare the high-dose (HD) MTX and cranial irradiation (CRT) regimens for CNS prophylaxis. In the H811A arm, doxorubicin (DOX) was employed as consolidation therapy.

ALL841. The main aim of this study was improvement of induction therapy. Patients in the LR group were assigned randomly to the two-drug induction regimen (VP) in the L841A arm or a three-drug regimen (VP plus L-asparaginase,LASP) in the L841B arm. The maintenance therapy consisted of the VPM-ML regimen in L841A or the VPM-ML regimen incorporating LASP in L841B. In HR patients, the efficacy of addition of cyclophosphamide (CPM) in induction and maintenance therapy was studied in the H851A and H851B arms. Starting in 1985, the treatment lasted 3 years after the point of achieving complete remission for all patients.

Table 1 Risk classification of ALL according to age and leukocyte count at diagnosis

WBC count $\times 10^9$*/l*	*Age (years)*[a]			
	1–3	*4–5*	*6–9*	*≧10*
≦5	LR (SR)	LR (SR)	IR (SR)	HR
>5, ≦10	LR (SR)	IR (SR)	HR	HR
>10, ≦50	IR (SR)	IR (SR)	HR	HR
>50	HR	HR	HR	HR
(>100)	(HHR)	(HHR)	(HHR)	(HHR)

Abbreviations: ALL, acute lymphoblastic leukemia; HR, high risk; HHR, high-high risk; IR, intermediate risk; LR, low risk; SR, standard risk.
[a]Patients < 1 year were assigned into IR (WBC count $\leqslant 10 \times 10^9$/l) or HR (WBC count $> 10 \times 10^9$/l) group.

ALL874. The primary aim of this study was to clarify whether CNS-protective chemotherapy without CRT for treatment of non-HR patients could be accepted without compromising outcomes delivered by conventional CRT regimens. LR and IR patients were assigned randomly to the conventional CRT regimen (L874A and I874A) and the HDMTX regimen without CRT (L874B and I874B). In the HR group, the consolidation regimen of intermediate-dose CPM and cytarabine (Ara-C) (CCM regimen) was compared with the regimen of high-dose CPM and Ara-C (CC regimen). In addition, reinduction therapy (VPLA) was newly employed at months 5 and 12 of therapy. The duration of treatment was 3 years for all patients, as in the ALL841 study.

ALL911. The primary aim of this study was to improve HR patient outcomes. For this, we further stratified HR patients into two groups of HR and HHR, with the latter group receiving more intensified chemotherapy. For this study, a non-randomized, single-arm study was selected because of the small number of patients per subset. The four-drug regimen (VPLA/VPLA') was used as an induction therapy for all patients, and a tetrahydropyranyl derivative of DOX (pirarubicin, THP) was used instead of DOX as the VPLA' regimen for LR and IR patients. The IR, HR and HHR groups received the same consolidation (CCM) and reinduction therapy (VLPA'). For CNS prophylaxis, CRT was omitted for the LR and IR patients. The duration of treatment was 2 years for the LR group and 3 years for the other three groups.

Late effects

A set of written questions on late adverse effects on patients treated with one of the four protocols (ALL811, ALL841, ALL874 and ALL911) was sent to all participating institutes in

Table 2 Outlines of JCCLSG protocols for childhood ALL

Study	*Protocols*	*Remission induction*	*Consolidation*	*Reinduction*	*CNS prophylaxis*[a]	*Maintenance chemotherapy*
ALL811	S811A	VP	—	—	CRT (18 Gy)	VPM-M
	S811B	As in S811A	—	—	As in S811A	MM-VP
	H811A	VPC	DOX ×3	—	HDMTX	VPM-HDMTX
	H811B	VPCA	—	—	CRT (18 Gy)	VPM-M-AC
ALL841	L841A	VP	—	—	CRT (18 Gy)	VPM-M
	L841B	VPL	—	—	As in L841A	VPM-ML
	I841B	As in L841B	—	—	As in L841A	As in L841B
	I841C	As in L841B	DOX ×4	—	HDMTX	VPM-M-AC
	H851A	VPC	As in I841C	—	HDMTX	VPM-HDMTX
	H851B	As in H851A	As in I841C	—	As in H851A	As in I841C
ALL874	L874A	VPL		—	CRT (18 Gy)	VPM-M
	L874B	As in L874A	—	—	HDMTX	As in L874A
	I874A	As in L874A	—	—	CRT (18 Gy)	VPMA-HDMTX
	I874B	As in L874A	—	—	HDMTX	As in I874A
	H874A	VPLA	CCM ×3	VPLA	CRT (24 Gy)+HDMTX	As in L874A
	H874B	As in 874A	CC ×3	As in 874A	As in H874A	As in L874A
ALL911	L911	VPLA'	—	—	HDMTX	VPMA-M
	I911	As in L911	CCM ×2	VPLA'	TIT	VPMA-M/VPM-M[b]
	H911	VPLA	CCM ×3	VPLA' ×2	CRT (18 Gy)	As in I911
	HH911	As in H911	As in H911	As in H911	CRT (24 Gy)	VPMA-M-EC/VPM-M-EC[b]

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial irradiation; DOX, doxorubicin; HDMTX, high-dose methotrexate; JCCLSG, Japanese Childhood Cancer and Leukemia Study Group; TIT, triple intrathecal therapy; VP, vincristine+prednisolone; VPC, vincristine+prednisolone+cyclophosphamide; VPCA, vincristine+prednisolone+cyclophosphamide+doxorubicin; VPL, vincristine+prednisolone+L-asparaginase; VPLA, VPL+doxorubicin; VPLA', VPL+pirarubicin.
[a]Proportion of patients who received prophylactic CRT in each study: 138/207 (66.6%) in ALL811, 85/220 (38.6%) in ALL841, 275/371 (74.1%) in ALL874 and 110/223 (49.3%) in ALL911.
[b]Anthracycline (DOX/THP) was omitted in the second and third years.

Table 3 Drug dosage and schedules for the JCCLSG ALL protocols

Regimen		*Administration*	*Daily dose*	*Days*
Induction phase				
VP	Vincristine	IV	2 mg/m^2	1, 8, 15, 22
	Prednisolone	Orally	60 mg/m^2	1–28
VPC (VP+CPM)	Cyclophosphamide	IV	1.2 g/m^2	1
VPCA (VP+CPM+DOX)	Cyclophosphamide	IV	300 mg/m^2	15
	Doxorubicin	IV	20 mg/m^2	1
VPL (VP+LASP)	L-asparaginase	IV	2000 U/m^2	1, 3, 5, 8, 10, 12, 15, 17, 19
VPLA (VPL+DOX)	Doxorubicin	IV	25 mg/m^2	8, 15, 22
VPLA′ (VPL+THP)	Pirarubicin	IV	30 mg/m^2	8, 15, 22
Consolidation phase				
DOX	Doxorubicin	IV	20 mg/m^2	1–4
CCM	Cyclophosphamide	IV	400 mg/m^2	1, 15
	Cytarabine	IV	75 mg/m^2 × 2	1–4, 15–18
	6-Mercaptopurine	Orally	60 mg/m^2	1–28
CC	Cyclophosphamide	IV	1.2 g/m^2	1
	Cytarabine	IV	1.5 g/m^2 × 2	15, 16
EC	Etoposide	IV	100 mg/m^2	1–3
	Cytarabine	IV	2 g/m^2 × 2	1–4
CNS prophylaxis				
See Table 6				
Maintenance phase				
VPM-M	Vincristine	IV	2 mg/m^2	1
	Prednisolone	Orally	120 mg/m^2	1–5
	6-Mercaptopurine	Orally	175 mg/m^2	1–5
	Methotrexate	IV	225 mg/m^2	14
MM-VP	6-Mercaptopurine	Orally	50 mg/m^2	1–28
	Methotrexate	Orally	20 mg/m^2	1–28
	Vincristine	IV	2 mg/m^2	1
	Prednisolone	Orally	120 mg/m^2	1–5
VPM-ML	Similar to VPM-M except for 6MP (250 mg/m^2) and LASP (2000 U/m^2), every 4 weeks			
VPM-M-AC	Similar to VPM-M except for CPM (300 mg/m^2), day 28 & DOX (20 mg/m^2), day 1			
VPM-HDMTX	Similar to VPM-M except for HDMTX (6 g/m^2), every 4 weeks			
VPMA-HDMTX	Similar to VPMA-M except for HDMTX (4.5 g/m^2), every 6 weeks.			
VPMA-M	Similar to VPM-M except for DOX 20 mg/m^2 or THP 30 mg/m^2, day 1			
VPMA-M-EC	Similar to VPMA-M except for VP16 (150 mg/m^2) and Ara-C (300 mg/m^2), day 28			
VPM-M-EC	Similar to VPM-M except for VP16 (150 mg/m^2) and Ara-C (300 mg/m^2), day 28			

Abbreviations: ALL, acute lymphoblastic leukemia; Ara-C, cytarabine; HDMTX, high-dose methotrexate; IV, intravenous; JCCLSG, Japanese Childhood Cancer and Leukemia Study Group.

March 2002, and the questionnaire was collected in June that year.

Statistical analysis

Final statistical analyses of ALL911 patients were based on data obtained in June 2008, while those of subjects in the ALL811, ALL841 and ALL874 studies used data obtained in June 2001, when the final survey on outcomes was taken. Survival curves were prepared by the Kaplan–Meier method and a log-rank test was used to detect significant differences between groups. Overall survival (OS) was defined as the time between disease diagnosis and death, and event-free survival (EFS) was defined as the time to first occurrence of induction failure, relapse at any site, death or secondary malignant neoplasm. For patients who experienced no events, EFS was the time to the most recent follow-up. CNS relapse-free survival and bone marrow relapse-free survival were measured from the end of induction and excluded patients who failed to achieve complete remission. The SPSS statistical analysis software (SPSS 12.0J, Japan Inc., Tokyo, Japan) was used for all computations.

Results

Survival outcomes

Long-term survival curves for patients over the four ALL studies are presented in Figure 1. The median follow-up duration of the four studies was as follows: 17.8 years (range 3.1–20.5 years) for 110 survivors in ALL811, 15.5 years (5.1–17.3 years) for 131 survivors in ALL841, 11.9 years (5.3–14.1 years) for 235 survivors in ALL874 and 15.8 years (4.3–18.3 years) for 159 survivors in ALL911. Their EFS and OS at 12 years were 41.0 ± 3.6 and 54.3 ± 3.3% in ALL811 (n = 207), 50.2 ± 3.5 and 60.2 ± 3.3% in ALL841 (n = 220), 57.3 ± 2.7 and 64.7 ± 2.5% in ALL874 (n = 371), and 63.4 ± 3.3 and 71.7 ± 3.0% in ALL911 (n = 223).

Treatment outcomes

Treatment outcomes for the four ALL studies are shown in Table 4 and survival outcomes at 5-year intervals according to treatment protocol and presenting features are shown in Tables 5a–5d.

ALL811. A total of 230 children were enrolled in the ALL811 study, of which 207 patients were evaluable. Ages ranged from

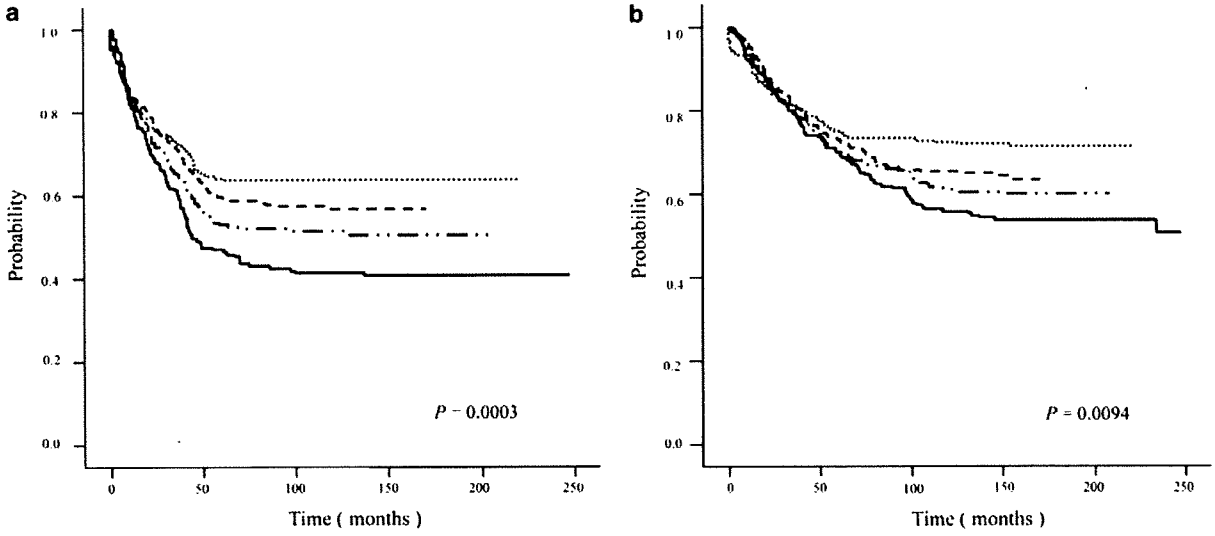

Figure 1 Kaplen–Meier curves for EFS (**a**) and OS (**b**) according to ALL studies ALL811 (——); ALL841 (–· ··–· ··); ALL874 (----) and ALL911 (· · · ·). ALL, acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival.

Table 4 Treatment outcome according to the JCCLSG ALL studies

Study	*ALL811*	*ALL841*	*ALL874*	*ALL911*	*Total*
Year	1981–1984	1984–1987	1987–1990	1991–1993	1981–1993
No. of patients	207	220	371	223	1021
Induction failure (%)	11 (5.3)	11 (5.2)	14 (3.7)	9 (4.0)	45 (4.4)
Death during remission (%)	2 (1.0)	1 (0.5)	3 (0.8)	9 (4.0)	15 (1.5)
Infection	2	1	3	6	12
Other causes	0	0	0	3	3
Relapses					
Hematological only	59	56	93	41	249
CNS only	15	29	19	15	78
Hematological+CNS	16	4	8	4	32
Testicular only	9	1	4	2	16
Other	1	0	0	0	1
Secondary cancer	2	1	2	2	7
12-year cumulative risk of BM relapse (%)	38.2 ± 4.1	31.4 ± 3.6	31.2 ± 2.7	21.9 ± 3.0	
12-year cumulative risk of CNS relapse (%)	10.8 ± 2.7	17.9 ± 3.1	7.7 ± 1.7	8.5 ± 2.1	
12-year cumulative risk of combined[a] relapse (%)	10.5 ± 2.6	2.5 ± 1.3	3.3 ± 1.2	2.7 ± 1.4	
12-year cumulative risk of testicular relapse (%)	8.7 ± 2.9	0.9 ± 0.9	1.8 ± 0.9	1.3 ± 1.0	
12-year EFS ± s.e. (%)	40.4 ± 3.6	50.2 ± 3.5	57.3 ± 2.7	63.4 ± 3.3	
P-value		0.0895 (vs ALL811)	0.1142 (vs ALL841)	0.2883 (vs ALL874)	
12-year OS ± s.e. (%)	54.3 ± 3.5	60.2 ± 3.3	64.7 ± 2.7	71.7 ± 3.0	
P-value		0.2523 (vs ALL811)	0.1142 (vs ALL841)	0.2883 (vs ALL874)	

Abbreviations: ALL, acute lymphoblastic leukemia; BM, bone marrow; EFS, event-free survival; OS, overall survival; JCCLSG, Japanese Childhood Cancer and Leukemia Study Group.
[a]BM+CNS relapse.

0.5 to 15.8 years, with a median of 4.5. In the SR group, the outcome of the S811A study was significantly superior to that of the S811B study. For the HR group, the H811B protocol was closed in 1982 because interim analysis showed an unexpectedly low remission induction rate (16/20, 80%). However, results of long-term outcomes showed that H811B patients seemed to have a better outcome than H811A patients, although the difference did not reach a statistically significant level. Unfavorable prognostic features included NCI high-risk (age <1 or >10 years, with WBC count $>50 \times 10^9$/l),[13] high WBC counts ($\geqq 50 \times 10^9$/l), older age (>10 years) and female gender, in descending order (Table 5a). Two S811A patients developed secondary cancers (one thyroid cancer and one rhabdoid tumor).

ALL841. A total of 237 children were enrolled in the ALL841 study, with 220 evaluable patients. Ages ranged from 0.4 to 15.7 years, with a median of 5.0. EFS for L841B was significantly higher than that for L841A. Although I841B patients received the same regimen as those in L841B, they showed a significantly lower EFS rate. In HR protocols, there was no significant difference between H851A and H851B. Unfavorable prognostic features included NCI high-risk, older age (>10 years) and high

Table 5a Survival outcomes according to treatment protocols and presenting features in patients treated in ALL811

Factors	*No. of patients*	*Event-free survival ± s.e. (%)*					*Overall survival ± s.e. (%)*				
		Year 5	*Year 10*	*Year 15*	*Year 20*	P-*value*	*Year 5*	*Year 10*	*Year 15*	*Year 20*	P-*value*
Protocols											
S811A	62	72.7 ± 5.8	65.4 ± 6.3	65.4 ± 6.3	65.4 ± 6.3	0.0015	87.1 ± 4.3	75.8 ± 5.4	72.4 ± 5.7	72.4 ± 5.7	0.0475
S811B	55	43.3 ± 7.0	34.6 ± 5.8	34.6 ± 5.8	34.6 ± 5.8		74.4 ± 5.9	59.2 ± 6.7	57.3 ± 6.8	57.3 ± 6.8	
H811A	69	24.6 ± 5.6	21.1 ± 5.3	19.2 ± 5.2	19.2 ± 5.2	0.1846	55.0 ± 6.0	35.6 ± 5.8	34.0 ± 5.8	34.0 ± 5.8	0.5225
H811B	21	47.1 ± 11.0	47.1 ± 11.0	47.1 ± 11.0	47.1 ± 11.0		57.1 ± 10.8	52.4 ± 10.9	52.4 ± 10.9	52.4 ± 10.9	
NCI risk											
Standard	142	56.4 ± 4.4	49.8 ± 4.4	49.8 ± 4.4	49.8 ± 4.4	<0.0001	80.2 ± 3.4	65.2 ± 4.0	62.9 ± 4.1	62.9 ± 4.1	<0.0001
High	65	26.1 ± 5.7	22.5 ± 5.4	20.2 ± 5.3	20.2 ± 5.3		47.6 ± 6.2	34.7 ± 6.0	32.9 ± 5.9	32.9 ± 5.9	
Sex											
Male	122	51.4 ± 4.7	46.7 ± 4.7	45.7 ± 4.7	45.7 ± 4.7	0.0732	75.3 ± 3.9	61.0 ± 4.5	58.3 ± 4.5	58.3 ± 4.5	0.0493
Female	85	40.0 ± 5.6	32.8 ± 5.5	32.8 ± 5.5	32.8 ± 5.5		62.3 ± 5.3	47.9 ± 5.4	46.7 ± 5.4	40.1 ± 7.7	
Age (years)											
<1	9	33.3 ± 15.7	33.3 ± 15.7	33.3 ± 15.7	33.3 ± 15.7		44.4 ± 16.6	33.3 ± 15.7	33.3 ± 15.7	33.3 ± 15.7	
1–9	162	49.7 ± 4.1	43.9 ± 4.1	43.9 ± 4.1	43.9 ± 4.1	0.0535	74.6 ± 3.4	60.2 ± 3.9	58.2 ± 3.9	55.1 ± 4.7	0.0063
>10	36	36.4 ± 8.6	29.5 ± 8.2	24.5 ± 8.2	24.5 ± 8.2		55.4 ± 8.3	40.8 ± 8.3	37.1 ± 8.3	37.1 ± 8.3	
WBC (× 10^9/l)											
<10	104	58.4 ± 5.1	50.5 ± 5.2	50.5 ± 5.2	50.5 ± 5.2		82.6 ± 3.7	65.8 ± 4.7	63.7 ± 4.8	58.8 ± 6.4	
10–49	65	49.6 ± 6.4	44.1 ± 6.5	42.1 ± 6.5	42.1 ± 6.5	0.0016	70.7 ± 5.7	61.3 ± 6.1	56.3 ± 6.2	56.3 ± 6.2	0.0003
50–99	18	12.4 ± 8.1	12.4 ± 8.1	12.4 ± 8.1	12.4 ± 8.1		33.1 ± 11.1	16.7 ± 8.8	16.7 ± 8.8	16.7 ± 8.8	
>100	20	10.0 ± 6.7	10.0 ± 6.7	10.0 ± 6.7	10.0 ± 6.7		35.0 ± 10.7	25.0 ± 9.7	25.0 ± 9.7	25.0 ± 9.7	

Abbreviation: ALL, acute lymphoblastic leukemia.

Table 5b Survival outcomes according to treatment protocols and presenting features in patients treated in ALL841

Factors	*No. of patients*	*Event-free survival ± s.e. (%)*				*Overall survival ± s.e. (%)*			
		Year 5	*Year 10*	*Year 15*	P-*value*	*Year 5*	*Year 10*	*Year 15*	P-*value*
Protocols									
L841A	39	64.1 ± 7.7	61.5 ± 7.8	61.5 ± 7.8	0.0333	84.6 ± 5.8	74.4 ± 7.0	74.4 ± 7.0	0.1660
L841B	21	90.0 ± 6.7	90.0 ± 6.7	90.0 ± 6.7		90.5 ± 6.4	90.5 ± 6.4	90.5 ± 6.4	
I841B	25	62.7 ± 10.5	62.7 ± 10.5	57.0 ± 11.0	0.7715	75.0 ± 8.8	61.4 ± 10.2	61.4 ± 10.2	0.2579
I841C	48	61.9 ± 7.1	59.7 ± 7.1	59.7 ± 7.1		81.6 ± 5.5	73.3 ± 6.4	73.3 ± 6.4	
H851A	44	23.8 ± 7.2	20.8 ± 6.9	20.8 ± 6.9	0.8468	47.7 ± 7.5	34.1 ± 7.2	31.8 ± 7.0	0.2899
H851B	43	33.5 ± 7.3	30.4 ± 7.2	30.4 ± 7.2		55.8 ± 7.6	46.4 ± 7.6	44.0 ± 7.6	
NCI risk									
SR	165	61.6 ± 3.9	59.6 ± 3.9	58.2 ± 4.0	<0.0001	79.4 ± 3.2	70.1 ± 3.6	69.4 ± 3.6	<0.0001
HR	55	24.1 ± 6.3	24.1 ± 6.3	24.1 ± 6.3		43.6 ± 6.7	32.7 ± 6.3	30.9 ± 6.2	
Sex									
Male	134	54.4 ± 4.5	52.7 ± 4.5	51.8 ± 4.5	0.4715	73.9 ± 3.8	64.0 ± 4.2	64.0 ± 4.2	0.0951
Female	86	50.4 ± 5.5	49.0 ± 5.5	47.6 ± 5.6		65.1 ± 5.1	55.6 ± 5.4	53.1 ± 5.4	
Age (years)									
<1	7	57.1 ± 18.7	57.1 ± 18.7	57.1 ± 18.7		71.4 ± 17.1	71.4 ± 17.1	71.4 ± 17.1	
1–9	181	58.3 ± 3.8	58.3 ± 3.8	58.3 ± 3.8	<0.0001	75.7 ± 3.2	66.6 ± 3.5	65.5 ± 3.6	<0.0001
>10	32	17.1 ± 7.4	17.1 ± 7.4	17.1 ± 7.4		40.6 ± 8.7	25.0 ± 7.7	25.0 ± 7.7	
WBC (× 10^9/l)									
<10	107	67.7 ± 4.7	66.6 ± 4.8	64.4 ± 4.9	0.0019	81.3 ± 3.8	72.7 ± 4.3	71.7 ± 4.4	0.0201
10–49	78	45.5 ± 5.8	42.6 ± 5.8	42.6 ± 5.8		69.2 ± 5.2	56.1 ± 5.7	56.1 ± 5.7	
50–99	14	19.6 ± 11.9	19.6 ± 11.9	19.6 ± 11.9	0.7781	35.7 ± 12.8	28.6 ± 12.1	21.4 ± 11.0	0.8368
>100	21	25.1 ± 9.7	25.1 ± 9.7	25.1 ± 9.7		42.9 ± 10.8	38.1 ± 10.6	38.1 ± 10.6	

Abbreviation: ALL, acute lymphoblastic leukemia.

WBC counts (≧50 × 10^9/l), in descending order (Table 5b). One HR851A patient developed acute myeloblastic leukemia with t(8; 21).

ALL874. A total of 389 children were enrolled in the ALL841 study, including 371 evaluable patients. Ages ranged from 0.9 to 16.7 years, with a median of 5.1. For the LR and IR groups,

Table 5c Survival outcomes according to treatment protocols and presenting features in patients treated in ALL874

Factors	*No. of patients*	*Event-free survival ± s.e. (%)*				*Overall survival ± s.e. (%)*			
		Year 5	*Year 10*	*Year 12*	P-*value*	*Year 5*	*Year 10*	*Year 12*	P-*value*
Protocols									
L874A	42	78.2 ± 6.4	73.1 ± 6.9	73.1 ± 6.9	0.9615	85.7 ± 5.4	83.3 ± 5.8	83.3 ± 5.8	0.5554
L874B	41	72.6 ± 7.4	72.6 ± 7.4	72.6 ± 7.4		87.5 ± 5.2	79.8 ± 6.4	76.9 ± 6.8	
I874A	55	63.5 ± 6.9	61.5 ± 7.0	61.5 ± 7.0	0.6666	87.0 ± 4.6	75.4 ± 5.9	75.4 ± 5.9	0.8647
I874B	55	62.4 ± 6.8	56.0 ± 7.1	56.0 ± 7.1		85.2 ± 4.8	74.1 ± 6.0	74.1 ± 6.0	
H874A	99	57.5 ± 5.2	56.3 ± 5.2	56.3 ± 5.2	0.0151	63.7 ± 4.8	57.8 ± 4.9	57.8 ± 4.9	0.0862
H874B	79	39.4 ± 6.0	34.7 ± 5.9	34.7 ± 5.9		51.9 ± 5.6	44.3 ± 5.6	44.3 ± 5.6	
NCI risk									
Standard	227	66.8 ± 3.2	63.8 ± 3.3	63.8 ± 3.3	<0.0001	83.7 ± 2.5	76.0 ± 2.9	75.5 ± 2.9	<0.0001
High	144	47.3 ± 4.6	43.6 ± 4.6	43.6 ± 4.6		55.6 ± 4.1	47.9 ± 4.2	47.9 ± 4.2	
Sex									
Male	228	58.1 ± 3.4	54.9 ± 3.5	54.9 ± 3.5	0.5118	72.4 ± 3.0	63.5 ± 3.2	63.5 ± 3.2	0.5801
Female	143	62.4 ± 4.3	59.0 ± 4.4	59.0 ± 4.4		73.4 ± 3.7	67.7 ± 3.9	66.8 ± 4.0	
Age (years)									
< 1	1	100	—	—		100	100	100	
1–9	283	64.3 ± 3.0	61.4 ± 3.0	61.4 ± 3.0	<0.0001	79.2 ± 2.4	71.6 ± 2.7	71.1 ± 2.7	<0.0001
> 10	87	43.0 ± 5.9	38.4 ± 5.8	38.4 ± 5.8		51.7 ± 5.4	43.7 ± 5.3	43.7 ± 5.3	
WBC × 10⁹/l									
< 10	179	68.2 ± 3.6	63.0 ± 3.8	63.0 ± 3.8	0.2395	79.3 ± 3.0	72.5 ± 3.4	71.9 ± 3.4	0.4621
10–49	111	57.0 ± 5.0	56.0 ± 5.0	56.0 ± 5.0		78.4 ± 3.9	67.3 ± 4.5	67.3 ± 4.5	
50–99	31	69.5 ± 8.5	65.4 ± 8.9	65.4 ± 8.9	0.0018	77.4 ± 7.5	74.2 ± 7.9	74.2 ± 7.9	0.0001
> 100	50	24.6 ± 7.0	24.6 ± 7.0	24.6 ± 7.0		34.0 ± 6.7	28.0 ± 6.4	28.0 ± 6.4	

Abbreviation: ALL, acute lymphoblastic leukemia.

Table 5d Survival outcomes according to treatment protocols and presenting features in patients treated in ALL911

Factors	*No. of patients*	*Event-free survival ± s.e. (%)*				*Overall survival ± s.e. (%)*			
		Year 5	*Year 10*	*Year 15*	P-*value*	*Year 5*	*Year 10*	*Year 15*	P-*value*
Protocols									
L911	47	73.4 ± 6.6	73.4 ± 6.6	73.4 ± 6.6	0.3985	89.3 ± 4.5	80.6 ± 5.8	78.4 ± 6.1	0.7210
I911	66	67.8 ± 6.0	67.8 ± 6.0	67.8 ± 6.0		80.3 ± 4.9	77.2 ± 5.2	77.2 ± 5.2	
H911	77	67.4 ± 5.5	67.4 ± 5.5	67.4 ± 5.5	0.0001	77.9 ± 4.7	76.6 ± 4.8	76.6 ± 4.8	<0.0001
HH911	33	28.7 ± 8.5	28.7 ± 8.5	28.7 ± 8.5		36.0 ± 8.5	36.0 ± 8.5	36.0 ± 8.5	
NCI risk									
Standard	139	72.1 ± 3.9	71.3 ± 3.9	71.3 ± 3.9	0.0008	85.6 ± 3.0	81.2 ± 3.3	79.7 ± 3.4	0.0001
High	84	50.0 ± 5.7	50.0 ± 5.7	50.0 ± 5.7		57.1 ± 5.4	57.1 ± 5.4	57.1 ± 5.4	
Sex									
Male	137	63.0 ± 4.3	63.0 ± 4.3	63.0 ± 4.3	0.8213	75.9 ± 3.7	72.9 ± 3.8	72.2 ± 3.8	0.5635
Female	86	65.2 ± 5.2	65.2 ± 5.2	65.2 ± 5.2		73.3 ± 4.8	70.9 ± 4.9	69.7 ± 5.0	
Age (years)									
< 1	2	50.0 ± 35.4	50.0 ± 35.4	50.0 ± 35.4		50.5 ± 35.4	50.5 ± 35.4	50.5 ± 35.4	
1–9	171	68.5 ± 3.7	67.9 ± 3.7	67.9 ± 3.7	0.0042	80.7 ± 3.0	77.1 ± 3.2	75.9 ± 3.3	0.0034
> 10	50	48.4 ± 7.4	48.4 ± 7.4	48.4 ± 7.4		56.0 ± 7.0	56.0 ± 7.0	56.0 ± 7.0	
WBC (× 10⁹/l)									
< 10	115	73.8 ± 4.2	72.9 ± 4.2	72.9 ± 4.2	0.1643	86.1 ± 3.2	81.7 ± 3.6	79.9 ± 3.8	0.2242
10–49	60	63.8 ± 6.5	63.8 ± 6.5	63.8 ± 6.5		75.0 ± 5.6	73.3 ± 5.7	73.3 ± 5.7	
50–99	13	61.5 ± 13.5	61.5 ± 13.5	61.5 ± 13.5	0.0940	76.9 ± 11.7	76.9 ± 11.7	76.9 ± 11.7	0.0354
> 100	35	30.0 ± 8.3	30.0 ± 8.3	30.0 ± 8.3		37.1 ± 8.2	37.1 ± 8.2	37.1 ± 8.2	

Abbreviation: ALL, acute lymphoblastic leukemia.

there was no significant difference in outcome between protocols. Conversely, in the HR group, H874A patients showed significantly better outcomes than those of H874B. Unfavorable prognostic features included older age (>10 years), NCI high-risk and very high WBC counts (≧100 × 10^9/l), in descending order (Table 5c). One LR874A patient developed a

Table 6 Life-table estimates of survival at 12 years by risk group for CNS regimens

	CNS regimens by risk group	*Measure of survival, % (s.e.)*			
		CNS relapse-free		*BM relapse-free*	
Low risk					
L874A	IT ×3+CRT (18 Gy)	97.2 (3.2)	ns	77.2 (6.8)	ns
L874B	IT ×13+HDMTX ×3	90.2 (5.4)		82.6 (6.5)	
L911	Same as in L874B	90.7 (4.5)		85.3 (5.6)	
Intermediate risk					
I841B	IT ×3+CRT (18 Gy)	87.5 (8.3)	ns	67.9 (11.1)	ns
I841C	IT ×1+HDMTX ×5	87.1 (5.4)		72.3 (6.9)	
I874A	IT ×3+HDMTX ×1+CRT (18 Gy)	100	$P=0.01$	68.1 (6.8)	ns
I874B	IT ×1+HDMTX ×4	79.3 (6.2)		70.6 (7.0)	
I911	TIT ×24	98.1 (1.9)		83.9 (1.9)	
High risk					
H851A	IT ×3+HDMTX ×6	74.7 (8.6)		31.9 (9.6)	
H851B	Same as in H851A	60.2 (9.6)		55.8 (9.8)	
H874A	TIT ×8+HDMTX ×3+CRT (18 Gy)	95.5 (2.5)		67.8 (5.4)	
H874B	Same as in H874A	88.3 (5.6)		43.3 (6.6)	
H911	TIT ×6+CRT (18 Gy)	92.4 (3.3)		77.4 (5.1)	
HH911	TIT ×6+CRT (24 Gy)	71.7 (11.1)		50.1 (11.0)	

Abbreviations: BM, bone marrow; CRT, cranial radiation; HDMTX, high-dose MTX; IT, intrathecal MTX; MTX, methotrexate; ns, not significant; TIT, triple IT.
HDMTX: 100 mg/kg for I841C; 2 g/m^2 for L874B/I874A/L911; 4.5 g/m^2 for I874B; 3 g/m^2 for H874A/B. Folinic acid (15 mg/m^2) was given orally every 6 h for a total seven doses. Rescue begins 36 h from the start of MTX infusion.

hepatocarcinoma and one further I874A patient developed a malignant fibrous histocytoma.

ALL911. A total of 230 children were enrolled in the ALL911 study, of which 223 patients were evaluable. Ages ranged from 0.7 to 15.8 years, with a median of 5.0. In this study, HHR patient outcome was extremely poor compared with that of HR patients. On the other hand, HR group outcomes compared favorably to those of both LR and IR groups. Unfavorable prognostic features included NCI high-risk, older age (>10 years) and very high WBC counts ($\geqq 100 \times 10^9$/l), in descending order (Table 5d). One HHR911 patient developed myelodysplatic syndrome and one IR911 patient developed chronic myelogenous leukemia.

Extramedullary relapse

Table 6 shows CNS relapse-free survival by the CNS prophylaxis regimen. In our four studies, more than half of the patients received prophylactic CRT and proportion of the patients in each study is shown in Table 2. From the three protocols including L874, I841 and I874, two regimens with or without CRT were compared with respect to their ability to prevent CNS leukemia and to improve the overall ALL outcome. The CRT regimens seem to be associated with better CNS-free survival outcome than the HDMTX regimen. However, the difference was significant in only I874 but not other studies (L874 and I841), and no significant difference in systemic survival rates was observed between the two CNS regimens in either risk group. The CNS remission rate of patients treated with the I911 protocol was significantly higher than that of patients given the HDMTX regimen in the I874B protocol ($P=0.0127$), and was comparable to that of patients given the CRT regimen in the I874A protocol. In HR groups, HDMTX regimens without CRT (H851A/B) showed very poor CNS-free survival outcomes.

The incidence of isolated testicular relapse was very different between maintenance regimens. In the randomized study of SR patients in ALL811, only one of 36 (2.8%) males who received an intermittent cyclic regimen of MTX and 6MP (S811A) developed testicular relapse, in contrast to seven of 31 (22.6%) males receiving continuous administration of low-dose MTX and 6MP for maintenance chemotherapy (S811B). In addition, from the 841 protocol, only seven additional testicular relapses were seen for 497 males (Table 4).

Late effects

Questionnaire results about late adverse effects in the four studies (ALL811, ALL841, ALL874 and ALL911) were obtained from 521 of 640 (81.4%) living patients and from 313 of 381 (82.1%) deceased patients. The results are shown in Table 7. Late effects were observed in 70/834 (8.4%) patients, of whom 17 had at least two late effects. Hepatitis and short stature were most commonly reported, followed by secondary malignancy, disturbed neurocognitive function, gonadal dysfunction and cardiomyopathy. There were no cases of osteoporosis or osteopenia. More than half the patients with short stature, leukoencephalopathy or visual disturbance received CRT.

Since late adverse effects are closely correlated with cumulative doses of cytotoxic drugs used in treatment protocols, we highlighted such cumulative doses of cytotoxic drugs and antimetabolites in each protocol (Table 8). In ALL811, CPM and DOX were used only for the HR protocols. In ALL841, CPM was used for only HR, but DOX was used for the HR and I841C protocols. In ALL874, CPM and anthracycline were used, as in ALL841. In ALL911, CPM was used for the IR and HR protocols and anthracycline was used for all the protocols, including SR patients. Consequently, cumulative doses of anthracycline exceeded 400 mg/m^2 in nine protocols (HR811B, IR841C, HR841B, IR874A and IR874B and 911LR/IR/HR/HHR) and

Table 7 Late adverse effects of patients in the JCCLSG ALL studies

Study	*ALL811*	*ALL841*	*ALL874*	*ALL911*	*Total*	*Relevant factors*	
No. of patients (alive/deceased)	*81/68*	*107/76*	*214/122*	*148/52*	*550/318*	*Relapse*	*CRT*
Short stature	2/0	4/0	7/0	7/0	20/0	5	12
Hepatitis	3/0	7/0	10/0	1/0	21/0	4	1
Leukoenchalopathy	0/0	0/2	1/1	1/0	2/3	4	4
Cardiomyopathy	2/0	0/1	1/0	0	3/1	4	3
MR/LD	1/0	1/0	3/0	1/0	6/0	2	3
Gonadal dysfunction	3/0	0	0	2/0	5/0	3	2
Liver dysfuction	0	0/1	1/0	0	1/1	0	0
Visual disturbance	0	0	0	3/0	3/0	2	2
EEG abnormality	0	0	0/1	0	0/1	0	1
DM	0	0	1/0	0	1/0	0	1
Sudden death	0	0	0	0/1	0/1	0	0
Secondary malignancy	1/1	0/1	1/1	2/0	4/3	1	5
Others	4/0	0	4/0	4/0	12/0	2	5
Subtotal	8/4	8/4	26/2	20/1	79/9	27	39

Abbreviations: ALL, acute lymphoblastic leukemia; CRT, cranial irradiation; DM, diabetes mellitus; JCCLSG, Japanese Childhood Cancer and Leukemia Study Group; LD, learning disturbance; MR, mental retardation.

Table 8 Cumulative doses of drugs used in the JCCLSG ALL studies

Study	*VCR (mg)*	*CPM (mg)*	*PSL (mg)*	*LASP (kg)*	*DOX (mg)*	*THP (mg)*	*6MP (mg)*	*MTX (mg)*	*HDMTX (g)*	*VP16 (mg)*	*Ara-C (mg)*
ALL811											
SR-A	86	0	25230	0	0	0	34125	8100	18	0	0
SR-B	86	0	25230	0	0	0	50750	2940	18	0	0
HR-A	60	1200	17280	0	300	0	22750	0	6.1	0	0
HR-B	110	7800	20490	0	540	0	23325	1500	0	0	0
ALL841											
LR-A	86	0	25230	0	0	0	34125	5850	30	0	0
LR/IR-B	86	0	25230	98	0	0	34125	5850	30	0	0
IR-C	108	0	16830	20	540	0	21875	0	10.5	0	0
HR-A	72	1200	17430	0	240	0	22750	0	183	0	0
HR-B	108	7800	14150	0	460	0	23100	1320	27	0	0
ALL874											
LR-A	86	0	25230	20	0	0	34125	8775	0	0	0
LR-B	86	0	25230	20	0	0	34125	8100	6	0	0
IR-A	94	0	15030	64	420	0	19250	225	92	0	0
IR-B	88	0	13680	64	450	0	18375	0	105.5	0	0
HR-A	84	2400	22270	38	225	0	31290	6750	7.5	0	3600
HR-B	84	3600	22270	38	225	0	26250	6750	7.5	0	18000
ALL911											
LR	60	0	17430	24	0	450	29250	6900	6	0	0
IR	92	1600	24370	44	0	450	33110	7650	0	0	2400
HR	88	2400	23470	44	225	240	33425	7200	0	0	3600
HHR	66	2400	16870	44	225	180	23415	4725	0	3600	10800

Abbreviations: ALL, acute lymphoblastic leukemia; Ara-C, cytarabine; CPM, cyclophosphamide; DOX, doxorubicin; HDMTX, high-dose MTX (≧500 mg/m^2); HR, high risk; HHR, high-high-risk; IR, intermediate risk; JCCLSG, Japanese Childhood Cancer and Leukemia Study Group; LASP, L-asparaginase; LR, low risk; 6MP, 6-mercaoutoprine; MTX, methotrexate; PSL, prednisolone; THP, pirarubicin; VCR, vincristine; VP16, etoposide. All doses are shown per square meter of body surface area.

cumulative doses of CPA exceeded 4 g/m^2 in two protocols (HR811B and HR851B).

Discussion

Our results reveal that the cure rate has gradually increased from 55% with ALL811 to 70% with ALL911 over an observation period of 15 years, while toxic death rates during remission were below 1% in all protocols except ALL911. These results are favorably comparable to those from large pediatric ALL trials by other study groups, and reflect the effectiveness of risk-directed therapy and improvements in supportive care of children with ALL.[2–4]

Improvement of outcome in each protocol study seems to be attributable to their respective aims. As shown in Table 4, better outcome in ALL841 as compared with that in the ALL811 is partly explained by a decrease in isolate testicular relapse.

This might be the result of the cyclic schedule of intermediate-dose MTX in maintenance therapy. Improvement in ALL874 as compared with ALL841 was mainly due to a decrease in isolated CNS relapse. This was achieved by the CRT regimen for HR patients and extended intrathecal treatment for LR patients. The better survival rates in ALL911 as compared with ALL874 were mainly due to improved outcomes of the HR patients. The intensified chemotherapy of this protocol decreased the incidence of bone marrow relapse, although therapy-related death during remission increased to 4%. More importantly, as shown in Tables 5a–5d, outcomes of patients with high ($50–99 \times 10^9$/l) WBC counts in ALL874 and ALL911 were markedly improved in comparison with those in the ALL811 and ALL841 studies. This is probably due to employment of consolidation therapy (CCM regimen) and reinduction therapy.[14]

Another major interest in our studies is a unique intermittent cyclic regimen for maintenance chemotherapy. In the ALL811 study, we showed that intermittent cyclic administration of intermediate-dose MTX (225 mg/m^2, intravenous) alternating biweekly 6MP (170 mg/day, orally for 5 days) was more effective than conventional administration of low-dose MTX (20 mg/m^2/week, orally) and 6MP (50 mg/m^2, orally, every day).[7] As a result of these data, intermittent cyclic administration of MTX and 6MP has become a standard regimen of maintenance chemotherapy in JCCLSG ALL protocols.

CNS protective chemotherapy without CRT for treatment of non-HR patients with ALL has been widely accepted.[15–19] In our study, the LR patients of L874B and L911 who received HDMTX therapy as CNS prophylaxis showed 7–9% cumulative incidence of isolated CNS relapse. However, BFM-based intensive chemotherapy using extended intrathecal chemotherapy has reported lower than 5% incidence of CNS relapse.[15,19–21] Similar results are seen in the I911 protocol, where an extended triple inrathecal MTX regimen with intensive systemic therapy achieved a 2% cumulative incidence of CNS relapse in the IR patients. Thus, it is likely that systemic intravenous infusions of HDMTX could not be substituted for intrathecal injections of MTX in the maintenance therapy for CNS protection. This is also supported by the results of meta-analysis of CNS-directed therapy, which show that radiotherapy can be replaced by long-term intrathecal therapy but not by intravenous MTX.[22]

Whether CRT can be excluded from preventive therapy for HR patients is still subject to controversy. In ALL851, we employed CNS chemoprophylaxis without CRT for the HR patients, but failed to prevent CNS relapse.[8] Since high incidence of CNS relapse is associated with high initial WBC count and T-cell phenotype,[23,24] development of a new strategy for these subgroups could overcome this difficult matter. In fact, a recent report from the Memphis group has shown that complete omission of prophylactic CRT without compromising OS can be achieved by using risk-adjusted chemotherapy based on minimal residual disease levels and pharmacogenetics.[25]

In the ALL841–911 studies, the incidence of isolated testicular relapse was 7 of 278 relapses (2.5%), which was considerably lower than the general rate of about 10%.[26] The cyclic schedule of MTX at an intermediate dose in our maintenance therapy may contribute to prevention of relapse in sanctuary sites, especially in the testes.

Development of curative therapy for pediatric ALL has produced a large population of childhood cancer survivors who face increased risk of a variety of health problems resulting from their cancer or its treatment. In particular, secondary malignancy by alkylating agents and anthracycline cardiotoxicity are the most serious late events in pediatric cancer treatment.[27,28] Fortunately, the incidences of secondary malignancies and cardiotoxicity were relatively small in our ALL studies. Although pirarubicin was chosen as an anthracyclin drug with less cardiotoxicity than DOX, it is unclear whether pirarubicin could reduce the incidence of cardiotoxicity without jeopardizing the overall outcome.[29,30] In fact, our observation period with a median of 13 years (range 8–22 years) after diagnosis is too short to estimate the true incidence of late adverse effects, because excess mortality continues at least as long as 25–30 years after treatment, for cancer survivors.[27] Therefore, establishment of a long-term, follow-up care system based on collaboration between clinical and laboratory investigators is our most urgent issue.[31,32]

Conflict of interest

The authors declare no conflict of interest.

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