Nine patients with normal karyotype were excluded from the study, because these patients had *MLL* gene rearrangements that were not detected by conventional cytogenetics. The remaining 74 were therefore classified into two subgroups: "ACA group", comprising those with additional chromosomal abnormalities other than 11q23 translocation, and "non-ACA group", comprising patients with sole 11q23 translocation with *MLL* gene rearrangements. Three-way 11q23 translocations and simple or complex structural chromosomal changes other than 11q23 abnormalities were also included in the additional chromosomal abnormalities (ACA) group, because several genetic changes in addition to *MLL* could be involved in these cases, as described in previous reports [16,17].

2.4. Statistical analysis

The analysis of treatment outcome was updated on 30 September 2007. Event-free survival (EFS) and Overall survival (OS) rates were estimated by the method of Kaplan–Meier and standard errors (SEs) with the Greenwood formula, and then were compared with the log-rank test. Confidence intervals (CIs) were computed with a 95% confidence level. The clinical and biologic features of patients in the two different subgroups were compared with χ^2 tests for homogeneity. A Cox regression model was used for the multivariate analysis. *P*-values, when cited, are two sided, with a value of 0.05 or less taken to indicate statistical significance.

Table 1
Eighteen *MLL* rearranged ALL infants with additional chromosomal abnormalities

Patient #	Karyotype	Sex	Age (month)	WBC, $\times 10^6$/L	CNS[a]	HSCT in CR1	Outcome
1	46,XX,add(11)(q25)[6]/46,XX[11]	F	4	193.8	–	No	BM relapse, DOD (2nd relapse) after UBMT
2	46,XY,t(4;11)(q21;q23),t(2;4)(q31;q32)[20] 46,XY,t(4;11)(q21;q23),t(2;4)(q31;q32) (2qter → 2q31::4q32 → 4q21::11q23 → cen → 11pter)	M	3	169.9	–	No	BM relapse, TRD after BMT
3[b]	46,XX[18],ish ins(4;11)(q21;q23.3q23.3)(RP11-216H7+, MLL5′+; MLL5′−,MLL3′+)[10]	F	2	953.0	+	No	BM relapse, DOD (2nd relapse) after UCBT
4	46,XX,t(4;11;15)(q21;q23;q22)[9]/46,XX[1]	F	0	121.6	+	RBMT	Death in CCR (TRD)
5	46,XX,add(1)(q32),der(2)t(2;4)(p1?;q21),add(4)(q21), del(11)(q?),add(16)(p11)[20]	F	8	7.7	–	No	CCR
6[b]	46,XX[20], ish ins(4;11)(q21;q23.3q23.3)(RP11-216H7+, MLL5′+,MLL3′+; MLL5′-,MLL3′-)	F	2	500.0	–	RBMT	CCR
7	48,XX,+X,t(4;11)(q21;q23),+der(4)t(4;11)(q21;q23) [20]	F	0	421.5	–	No	BM relapse, DOD
8	46,XY,der(9)t(9;11)(p22;q13),add(11)(q13)[20]	M	1	473.5	+	No	Induction failure, TRD after RBMT
9	46,XY,t(4;11;5)(q21;q23;p11)[20]	M	3	1000.0	–	UCBT	Death in CCR (TRD after 2nd UCBT because of rejection)
10	46,XX,t(2;9)(p10;q10),add(7)(p22),add(9)(p13), add(11)(p11)[20]	F	7	1.7	–	UCBT	CCR
11	46,XX,t(4;11;9)(q21;q23;q22)[20]	F	9	250.7	+	UCBT	Death in CCR (TRD)
12	46,XX,add(4)(q11)[4]/46,XX[6]	F	5	12.1	+	ABMT	Relapse, TRD after UCBT
13	46,XY, t(6;11)(p10;q10),add(11)(q23)[20]	M	5	NA	NA	No	CNS relapse, TRD after RBMT
14	48,XY,+X,add(2)(p21),del(2)(p?),+6,der(7)add(7)(p11) add(7)(q32),del(11)(q?),add(12)(q13),-17,- 17,add(19)(p13), +der(?)t(?;17)(?;q21),+mar1 [20]	M	2	25.6	+	No	DOD before initial therapy
15[b]	46,XY[20],ish ins(10;11)(p12;q23.3q23.3) (MLL5′+,MLL3′+;MLL5′, MLL3′−)	M	2	537.0	–	No	BM relapse, CCR after UBMT in CR2
16	47XX,t(4;11)(q21;q23),+?i(8)(q10)[20]	F	5	59.0	NA	No	BM relapse, DOD
17	47XX,+5,t(9;11)(p22;q23)[5]/46,XX[2]	F	3	22.8	–	UCBT	CCR
18[b]	46,XX,t(4;11)(q21;q23)[20],ish t(4;11;21)(q21;q23;q22) (216H7+; 216H7+,MLL5′+,MLL3′-; MLL3′+)	F	0	198.2	–	No	Induction failure, CCR after UBMT

F, female; M, male; WBC, white blood cell; BM, bone marrow; CNS, central nervous system; CR1, first complete remission; CCR, continuous complete remission; ABMT, autologous bone marrow transplantation; RBMT, related donor bone marrow transplantation; UCBT, unrelated cord blood transplantation; UBMT, unrelated bone marrow transplantation; DOD, death of disease; TRD, treatment related death; NA, data not available.

[a] CNS disease was diagnosed if more than five leukemic cells/μl were found in cerebrospinal fluid.

[b] FISH analysis has proven complex chromosomal abnormality in these patients. Cloning of the breakpoint regions revealed that patient #6 had 46,XX, ins(4;11)(4pter → 4q21::11q24.1 → 11q23.3(MLL3′)::11q23.3 → 11q23.3(MLL5′)::4q21 → 4qter;11pter → 11q23.3:: 11q24.1 → 11qter), and patient #15 had 46,XY, ins(10;11)(10pter → 10p12::11q23.3 → 11q23.3(MLL3′)::11q23.3 → 11q23.3(MLL5′)::10p12 → 10qter;11pter → 11q23.3:: 11q23.3 → 11qter).

3. Results

Among the 74 eligible infants, 18 (24.3%) were classified as the ACA group, as shown in Table 1. Four patients (patients #4, #9, #11, and #18) had three-way 11q23 translocation. Other novel translocations were also observed in four patients: t(2;4)(q31;q32) in patient #2, t(9;11)(p22;q13) in patient #8, t(2;9)(p10;q10) in patient #10, and t(6;11)(p10;q10) in patient #13. FISH analysis confirmed complex structural chromosomal changes in four patients including insertion of 4q21 fragment to 11q23 locus and *vice versa* resulting in *MLL-AF4* fusion gene (patients #3, #6, and #18) or insertion of 10p12 to 11q23 locus resulting in *MLL-AF10* fusion gene (patient #15). Other frequent chromosomal changes were +X in two patients, involvement in chromosome 4 in two, chromosome 5 in two, chromosome 7 in two, and chromosome 11 except 11q23 in four.

The clinical and biologic findings were compared between the ACA and non-ACA groups, including age at disease onset, sex, initial white blood cell (WBC) count, central nervous system (CNS) involvement, and type of 11q23 translocation. As shown in Table 2, the frequency of sole t(4;11)(q21;q23) was significantly higher in the non-ACA group than in the ACA group. The frequency of positive central nervous system leukemia or young age at onset also tended to be higher in the ACA group than the non-ACA group, although the difference was not statistically significant.

Among the 18 patients in the ACA group, a total of 14 events were observed: one leukemic death before initiating therapy (patient #14); two induction failure (patients #8, and #18); eight relapses (patients #1, #2, #3, #7, #12, #13, #15, and #16); three treatment-related deaths (patients #4, #9, and #11). Only four patients in this group survived without any evidence of disease (patients #5, #6, #10, and #17) (Table 1).

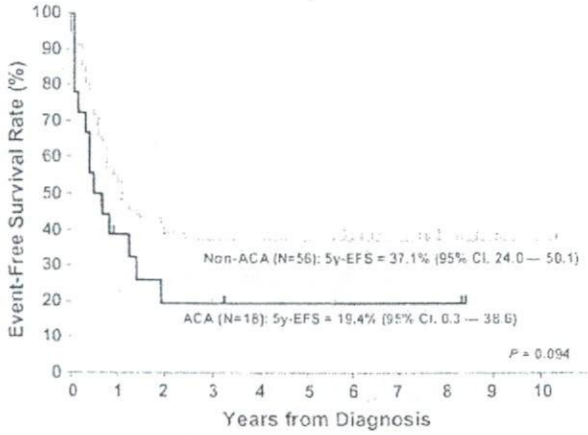

Fig. 1. Event-free survival estimates for 74 infants with ALL and *MLL* gene rearrangements in the MLL96 and MLL98 studies; a comparison between patients with additional chromosomal abnormalities and patients with sole 11q23 abnormality excluding normal karyotype with *MLL* gene rearrangements. Median follow-up period: 78 months (range, 8–124 months).

The EFS and OS rates were also compared between two groups. The 5-year EFS rate in the ACA group tended to be worse than that in the non-ACA group, without a statistically significant difference between two groups (Fig. 1). The 5-year OS in the ACA group was significantly worse than that in the non-ACA group; 26.7% (95% CI, 4.7–48.8%) *vs.* 52.1%

Table 2
Comparison in clinical and laboratory findings between the ACA and non-ACA groups

	Total number of Pt. (%)	ACA group number of Pt. (%)	Non-ACA group number of Pt. (%)	*P*-value[a]
Total number of patients	74	18	56	
Age, month				0.136
<3	21 (28.4)	8 (44.4)	13 (23.2)	
≥ 3, <6	29 (39.2)	7 (38.9)	22 (39.3)	
≥ 6	24 (32.4)	3 (16.7)	21 (37.5)	
Sex				0.650
Male	28 (37.8)	6 (33.3)	22 (39.3)	
Female	46 (62.2)	12 (66.7)	34 (60.7)	
WBC count, $\times 10^9$/L				0.599
<100	23 (31.1)	6 (33.3)	17 (30.3)	
≥ 100, <300	29 (39.2)	5 (27.8)	24 (42.9)	
>300	21 (28.4)	6 (33.3)	15 (26.8)	
NA	1 (1.3)	1 (5.6)	0 (0.0)	
CNS disease[b]				0.131
Positive	16 (21.6)	6 (33.3)	10 (17.9)	
Negative	52 (70.3)	10 (55.6)	42 (75.0)	
Unknown	6 (8.1)	2 (11.1)	4 (7.1)	
Karyotype				0.012
t(4;11)(q21;q23)	47 (63.5)	7 (38.9)	40 (71.4)	
Other 11q23	27 (36.5)	11 (61.1)	16 (28.6)	

ACA, additional chromosomal abnormalities other than 11q23 translocation; Pt., patients; WBC, white blood cell; CNS, central nervous system; NA, data not available.

[a] Comparison between two different groups.

[b] CNS disease was diagnosed if more than five leukemic cells/μL were found in cerebrospinal fluid.

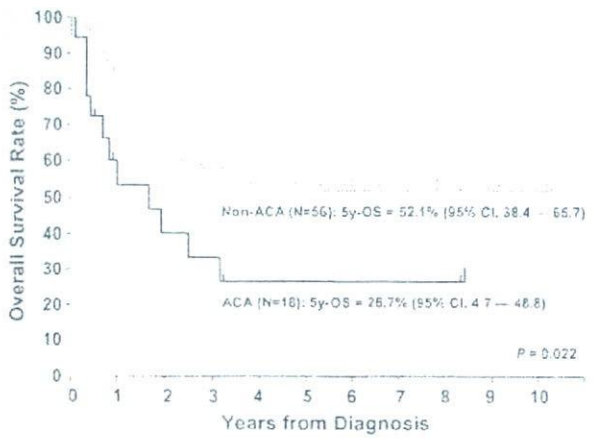

Fig. 2. Overall survival estimates for 74 infants with ALL and *MLL* gene rearrangements in the MLL96 and MLL98 studies; a comparison between patients with additional chromosomal abnormalities and patients with sole 11q23 abnormality excluding normal karyotype with *MLL* gene rearrangements. Median follow-up period: 78 months (range, 8–124 months).

Table 3
Multivariate analysis of prognostic factors in *MLL* rearranged ALL infants

	Parameter estimates	Risk ratio (95% CI)	*P*-value
Age, less than 6 months	0.724	2.063 (1.026–4.146)	0.041
Additional chromosomal abnormalities	0.418	1.519 (0.771–2.993)	0.226
t(4;11)(q21;q23)	0.345	1.413 (0.744–2.683)	0.290
WBC ≥ 300,000/uL	0.387	1.473 (0.771–2.812)	0.239
CNS leukemia	1.166	3.209 (1.497–6.881)	0.002
Registered in the MLL98 study	0.387	1.472 (0.756–2.865)	0.254

CI, confidence intervals; WBC, white blood cell; CNS, central nervous system.

(95% CI, 38.4–65.7%) ($P = 0.022$) (Fig. 2). In a multivariate analysis, only age at diagnosis (younger than 6 months) and positive central nervous system leukemia were significant prognostic factors for poor outcome in this study (Table 3).

4. Discussion

This study demonstrated that complex chromosomal abnormalities were associated with poor outcome in infant ALL with *MLL* gene rearrangements. The previous study described by Moorman et al. showed different findings, in that no prognostic effect of additional chromosomal abnormalities was observed in infants and children with ALL and 11q23 abnormalities [17]. However, it is difficult to simply compare between the study by Moorman et al. and ours as follows. First, Moorman et al. collected data from several cooperative study groups, which comprise different treatment cohorts. Secondly, accurate analyses of karyotypes and *MLL* gene rearrangements were not performed in all patients. Thirdly, the EFS rate in this previous study was too low to evaluate the effect of the additional chromosomal abnormalities in infants with *MLL*-rearranged ALL.

Moorman et al. stated that the frequency of additional chromosomal abnormalities depends on the different 11q23 translocations: high frequency of +X in t(4;11) and t(11;19), involvements in chromosomes 6, 9, and 12 in del(11)(q23) and other 11q23 [17]. In our study, several novel translocations were observed: t(2;4)(q31;q32), t(9;11)(p22;q13), t(2;9)(p10;q10), and t(6;11)(p10;q10). Other frequent chromosomal changes were +X and involvements of chromosomes 4, 7, and 11. In our study, a three-way 11q23 translocation was observed in four patients: t(4;11;15), t(4;11;5), t(4;11;9), and t(4; 11; 21). Different three-way translocations have been also detected in several other reports [15,17,19]. Complex structural chromosomal changes were observed in four patients, including insertion of a 4q21 fragment to the 11q23 locus or insertion of 10p12 to the 11q23 locus in our study. Kowarz et al. described ten patients with three-way translocation or complex structural chromosomal changes in MLL-AF4$^+$/AF4-MLL$^-$ ALL [16]. These findings indicate that complex chromosomal changes in leukemic cells disrupt several genes owing to the "cut and paste" recombination mechanism [16].

Recently, the functions of the partner genes fused to *MLL* gene located in 11q23 locus have been clarified: *AF4* at 4q21, *AF9* at 9p22, *ENL* at 19p133, *ELL* at 19p13.1, *AFX* at Xq13, and *AF6q21* at 6q21 are all transcription factors; *CBP* at 16p13 is a transcriptional coactivator; *AF1q* at 1q21 is a growth factor; and *AF17* at 17q21 is a dimerization protein [7]. In addition, several known genetic changes, such as *p53*, *p16*, and *RAS* mutations, are present in some cases in addition to *MLL* gene rearrangement, which might indicate the essential role of additional genetic changes in combination with *MLL* gene translocation in leukemogenesis [20]. Disruption of the Ikaros gene is also detected as an additional alteration in infant ALL [21]. Table 4 summarizes the genes at the breakpoint region of complex chromosomal abnormalities observed in our study, which have been reported only in hematologic malignancies, such as leukemia or lymphoma [22–29]. The function of each gene varies: *PMS1* at 2q31 and *FANCG* at 9p13 are a mismatch or DNA repair gene [23,27]; *Pax5* also located at 9p13, a differentiation factor of B-cells; and *HOXD13* also located at 2q13, a homeobox gene [24,28]. *PML* at 15q22, usually observed as *PMR-RARα* in acute promyelocytic leukemia with t(15;17), and *E2A* at 19p13, usually observed as *E2A-PBX1* in pre-B ALL with t(1;19), are both transcription factors [34,37]. Other genes such as *CHIC2* at 4q11 is associated with exocytosis, *SYK* and *NR4A3* at 9q22 are a tyrosine kinase and membrane receptor, respectively [29], and *CCND1* (*BCL1*) at 11q13 is associated with cell cycle [31]. Thus, if these genes are functionally disrupted after chromosomal changes, this could promote leukemogenesis.

In our study, the overall survival was significantly worse in the ACA group than that in the non-ACA group, but ACA was

Table 4
Breakpoint of chromosomes and possible located genes

Breakpoint	Located genes	Function	Associated translocation	Associated disease	Reference
1q32			t(1;13)(q32;q14)	Diffuse large B-cell lymphoma	[22]
2q31	*PMS1*	Mismatch repair gene	t(2;12)(q31;p13)	Non-Hodgkin lymphoma, MDS	[23]
	HOXD13	Homeobox gene	t(2;11)(q31;p15)	Therapy-related AML	[24]
4q11	*CHIC2*	Exocytosis	t(4;12)(411;p13)	AML	[25]
7p11			dic(7;9)(p11-13;p11)	Pre-B ALL	[26]
9p13	*FANCG*	DNA repair	t(2;9)(p11;p13)	Pre-B ALL	[27]
	Pax5	B-cell differentiation	t(7;9)(q11;p13)	B-ALL	[28]
9q22	*SYK*	Tyrosine kinase	t(5;9)(q33;q22)	Peripheral T-cell lymphoma	[29]
	NR4A3	Membrane receptor	t(9;12)(q22;p12)	MDS	[29]
11p11			t(11;14)(p11;q32)	Splenic marginal-zone B-cell lymphoma	[30]
11q13	*CCND1 (BCL1)*	Cell cycle control	t(11;14)(q13;q32)	Mantle cell lymphoma, others	[31]
	MYBOV (Cyclin D)			Multiple myeloma	[32]
15q22	*PML*	Transcription factor	t(5;15)(q33;q22)	CML	[33]
			t(15;17)(q22;q21)	APL	[34]
16p11			t(3;16)(q27;p11)	Diffuse large B-cell lymphoma	[35]
			t(16;21)(p11;q22)	AML	[36]
19p13	*E2A*	Transcription factor	t(1;19)(q23;p13)	Pre-B ALL	[37]
			t(2;19)(p11;p13)	AML	[38]
	LYL1	Transcription factor	t(7;19)(q34;p13)	T-ALL	[39]
			t(17;19)(q22;p13)	ALL	[37]

MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia.

not a significant factor in the multivariate analysis. However, given that young age and central nervous system leukemia are significant prognostic factors by multivariate analysis, it is likely that the poor survival outcome seen in the ACA group is associated with the combination of young age, positive central nervous system leukemia and ACA. Since another report showed no effect of additional chromosomal changes in *MLL* positive infant ALL [17], an analysis of the data from a greater number of patients treated with identical treatment protocols is underway to address this issue. In our study, the genes affected by the chromosomal changes varied among the patients, and the function of each gene was different. However, it can be postulated that some genetic alterations induced by additional chromosomal changes might be associated with leukemogenesis and disease progression in *MLL* positive infant ALL.

5. Conflict of interest

All the authors do not have any commercial or other associations that might pose a conflict of interest.

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The Role of Hematopoietic Stem Cell Transplantation With Relapsed or Primary Refractory Childhood B-Cell Non-Hodgkin Lymphoma and Mature B-Cell Leukemia: A Retrospective Analysis of Enrolled Cases in Japan

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Background. There have been excellent treatment results for children with B-cell non-Hodgkin lymphoma (B-NHL) and mature B-cell leukemia (B-ALL) in the last few decades. However, a small subset of relapsed or refractory patients, after first-line therapy, still have a poor prognosis. ***Procedure.*** Thirty-three patients with relapsed or primary refractory B-NHL/B-ALL among 327 newly diagnosed patients between 1996 and 2004 were analyzed retrospectively. ***Results.*** After salvage therapy, 18 patients were chemotherapy-sensitive and 15 patients suffered from progression. Among 18 patients who had a chemotherapy-sensitive disease, 4 of 5 patients who underwent hematopoietic stem cell transplantation (HSCT) during remission survived without progression, while 3 of 12 patients who did not receive HSCT were alive without disease progression. Fifteen patients never sensitive to salvage therapy died. ***Conclusions.*** Patients with relapsed/primary refractory B-NHL/B-ALL have a poor prognosis with current treatment approaches, while the patients sensitive to salvage therapy have a respectable chance to achieve a sustained complete second remission with HSCT. Pediatr Blood Cancer 2008;51:188–192. © 2008 Wiley-Liss, Inc

Key words: childhood; mature B-cell leukemia (B-ALL); non-Hodgkin lymphoma; refractory; relapsed; stem cell transplantation

INTRODUCTION

There have been excellent treatment results for children with B-cell non-Hodgkin lymphoma (B-NHL) and mature B-cell leukemia (B-ALL) in the last few decades along with the assignment of highly intensive and sequential chemotherapeutic regimens stratified according to risk [1–5]. However, patients with relapsed or refractory disease still have a poor prognosis, particularly in patients treated with intensive first-line therapy. And there are few reports on treatment in relapsed or refractory pediatric B-NHL/B-ALL. It is, therefore, very difficult to assess the role of megatherapy or other treatment. In this study, we summarized the results of 33 pediatric patients who had relapsed or primary resistant disease after first-line therapy with B-NHL/B-ALL enrolled in a national survey of Japan, and validate the availability of hematopoietic stem cell transplantation (HSCT) for these patients.

In Japan, there have been four study groups for pediatric hematological tumors; such as, the Japan Children's Cancer and Leukemia Study Group (JCCLSG), the Japan Association of Childhood Leukemia Study (JACLS), the Kyushu-Yamaguchi Children's Cancer Study Group (KYCCSG) and the Tokyo Children's Cancer Study Group (TCCSG). Treatment protocols of these groups for B-NHL modified French LMB89 [2] or German BFM90 [3] consist of short-duration, intensive, alkylating agent therapy (i.e., cyclophosphamide) coupled with other agents, such as intermediate- or high-dose methotrexate, vincristine, anthracyclines, etoposide and cytarabine. Result in survival rates of these collaborative groups with each chemotherapy regimens were 70–80% in stages III–IV.

PATIENTS AND METHODS

We analyzed the data on all children with relapsed/refractory B-NHL/B-ALL have been enrolled in four multicenter trials of childhood NHL. JCCLSG, JACLS, KYCCSG and TCCSG had enrolled 54 patients (JCCLSG NHL-960 study; 1996–2004), 125 patients (JACLS NHL-98 study; 1998–2002), 9 patients (KYCCSG NHL 96 study; 1996–2004) and 139 patients (TCCSG NHL 96 study; 1996–2001) respectively. The first-line treatments used in each study differed, however there were no considerable differences in therapeutic results. Of the 327 patients included in these series, 26 patients relapsed after achieving first complete remission (CR) and 7 patients did not achieve first CR. CR and partial remission (PR) were defined as previously described [6]. The medical records for these 33 patients were retrospectively collected from each study group. Details of salvage or second-line treatment are shown in Table I. NHL-B02 pilot regimen is now used for the patients with childhood B-NHL/B-ALL in Japan, and in other cases childhood ALL regimen of each group was used for relapsed B-NHL/B-ALL. Several patients were treated with regimens published in parts elsewhere [7–10]. Overall survival rate (OS) and progression-free survival rate (PFS) were estimated using the Kaplan–Meier method and data were compared by the log-rank test. The prognostic analysis was based on PFS. Multivariate Cox model was also fitted to adjust the potential effects of the baseline characteristics. Results were analyzed as of January 31, 2006.

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TABLE I. Salvage TherapyDose/Schedule

	Therapy dose/schedule
NHL-B02 pilot	HDMTX 5,000 mg/m^2 day 1 in 24 hr infusion l-rescue
A	Dexamethasone 10 mg/m^2 (divided doses) days 1–7 then reduce over 4 days to 0
	Vincristine 1.5 mg/m^2 day 2 (maximum: 2.0 mg)
	Cyclophosphamide 1,000 mg/m^2 days 4, 5
	Pirarubicin 30 mg/m^2 days 4, 5 (maximum: 45 mg)
	IT MTX 3–12 mg/m^2 days 1, 8
	IT hydrocortisone 10–25 mg/m^2 days 1, 8
	IT cytarabine 6–30 mg/m^2 days 1, 8
B	Vincristine 1.5 mg/m^2 day 1 (maximum: 2.0 mg)
	Dexamethasone 10 mg/m^2 (divided doses) days 1–5 then reduce over 3 days to 0
	HD Ara-C 2,000 mg/m^2 every 12 hr days 2–4
	Etoposide 150 mg/m^2 days 2–5
	IT MTX 3–12 mg/m^2 days 1, 8
	IT hydrocortisone 10–25 mg/m^2 days 1, 8
	IT cytarabine 6–30 mg/m^2 days 8
JCCLSG NHL 960	HD Ara-C 2,000 mg/m^2 days 1–4
	Etoposide 200 mg/m^2 days 1–4
	IT MTX 7.5–1.5 mg/m^2 day 2
	IT hydrocortisone 30–50 mg/m^2 day 2
JACLS ALL-97	Vincristine 1.5 mg/m^2 days 1, 8, 15, 22, 29 (maximum: 2.0 mg)
HR	Dexamethasone 10 mg/m^2 days 1–7
	Pirarubicin 25 mg/m^2 days 2, 4
	Prednisone 40 mg/m^2 (divided doses) days 8–29 then reduce over 5 days to 0
	L-asparaginase 10,000 U/m^2 days 9, 11, 13, 16, 18, 20
	IT MTX 8–12 mg/m^2 days 1, 29
	IT hydrocortisone 15–25 mg/m^2 days 1, 29
	IT cytarabine 20–30 mg/m^2 days 1, 29
F	Mitoxantorone 8 mg/m^2 days 1–3
	Cytarabine 500 mg/m^2 days 1–3, 8–10
	Prednisone 40 mg/m^2 (divided doses) days 1–3, 8–10
	Etoposide 200 mg/m^2 days 8–10
	IT MTX 8–12 mg/m^2 day 1
	IT hydrocortisone 15–25 mg/m^2 day 1
	IT cytarabine 20–30 mg/m^2 day 1
TCCSG L99	Vincristine 1.5 mg/m^2 days 1, 8, 15, 22, 29 (maximum: 2.0 mg)
HEX	Cyclophosphamide 1,000 mg/m^2 days 1, 30
	Prednisone 60 mg/m^2 (divided doses) days 1–28 then reduce over 7 days to 0
	Pirarubicin 20 mg/m^2 days 2, 3, 31, 32
	Prednisone 60 mg/m^2 (divided doses) days 8–29 then reduce over 5 days to 0
	L-asparaginase 6,000 U/m^2 days 1, 3, 5, 7, 8, 10, 12, 14, 15, 17, 19, 21
	IT MTX 6–12.5 mg/m^2 days 8, 15, 22
	IT hydrocortisone 12–25 mg/m^2 days 8, 15, 22
	IT cytarabine 12–25 mg/m^2 days 8, 15, 29
Rituximab	Rituximab 375 mg/m^2 days 1, 8, 15, 22

HDMTX, high dose methotrexated; IT, intrathecal.

RESULTS

Characteristics of Patients

Twenty-three were males and 10 were females with a median age at onset of 13 years (range 1–16 years). Histological classification showed 20 Burkitt lymphoma/leukemia (BL), 12 diffuse large B-cell lymphoma (DLBCL) and one mature B-ALL not further classified. The diagnosis of B-NHL/B-ALL was based on histopathology and immunohistochemistry. From 24 of these 33 patients, the histopathological material was reviewed centrally by a reference laboratory utilized by the study [11]. Cytogenetic studies were performed in 14 patients and showed no abnormality in 5 patients, t(8;14) in 5 patients, and other abnormalities in 4. Murphy's stage was stage I or II in 3 cases and stage III or IV in 30 cases. Sites of relapse/progress included the primary sites in 23 and new sites in 10 cases. Fifteen had bone marrow (BM) involvement (include 6 cases with new BM lesion) and 6 had central nervous system (CNS) disease (include one case with new CNS lesion). Twenty-eight patients progressed or relapsed in the first 12 months from first diagnosis. Characteristics, details of treatment and follow-up of the patients with relapsed or refractory conditions are shown in the Tables II and III.

Patient Outcome After First Relapse/Progress

After a median follow-up period of 48 months, the 4-year OS and PFS rates for these patients were $20.8 \pm 8.2\%$ and $20.5 \pm 7.2\%$,

TABLE II. Characteristics, Treatment, and Outcome of the Patients With Relapsed B-NHL

Patient number	Stage	Time to relapse (months)	Histology	Site of relapse	Treatment of relapse (Table I)	Outcome
1	I	67	DLBCL	Abdomen	CHOP [7] + Rit + operation	Alive
2	III	18	DLBCL	Bone – spleen	NHL-B02 pilot: A, B + Rit + RT	Alive
3	III	35	DLBCL	Primary site (abdomen) + Neck	NHL-B02 pilot: A, B	Alive
4	III	25	BL	Primary site (neck)	NHL-B02 pilot: A, B + Rit + auto PBSCT	Alive
5	III	23	DLBCL	Primary site (abdomen + neck)	JACLS ALL97 HR + auto PBSCT	Alive
6	IV	5	BL	Primary site (abdomen + CNS)	JCCLSG NHL 960	Alive
7	III	12	DLBCL	Primary site (mediastinum)	NHL-B02 pilot: A, B	Died
8	IV	6	BL	Primary site (BM)	CA 100 mg/m^2 + VP 100 mg/m^2 days 1–3	Died
9	IV	5	BL	Primary site (BM)	ICE [8] + Rit + CBT	Died
10	IV	7	BL	BM	CBT	Died
11	IV	3	BL	Primary site (abdomen + CNS)	ALL-REZ BFM 90[9] + RT	Died
12	III	4	BL	BM	Palliatve	Died
13	IV	6	BL	Primary site (BM)	Not available	Died
14	III	4	DLBCL	Primary site (mediastinum + abdomen)	ICE [8] + Rit + related PBSCT	Died
15	IV	2	BL	Primary site (bone + BM)	HD-CA + VP + VCR + Dex + RT + related BMT	Died
16	III	8	DLBCL	CNS	Related PBSCT	Died
17	IV	8	B-ALL	Primary site (CNS) + BM	JACLS ALL97 F + related BMT	Died
18	III	7	BL	Primary site (mediastinum + abdomen)	ESHAP [10] + Rit + related PBSCT	Died
19	IV	6	BL	Primary site (BM)	TCCSG L99 HEX	Died
20	IV	5	BL	Primary site (BM)	TCCSG L99 HEX + related PBSCT	Died
21	III	5	BL	BM + abdomen	VP + VCR + PSL	Died
22	IV	4	BL	Primary site (neck + BM)	NHL-BFM 90[3]	Died
23	II	7	DLBCL	Neck	TCCSG L99 HEX	Died
24	III	6	BL	Primary site (abdomen) + BM	RT	Died
25	IV	5	BL	Primary site (BM)	TCCSG L99 HEX + related PBSCT	Died
26	III	4	BL	BM	Not available	Died

DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; CNS, central nervous system; BM, bone marrow; Rit, Rituximab; RT, radiation therapy; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation; BMT, bone marrow transplantation; CA, cytarabine; VP, etoposide; HD-CA, high dose cytarabine; VCR, vincristine; Dex, dexamethasone; PSL, prednisolone.

respectively. Nine of 33 patients are alive and 24 patients died. Twenty-one patients died of their primary disease, and 3 patients died of therapy-related toxicity. Outcomes according to the kinetics of response to therapy are depicted in Figure 1. All of 15 cases never reaching CR or PR died after salvage therapy with or without HSCT. Ten cases achieved CR and 8 cases achieved PR.

HSCT and Outcome

Among the patients achieving CR or PR, 4 of 5 patients who underwent HSCT and 3 of the 12 patients who did not receive HSCT were alive without disease progression. The other one patient who underwent HSCT with progression died of lymphoma (Fig. 1).

TABLE III. Characteristics, Treatment, and Outcome of the Patients With Primary Refractory B-NHL

Patient number	Stage	Histology	Site of progress	Treatment of progress	Outcome
27	II	DLBCL	Abdomen	Continuation of 1st-line treatment	Alive in CR
28	IV	DLBCL	CNS	Continuation of 1st-line treatment + auto PBSCT	Alive in PR
29	IV	BL	BM	Continuation of 1st-line treatment + related BMT	Alive in CR
30	IV	BL	BM + head + abdomen	Continuation of 1st-line treatment	Died
31	III	DLBCL	Abdomen	ICE[8] – Rituximab	Died
32	III	BL	Abdomen	Not available	Died
33	IV	DLBCL	Bone + CNS + abdomen	Continuation of 1st-line treatment	Died

CR, complete remission; PR, partial remission.

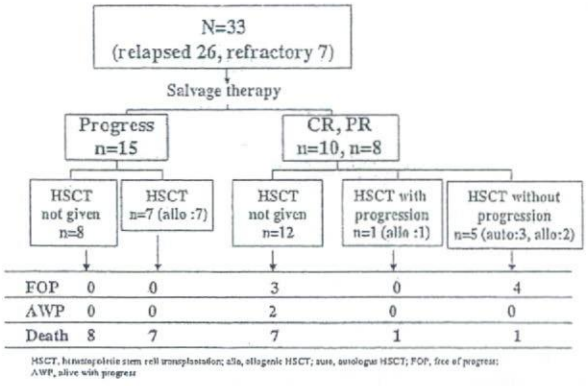

Fig. 1. Outcome in patients with relapsed/refractory B-NHL/B-ALL.

Details of treatment and outcome of the patients with HSCT are shown in Table IV. Disease status at the time of HSCT had an influence on prognosis, however, neither high-dose chemotherapy (HDC) regimens nor kind of graft related to. There were three survivors without disease progression who were not given HSCT. Two of the survivors had stage I or II at initial diagnosis and achieved second remissions after short intensive courses of chemotherapy. Another patient had stage IV DLBCL and relapsed at 18 months after diagnosis, he received a second-line treatment consisting of an intensive chemotherapy according to the NHL-B02 pilot regimen. The patient achieved a CR, however he could not receive HSCT because of contracting by Aspergillus pneumonia. Rituximab and local radiotherapy were successful and he continues in remission 38 months from diagnosis.

Prognostic Factors

In the multivariate analysis, response to salvage therapy was the only significant prognostic factor. PFS was worse among patients with poor response to salvage therapy as compared to the other ($P = 0.037$). On the contrary the PFS was not associated with histologic type, time to relapse, BM or CNS involvement.

DISCUSSION

Outcome of children with B-cell NHL/B-ALL has dramatically improved, while, for relapsed or primary resistant patients, the chance of cure with currently available therapy is low [12,13]. Also in this analysis, the 4-year OS and PFS rates for these patients is about 20%. None of the 15 patients who never reached CR or PR after salvage therapy was alive whereas, 9 of 18 children undergoing salvage therapy in CR or PR were alive. In our series, various retrieval chemotherapy regimens were used, making it difficult to make efficacy comparisons; however, the results of this are in line with previous reports [14,15] showing that chemoresistance is associated with a very poor outcome.

For the patients with second CR or PR, HSCT seems to be an effective strategy, as shown that 4 of 5 patients who received HSCT after having achieved a second CR or PR without progress were PFS, while only 3 of 12 not given HSCT were alive without disease. However, there was no theoretic influence of HDC regimens and previous reports observed in a small group of pediatric patients [16,17], so the optimum conditioning regimen in children is under discussion [18,19]. Previous reports [15,20,21] showed that the major determinant of survival was the remission status of patients before HDC, neither HDC regimens nor type of graft, and our results showed similar findings. In our study, 7 cases received chemotherapy combined with rituximab but there was no significant contribution to their response rate (data not shown).

Another finding from this analysis of factors contributing to PFS reveals that response to salvage therapy was the only significant prognostic factor. It appears important to focus on the salvage therapy. The schedule of a salvage therapy should be tailored to the known features of the tumor (e.g., cell resistance) and be selected of drugs for use nonoverlapping first-line therapy.

In summary, this study demonstrates that the prognosis for patients with relapsed/refractory childhood B-NHL/B-ALL was poor. However, for the patients sensitive to salvage therapy, HSCT seems to be an effective strategy.

TABLE IV. Details of the 13 Patients Treated With HSCT

Patient number	Status before HDC	HDC regimen	Graft (match of HLA)	HSCT	Outcome
4	CR	BU + L-PAM	Autologous	PBSCT	Alive in CR
5	CR	CY + VP + TBI	Autologous	PBSCT	Alive in CR
9	Progress	CY + TEPA + TBI	Unrelated (4/6)	CBT	Died of lymphoma
10	Progress	L-PAM + CA + TBI	Unrelated (6/6)	CBT	Died of HDC
14	Progress	Flu + ATG + L-PAM + TBI	Related (4/6)	PBSCT	Died of lymphoma
15	Progress	BU + L-PAM	Unrelated (6/6)	BMT	Died of HDC
16	Progress	CY + VP + CBDCA − MCNU	Allogeneic (not available)	PBSCT	Died of lymphoma
17	CR	Not available	Sibling (6/6)	BMT	Died of lymphoma
18	Progress	VP + TBI	Sibling (6/6)	PBSCT	Died of lymphoma
20	Progress	Flu + ALG + L-PAM + IDA	Related (4/6)	PBSCT	Died of lymphoma
25	Progress	Not available	Sibling (6/6)	PBSCT	Died of lymphoma
28	PR	TEPA + L-PAM	Autologous	PBSCT	Alive in PR
29	PR	CY + TBI	Sibling (6/6)	BMT	Alive in CR

HDC, high-dose chemotherapy; BU, busfan; L-PAM, melphalan; CY, cyclophosphamide; VP, etoposide; TBI, total body irradiation; TEPA, thiotepa; CA, cytarabine; Flu, fludarabine; ATG, anti-thymocyte globuline; CBDCA, carboplatin; MCNU, ranimustine; ALG, anti-lymphocyte globuline; IDA, idarubicin hydrochloride; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation; BMT, bone marrow transplantation.

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